Oral cancer in Nevada: A Public health perspective

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ORAL CANCER IN NEVADA: A PUBLIC HEALTH PERSPECTIVE

by

Karl Kingsley, PhD
Doctor of Philosophy
Biological Sciences
University of Nevada, Las Vegas
2001

A thesis submitted in partial fulfillment of the requirements for the

Masters of Public Health
School of Community Health Sciences
Division of Health Sciences

Graduate College
University of Nevada, Las Vegas
May 2010
THE GRADUATE COLLEGE

We recommend the thesis prepared under our supervision by

Karl Kingsley, Ph.D.

entitled

Oral Cancer in Nevada: A Public Health Perspective

be accepted in partial fulfillment of the requirements for the degree of

Master of Public Health
School of Community Health Sciences

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May 2010
ABSTRACT

Oral Cancer in Nevada: A Public Health Perspective

by

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Cancer is the second leading cause of death in the United States, and oral cancer remains the eighth leading cause of cancer death among US males. Although previous epidemiologic studies have found that overall rates of cancer, including oral cancer, have declined in the US in recent decades – these declines are neither uniform nor consistent within this population. Anecdotal evidence has suggested that rates of oral cancer in Nevada are relatively high, although no evidence was available to support these assertions.

Oral Cancer Epidemiology: Based upon this information, a detailed and thorough epidemiologic examination of oral cancer rates in Nevada was undertaken. Chapter 1 describes a landmark publication in the journal BMC Public Health, which clearly demonstrated that oral cancer rates are, in fact, rising in specific geographic areas. Moreover, the state with the highest documented sustained increases was Nevada. In addition, although previous research has demonstrated increasing oral cancer rates among women and minorities, due to increased wealth, status and access over these past few decades – the observed increases in Nevada’s oral cancer rates were overwhelmingly within the white male population.

Risk Factor Analysis: In a follow-up study to determine the factors responsible for the rising rates of oral cancer in Nevada, an in-depth analysis of the primary risk
factor for oral cancer development (tobacco usage) was performed. Chapter 2 outlines this study, submitted for publication in the journal Tobacco-Induced Diseases. These results demonstrated that the increased incidence and mortality of oral cancer in Nevada was a state-specific phenomenon and not part of a larger, regional increase. Moreover, trend analysis revealed that tobacco usage rates, although historically higher and linked to other factors, such as lower pricing, taxes and fewer workplace smoking bans, were recently found to be declining. These findings are the first to provide evidence that suggests that rates of oral cancer within this specific geographic area may soon begin to decline.

*Environmental Factors:* In addition to tobacco usage (smoking), many other risk factors may play a role in the development of oral cancers. These additional risk factors include environmental factors, such as nutrition and diet, which are examined in Chapter 3. For example, the recent adoption for required folate fortification in some food products, which has been shown to reduce negative health outcomes related to folate deficiency, has also been demonstrated to increase the rate of growth in undiagnosed (but pre-existing) colorectal cancers. This raises the question of whether folate may play a similar and significant role in the accelerated growth of other slow developing cancers, such as oral cancers. The timing of folate fortification in the US parallels the increased incidence of oral cancer in Nevada, suggesting that this environmental influence may also play an important role in the development and progression of this disease.
ACKNOWLEDGMENTS

Support for this project has been provided by Dr. Gillian Galbraith of the Department of Biomedical Sciences, School of Dental Medicine – University of Nevada, Las Vegas (UNLV), as well as the School of Community Health Sciences.

I would like to acknowledge the guidance and support of Dr. Michelle Chino, my thesis chair and advisor. I also would like to express my gratitude to the committee members, Dr. Connie Mobley, Dr. Patricia Cruz and Dr. Carolee Dodge-Francis, as well as Dr. Shawn Gerstenberger, for their assistance and support.

A gracious thanks to the members of the Kingsley Lab for their guidance, friendship, hard work and support through these past few years. I am particularly grateful to Susan O’Malley, who was my constant guide and the most exacting editor I have ever encountered. Your contributions to my life, personally and professionally, have been significant and powerful - and I am forever in your debt.

Finally, I would like to personally thank Mark Alan Keiserman, who has encouraged and supported my every effort without question. Without his love and support I would have been unable to complete my MPH or made it through a single day of these past ten years. Mark, you have been, and continue to be, my inspiration. Infinities of love – now and forever.
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CHAPTER 1
ANALYSIS OF ORAL CANCER EPIDEMIOLOGY IN THE US REVEALS
STATE-SPECIFIC TRENDS: IMPLICATIONS FOR ORAL CANCER
PREVENTION

This chapter has been published in the peer-reviewed scientific journal BMC Public Health and is presented in the style of that journal. The complete citation is:


Abstract

Background: Downward trends have been observed in oral cancer incidence and mortality in the US over the past 30 years; however, these declines are not uniform within this population. Several studies have now demonstrated an increase in the incidence and mortality from oral cancers among certain demographic groups, which may have resulted from increased risks or risk behaviors. This study examines the underlying data that comprise these trends, to identify specific populations that may be at greater risk for morbidity and mortality from oral cancers.

Methods: Oral cancer incidence and mortality data analyzed for this study were generated using the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) program.

Results: While oral cancer incidence and mortality rates have been declining over the past thirty years, these declines have reversed in the past five years among some demographic groups, including black females and white males. Sorting of these data by state revealed that eight states exhibited increasing rates of oral cancer deaths, Nevada, North Carolina, Iowa, Ohio, Maine, Idaho, North Dakota, and Wyoming, in stark contrast to the national downward trend. Furthermore, a detailed analysis of
data from these states revealed increasing rates of oral cancer among older white males, also contrary to the overall trends observed at the national level.

Conclusions: These results signify that, despite the declining long-term trends in oral cancer incidence and mortality nationally, localized geographic areas exist where the incidence and mortality from oral cancers have been increasing. These areas represent sites where public health education and prevention efforts may be focused to target these specific populations in an effort to improve health outcomes and reduce disparities within these populations.

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Background

Although rates of oral cancer incidence and mortality in the US have declined over the past few decades, these declines have not been consistent or uniform within this population [1-4]. Collaborative reports using data from the National Cancer Institute (NCI), the Centers for Disease Control and Prevention (CDC) and the
American Cancer Society (ACS) have found increases in the incidence of oral cancer among specific segments of the population, including minorities [5-7]. While many advances in treatment and diagnosis have been made over the past three decades, oral cancer remains the eighth leading cause of cancer death among US males [8] and the five-year survival rate has remained low and relatively unchanged [9, 10]. Cancer remains the second leading cause of death in the US [11], and these observed increases in oral cancer provide compelling rationale for this study examining data underlying the general declining trends to elucidate which specific subsets of the population, as well as specific states or regions, that face increasing oral cancer rates.

Recently, studies of oral cancer epidemiology demonstrated statistically significant differences in oral cancer rates among population subgroups, including minorities and various age groups, and between genders [12]. One such study demonstrated that although incidence rates of oral cancer have been steadily decreasing among white males, incidence rates among older black males (>65 years old) have been increasing [13]. In addition, this study demonstrated that oral cancer rates among females, in particular, have increased [13]. Although these data provide some evidence of the disparities in oral cancer rates between these populations, a more detailed examination may identify states, metropolitan areas or communities, as well as additional population sub-groups within these areas, which are experiencing increases in oral cancer incidence or mortality.

This study will examine the underlying data that comprise the general trends, to identify specific populations within the US that may be at greater risk for morbidity and mortality from oral cancers. Epidemiology studies of oral cancer in Europe have found incidence and mortality rates have been declining steadily over the past few decades, similar to the trends found in the US, although more detailed analyses of the
underlying data revealed that persistent upward trends were still present in a small subset of eastern European countries [14-18]. To perform a similar analysis for specific US states and counties, the NCI Surveillance, Epidemiology and End Results (SEER) website [19], a collaborative effort between the NCI and CDC, in conjunction with all US state registries, provides an interface for epidemiologists and other researchers to access and generate oral cancer statistics [20]. Due to the recently observed increases in oral cancer among particular segments of the US population, a more detailed analysis of the underlying data which comprise these general, long-term declining trends provides valuable information about significant short-term increases in specific geographic areas and among specific demographic groups.

Methods

Data sources: Population-based data for the US, specific to oral cancer, were obtained from the Surveillance, Epidemiology, and End Results (SEER) program. SEER provides cancer incidence and survival data from population-based cancer registries, representing approximately 25% of the US population [21]. All oral cancer statistics in this report are based on SEER incidence and National Center for Health Statistics (NCHS) mortality statistics, which consisted of cancers of the oral cavity and pharynx, including the lip, oral cavity and pharynx [22].

Incidence: Oral cancer incidence rates for each year between 1975 and 2004 were obtained from SEER, age-adjusted to the year 2000 standard US population. The overall incidence trends for each time period (1975-2004; 1995-2004; 2000-2004) were then calculated and subsequently graphed based on these data, dividing the most recent incidence rate by each specific earlier rate.

Mortality: Oral cancer mortality rates for each year between 1975 and 2004, age-adjusted to the year 2000 standard US population, were also obtained from SEER.
Data qualified for inclusion in SEER as oral cavity and pharyngeal cancer if the underlying cause of death was specific for oral cancers [20]. The overall mortality trends over time for each time period (1975-2004; 1995-2004; 2000-2004) were calculated and graphed based on data from 1975-2004, dividing the most recent mortality rate by earlier rates.

Annual percent change (APC) 1999-2003: Recent trend data in death rates from oral cancer from individual US states were calculated from the State Cancer Registries in SEER using the Joinpoint Regression Progression and are expressed as the APC over the reported trend period (1999-2003). Current annual death rates of oral cancers from individual US states were similarly obtained and the most recent data available (2003, 2004) at the time of article preparation were reported. Data were exported to Microsoft Excel, sorted in ascending order and graphed.

US state data: Historical mortality data for cancers of the oral cavity and pharynx from selected US states, including Nevada, Idaho, North Dakota, and North Carolina, were calculated by NCI SEER*Stat, from data provided by the National Vital Statistics System public use data file. Trends are based upon analysis calculated using the Joinpoint Regression Program statistical software program, which models the natural logarithm of the rates, identifying years at which any given trend changes, connecting these years graphically by a series of straight line segments [23, 24].

Results

Age-adjusted incidence and mortality rates: Age-Adjusted Incidence Rates (AAIR) and Age-Adjusted Mortality Rates (AAMR) were generated and sorted by race and gender to gather more detailed information regarding oral cancer trends (Fig. 1). The oral cancer incidence and mortality trends were then further delineated into
three, distinct time periods, 1975-2004 (30 year), 1995-2004 (10 year) and 2000-2004 (5 year), to allow for greater specificity within the overall temporal trend analysis.

*Age-adjusted incidence rates (AAIR):* Analysis of the AAIR data revealed an overall declining trend in oral cancer incidence over the past 30 years (Fig. 1A). More specifically, over the past 30 years, oral cancer incidence has declined among white males (-1.21%), white females (-0.66%), black males (-1.53%) and black females (-1.38%), although these observed declines have not been uniform across time or demographic groups. For example, although the incidence of oral cancer among black males has declined over the past 30 years, the temporal stratification of these data revealed that this decline was greatest over the past five years (-6.64%). Furthermore, this stratification also revealed a contrasting trend; the incidence of oral cancer among black females rose from -1.38%, over the entire 30 year period, to +3.18% during the most recent five year period.

*Age-adjusted mortality rates (AAMR):* Analysis of the AAMR data also revealed an overall declining trend in oral cancer mortality over the past 30 years (Fig. 1B). Although overall mortality decreased over 30 years for all groups analyzed, white males (-2.16%), white females (-1.62%), black males (-1.92%) and black females (-1.71%), more specific temporal analysis of oral cancer mortality revealed at least two distinct trends. First, the decreases in mortality were greatest over the last 10 year period compared to the last 30 years and much less pronounced over the more recent five year period. This trend was observed for white females, black males, and black females, but not white males. The second trend, found only among white males, revealed that mortality, although still declining, was declining by ever smaller amounts over each time period: 30 years (-2.16%), 10 years (-1.83%), and five years (-0.33%).
Geographic distribution: To determine if the temporal shifts observed in oral cancer incidence and mortality were associated with specific geographic regions or states, AAIR and AAMR were generated for all US states (Fig. 2). AAIR and AAMR data were then further delineated into quantile intervals to highlight the rates for each state relative to the US averages, from highest (red) to lowest (dark blue).

**AAIR geographic distribution:** Analysis of the AAIR geographic distribution data identified seven states in the highest quantile (11.7 to 13.7 cases per 100,000), the District of Columbia (13.7), Oklahoma (12.7), Louisiana (12.7), Georgia (12.6), Florida (12.5), Maine (12.2) and New Hampshire (11.8) (Fig. 2A). Seven additional states were identified within the second highest quantile (11.0 to 11.6), Maryland (11.6), Alabama (11.5), Wisconsin (11.5), Missouri (11.4), Kentucky (11.4), Nevada (11.2) and Massachusetts (11.0). All states within the two highest quantiles were located in the Eastern and Central zones, with the exception of Nevada (Pacific).

**AAMR geographic distribution:** Analysis of the AAMR geographic distribution data revealed seven states within the highest quantile (3.3 to 4.4 deaths per 100,000), the District of Columbia (4.4), Arkansas (3.5), South Carolina (3.5), Louisiana (3.4), Alabama (3.3), Maine (3.3) and Nevada (3.3) (Fig. 2B). The second highest quantile was comprised of four states, New Hampshire (3.2), Wyoming (3.2), Mississippi (3.0) and Tennessee (3.0). Once again, the majority of states within the two highest quantiles were located in the Eastern and Central zones of the US, with the exception of Nevada (Pacific) and Wyoming (Mountain).

**Annual percent change in US states:** The graphic organization of specific states with the highest levels of oral cancer incidence and mortality provides significant information regarding the geographic regions which are associated with these highest levels. This information does not, however, delineate the areas which
have high levels of oral cancer incidence and mortality that are slowly decreasing over time and those that are increasing. To make this determination, the most recent five year interval was selected to provide a more detailed temporal and geographic breakdown of the states reporting oral cancer incidence or mortality within the two highest quantiles, to determine if the annual percent change (APC) was decreasing at a slower rate, or increasing over time (Table 1).

**APC in US states with elevated incidence:** Analysis of APC from the stratified AAIR data identified 14 states that were in the highest quantiles for oral cancer incidence (Table 1). Of these states, 12 were found to have negative APC, which indicates a continuing decreasing trend in oral cancer incidence over the most recent five-year interval, although most of these decreases were comparatively lower than observed over the longest time interval (30 years). Two states which did not follow this trend, however, and that were found to have increasing APC, were Maine (+2.2%) and Nevada (+4.6%).

**APC in US states with elevated mortality:** Analysis of APC from the stratified AAMR data identified 11 states that were in the highest quantiles for oral cancer mortality (Table 1). Of these states, eight were found to have negative APC, which suggests a continuing decreasing trend in oral cancer mortality, although most of the decreases were also comparatively lower than observed over the longest time interval (30 years). Three states, however, were found to have increasing APC, Maine (+2.2%), Nevada (+4.6%) and Wyoming (+0.1%).

**US states with positive APC:** Although we identified states with positive APC, in the highest quantiles for both oral cancer incidence and mortality (Maine, Nevada), one additional state was found to have positive APC, which was only found among the states with elevated mortality. To determine if other states had increasing APC,
but were not among the states with the highest overall levels of oral cancer incidence or mortality, we expanded this analysis to include data for all US states. This analysis revealed that eight states had increasing APC in oral cancer mortality (Fig. 3). These states were Nevada (+4.6%), North Carolina (+4.0%), Iowa (+3.5%), Ohio (+3.4%), Maine (+2.2%), Idaho (+1.0%), North Dakota (+0.5%) and Wyoming (+0.15), only three of which were among the states with either the highest oral cancer incidence or mortality.

Having identified eight states with recent increasing or positive trends (APC), a more detailed analysis of each of these states was performed to further examine these trends within each state. The more detailed analysis of each state, year-to-year, spanning a 25 year period revealed significant, increasing trends in only four of these states, Nevada (Fig. 4), Idaho (Fig. 5), North Dakota (Fig. 6) and North Carolina (Fig. 7).

**Nevada:** Oral cancer mortality data for Nevada, the state with the highest five-year APC (+4.6%), were stratified by race and gender (Fig. 4). The analysis revealed that although the rates of oral cancer were decreasing for many years (1980-1997), a distinct upward trend was noted (1998-2004). Moreover, this trend was most closely associated with white males (Fig. 4A). The data for white males were then further stratified by age, revealing that the recent upward trends in oral cancer mortality were almost exclusively associated with white males over 50, and especially with white males over 65 (Fig. 4B).

**Idaho:** Oral cancer mortality data for Idaho, another state identified with a positive five-year APC (+1.0), were also sorted by both race and gender (Fig. 5). The results from this stratification revealed that the rates of oral cancer in Idaho have been slowly increasing for many years (1980-2004). More specifically, this trend was
associated almost exclusively with white males (Fig. 5A), with too few data points to support trend analysis for any other race or gender grouping. Separating the data for white males by age revealed that this upward trend was associated with white males over 50, but not older than 65 (Fig. 5B).

**North Dakota:** Oral cancer mortality data for North Dakota, a state with a small, positive five-year APC (+0.5%), were also sorted by race and gender (Fig. 6). The results from this analysis revealed that rates of oral cancer in North Dakota have been slowly increasing over many years (1980-2004) and the increases were also associated with white males (Fig. 6A). After separating these data by age, the results did not find this trend was associated with any specific age group (Fig. 6B).

**North Carolina:** Oral cancer mortality data for North Carolina, a state with a positive five-year APC (+4.5%), were also sorted by race and gender (Fig. 7). The results from this analysis, however, revealed that the recent increasing trend in oral cancer mortality (2001-2004) was primarily associated with black males (Fig. 7A). After the data for black males were further stratified by age, the upward trend was most closely associated with black males over 50, but not older than 65 (Fig. 7B).

**Discussion**

Although cancer ranks as the second leading cause of death in the United States, after heart disease, and remains an important problem facing public health professionals, the overall rates of cancer deaths have been steadily declining over the past few decades [25]. While this declining trend is welcome news for the general population and health professionals, it does not accurately describe the details which underlie these trends in which rates for some types of cancer have decreased significantly, while rates of other cancers have displayed opposing, increasing trends [11]. For example, although rates of lung cancer have steadily declined for decades,
cancers of the liver and thyroid have increased over the same period [3, 11, 26]. In the same fashion, the overall declining rates observed for oral cancer may obfuscate the underlying data which suggest that while the rates are declining among whites, they may be simultaneously increasing among other ethnic or demographic groups, such as blacks and females [13, 27].

To accurately understand the changes in oral cancer incidence and mortality, it is important to examine not only the composite data which describe the general trends for the US population over many years, but also to scrutinize the primary core data which convey more detailed information. For example, these core data may include shorter intervals and year-by-year trends, as well as demographic and geographic breakdowns. Although previous reports have noted that oral cancer incidence and mortality rates are not uniform across demographic groups [13, 27], this report is among the first to describe that oral cancer rates may be increasing over the short term, and that these increases are restricted to a small subset of states and particular demographic groups.

Previous studies have described an overall declining trend in oral cancer incidence and mortality with the understanding that these decreases were found primarily among whites, and were not offset by smaller increases among other demographic groups [20, 28]. This report, however, provides evidence of three distinct trends, not previously articulated. First, although oral cancer incidence and mortality have declined over the past thirty years, with the most significant declines observed over the past ten years, a reversal of these trends has emerged from the short-term (over the past five years) trend analysis, which may signify an important development in the epidemiology of this cancer. Next, this report provides a geographic profile of oral cancer rates over time, revealing that although oral cancer
rates are continuing to decline in most states, they are now in fact increasing in a small subset of states. Finally, in-depth stratification of data from these specific states revealed that oral cancer rates are increasing almost exclusively among older white males in three of these states, in sharp contrast to the general national trends.

The identification of differential oral cancer trends among specific geographic areas and demographic groups in the US could indicate a shift in the epidemiology of this cancer. A recent large-scale study among European countries revealed similar temporal and geographic trends [18]. For example, although oral cancer incidence and mortality has steadily declined in Europe as a whole since the 1980s, more detailed analysis by geographic region (country) revealed that mortality was rising in a subset of eastern European countries, most notably in Bulgaria, Romania, Hungary, Slovakia and Slovenia [16, 17]. Based upon these observations, the study authors speculated that the temporal and geographic nature of these patterns was related to changes in exposure to the two major risk factors for oral cancer, alcohol and tobacco. These items became more readily available and widely disseminated in these areas following the disintegration and break-up of the Soviet Union [18].

Perhaps the increasing oral cancer trends identified in this study, in specific states and among specific demographic groups, are related to identifiable trends in oral cancer risk factors and behaviors, such as increased tobacco use or alcohol consumption, as was found in eastern European countries. The most recent Behavioral Risk Factor Surveillance System (BRFSS) data confirms that six of the eight states identified in this report with increasing trends in oral cancer mortality were also among the states with higher than average rates of current smokers, which include Ohio, Nevada, North Carolina, Wyoming, Iowa and Maine [29]. Moreover, these states were also among the states with higher than average rates of heavy
alcohol consumers, with the exception of North Carolina. Although these data suggest a correlation between alcohol and tobacco consumption patterns and oral cancer in these areas and among these demographic groups, the BRFSS data also provide some conflicting evidence, revealing that the states with the highest levels of current smokers and heavy alcohol consumers (Kentucky and Wisconsin, respectively) were not among those states with increasing rates of oral cancer incidence and mortality, but rather have decreasing rates, indicating that other risk factors may also be significant contributing factors.

Although tobacco and alcohol consumption are the main risk factors for developing oral cancer, implicated in as many as 90 to 95% of head and neck cancers, other potential risk factors have recently emerged [30]. For instance, evidence for the role of infectious agents in the etiology of oral cancers has been mounting, demonstrating that oral infection with high-risk human papillomavirus (HPV) may not only increase the risk of developing oral cancer, but may also contribute to its progression [31, 32]. Other infectious agents and immune modulators, such as infection with the human immunodeficiency virus (HIV) and immune suppression, induced mainly via pharmacologic means to prevent rejection of transplanted organs, also significantly increase the risk of developing oral cancer [12]. In addition, recent evidence demonstrates that nutrition may play an important role in retarding the development and progression of oral cancers, revealing a nearly 50% reduction in oral cancer risk for each additional portion of fruits or vegetables consumed per day, even among tobacco and alcohol consumers [33-36]. Identifying those demographic groups and geographic areas experiencing increases in oral cancer will help direct public health research to understand how and why these rates may be increasing.
Conclusions

It is imperative that further analysis of the contributing factors that underlie these temporal and geographic trends be undertaken. This information may be indispensable to public health professionals as they strive to design population-specific prevention and education programs, which are often funded and implemented at the local, regional and state levels. Because many of the lifestyle behaviors which contribute to oral cancer risk are possible to impact through public health education and prevention strategies, more effective targeting of public health monies and efforts, towards the specific geographic regions and demographic populations which face these increased risks, may help to reverse these disturbing trends of increasing oral cancer, as outlined in this study.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

KK performed the statistical analyses. SO and MD assisted with the interpretation and analysis of data generated and made significant contributions to the writing and editing of this manuscript. MC and KK conceived and coordinated the design of this project. All authors have read and approved the final version of this manuscript.

Acknowledgements

KK would like to acknowledge the American Cancer Society for previous grant support and also the Departments of Biomedical Sciences and Occupational and Environmental Health in the Schools of Dental Medicine and Public Health, respectively.
References

21. National Cancer Institute, Surveillance, Epidemiology and End Results Database (NCI-SEER) [http://seer.cancer.gov/about/].
Figures

Figure 1 - Incidence and mortality trends for oral cancer in the US: Trends for the incidence (A) and mortality (B) rates of oral cancer cases reported to the SEER program from 1975-2004 in the US were sorted by time period (30 year, 10 year and 5 year), and by race/ethnicity and gender.

Figure 2 - Geographic distribution of current incidence and mortality rates for oral cancer in the US: Age-adjusted (A) and mortality (B) rates for all US states, for all races, all ages and both sexes, were ranked in quantiles, based upon cases per 100,000 and mapped: created by statecancerprofiles.cancer.gov.
Figure 3 - Annual percent change (APC) in mortality rates for oral cancer, 1999-2003: Annual Percent Change (APC) for the age-adjusted mortality rates for cancer of the oral cavity and pharynx, for all ages, genders and races, sorted by US state, 1999-2003, were created by statecancerprofiles.cancer.gov, using NCI SEER*Stat and sorted. Eight states were identified with positive, increasing APC using this method. *N/Q: Data not provided because it did not meet United States Cancer Statistics (USCS) data quality standards for one or more years during the rate period of data collection.

<table>
<thead>
<tr>
<th>US states (positive APC)</th>
<th>APC</th>
<th>Mortality Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevada</td>
<td>+4.6%</td>
<td>3.3/100,000 11.2/100,000</td>
</tr>
<tr>
<td>North Carolina</td>
<td>+4.0</td>
<td>2.9  11.2</td>
</tr>
<tr>
<td>Iowa</td>
<td>+3.5</td>
<td>2.4  11.0</td>
</tr>
<tr>
<td>Ohio</td>
<td>+3.4</td>
<td>2.9  9.1</td>
</tr>
<tr>
<td>Maine</td>
<td>+2.2</td>
<td>3.3  12.2</td>
</tr>
<tr>
<td>Idaho</td>
<td>+1.0</td>
<td>2.3  10.6</td>
</tr>
<tr>
<td>North Dakota</td>
<td>+0.5</td>
<td>2.1  9.4</td>
</tr>
<tr>
<td>Wyoming</td>
<td>+0.1</td>
<td>3.2  N/Q*</td>
</tr>
<tr>
<td>United States</td>
<td>-1.1%</td>
<td>2.6/100,000 10.4/100,000</td>
</tr>
</tbody>
</table>

Figure 4 - Historical trends for oral cancer mortality in Nevada: Historical trends (1980-2004) of mortality from oral cancer were sorted by race/ethnicity and gender (A) using NCI SEER*Stat and regression lines calculated using the Joinpoint Regression Program. Increasing trend in mortality among white males (1997-2004) was further delineated by age (B).
Figure 5 - Historical trends for oral cancer mortality in Idaho: Historical trends (1980-2004) of mortality from oral cancer were sorted by race/ethnicity and gender (A) using NCI SEER*Stat and regression lines calculated using the Joinpoint Regression Program. Mortality among white males was sorted further by age (B).

Figure 6 - Historical trends for oral cancer mortality in North Dakota: Historical trends (1980-2004) of mortality from oral cancer were sorted by race/ethnicity and gender (A) using NCI SEER*Stat and regression lines calculated using the Joinpoint Regression Program. Mortality among white males was then stratified by age (B).
Figure 7 - Historical trends for oral cancer mortality in North Carolina: Historical trends (1980-2004) of mortality from oral cancer were sorted by race/ethnicity and gender (A) using NCI SEER*Stat and regression lines calculated using the Joinpoint Regression Program. The increasing trend among black males was sorted further by age (B).
Tables
Table 1 - Comparison of annual percent change (APC) in oral cancer mortality among US states with higher than average incidence and mortality: US states from the highest two quantiles of current oral cancer incidence and mortality were sorted in descending order to compare with recent (1999-2003) APC rate trends in mortality. Among these, three states were found to have increasing APC, Maine, Nevada, and Wyoming.

<table>
<thead>
<tr>
<th>US states (elevated incidence)</th>
<th>APC trend (recent)</th>
<th>Mortality rate (current)</th>
<th>Incidence rate (current)</th>
</tr>
</thead>
<tbody>
<tr>
<td>District of Columbia</td>
<td>-4.6%</td>
<td>4.4/100,000</td>
<td>13.7/100,000</td>
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*N/Q  Data not provided because it did not meet United States Cancer Statistics (USCS) data quality standards for one or more years during the rate period of data collection.
CHAPTER 2

ANALYSIS OF PRIMARY RISK FACTORS FOR ORAL CANCER FROM SELECT US STATES WITH INCREASING RATES

This chapter has been accepted for publication in the peer-reviewed scientific journal Tobacco Induced Diseases and is presented in the style of that journal. The complete citation is:


Abstract

Objectives: To examine the primary risk factor for oral cancer in the US, smoking and tobacco use, among the specific US states that experienced short-term increases in oral cancer incidence and mortality.

Methods: Population-based data on oral cancer morbidity and mortality in the US were obtained from the National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER) database for analysis of recent trends. Data were also obtained from the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System (BRFSS) to measure current and former trends of tobacco usage. To comprehensive measures of previous state tobacco use and tobacco-related policies, the Initial Outcomes Index (IOI, 1992-1993) and the Strength of Tobacco Control index (SoTC, 1999-2000) were also used for evaluation and comparison.

Results: Analysis of the NCI-SEER data confirmed a previous report of geographic increases in oral cancer and demonstrated these were state-specific, were not regional, and were unrelated to previously observed increases among females and minorities. Analysis of the CDC-BRFSS data revealed these states had relatively higher percentages of smokers currently, as well as historically. In addition, analysis
of the IOI and SoTC indexes suggest that many factors, including cigarette pricing, taxes and home or workplace bans, may have had significant influence on smoking prevalence in these areas. Trend analysis of these data uncovered a recent and significant reversal in smoking rates that suggest oral cancer incidence and mortality may also begin to decline in the near future.

Conclusion: Due to the rising costs of health care in the US and the limited resources available for health prevention efforts, it is essential to organize and direct more effective efforts by public health officials and epidemiologists, as well as funding from local, state and federal governments, to reduce and eliminate identified health disparities. This study provides evidence how these efforts may be directed to specific geographic areas, and towards the white males, previously thought to be unaffected by the increases in oral cancer among females and minorities.

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Background

Although oral cancer incidence and mortality rates have increased worldwide, these rates have been slowly and steadily declining among the US population over the past thirty years [1,2]. Despite the overall declining trends of oral cancer in the US, these declines are neither consistent nor uniform within this population [3,4]. Researchers have found that the incidence among specific demographic subgroups may have actually increased over this same time period [5-7]. Recent studies have shown that rates of oral cancer have been steadily declining among males, but have risen sharply among females [8]. More specifically, the declining rates observed among males were specific mainly to white males, while increasing incidence was found among minorities, and black males, in particular [8]. A new study of oral cancer epidemiology has found that increases in incidence and mortality may also exhibit geographic specificity within the US [9], providing compelling rationale to analyze the risk factors for oral cancer within these specific geographic areas and among these specific demographic subgroups.

Oral cancer incidence and mortality are correlated strongly with two major risk factors, tobacco use – consisting primarily of smoking in the US, and to a lesser extent, heavy alcohol use, which together account for the overwhelming majority of
cases [10]. A recent study of smoking and tobacco use in the US found that rates declined sharply among males between 1965 and 1990, while the rates among females and minorities had less pronounced declines, and in some instances, may have increased [11]. In fact, more recent studies provide strong evidence that increasing usage of non-traditional forms of tobacco in the US, such as cigars and water pipe smoking, have become increasingly popular among females and minorities [12]. Although many studies have found correlations and linkages between increased workplace participation and social mobility, as well as acceptance and availability of tobacco products with the increasing rates of oral cancer among females and minorities, no studies to date have yet examined the relationship between increasing rates of oral cancer in a small subset of US states and the primary risk factors for oral cancer.

A review of oral cancer epidemiology in Europe revealed morbidity and mortality have been steadily decreasing since the early 1980s, similar to the trends observed in the US [13]. Temporal and geographic patterns, however, have demonstrated increasing oral cancer rates among specific eastern European countries following the disintegration and dissolution of the Soviet Union [14,15]. These studies have demonstrated the increases were highly correlated to changes in exposure to the primary risk factors for oral cancer, including tobacco and alcohol, which became more readily available during this time [14,15]. Although no analogous geopolitical events have precipitated rapid, sharp increases in the availability of either tobacco or alcohol within these select US states with increasing oral cancer rates, significant differences in cigarette pricing and taxes, as well as specific laws regarding smoking bans, may have created state-specific environments that influence the prevalence of these oral cancer risk factors over time.
This study sought to examine the primary risk factors for oral cancer, focusing specifically on tobacco use and smoking prevalence, among the US states recently found to have increasing short-term oral cancer incidence and mortality rates, including Nevada, North Carolina, Iowa, Ohio, Maine, Idaho, North Dakota and Wyoming [9]. More specifically, the working hypothesis for this study was that state-specific environmental factors may have led to increased tobacco use within these states. Data from the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) database, and the Behavioral Risk Factor Surveillance System (BRFSS), supported by the Centers for Disease Control and Prevention (CDC), were used to access and generate oral cancer statistics and comparisons of risk factor prevalence in these specific US states, over time. The identification of states, regions, or geographic areas with increased risk for oral cancer, as well as increased morbidity and mortality, is important because these represent sites where public health education and prevention efforts could be more effectively focused to improve health outcomes and reduce health disparities.

Methods

Mortality data: Surveillance, Epidemiology, and End Results (SEER): Population-based data on oral cancer in the US were obtained from the Surveillance, Epidemiology, and End Results (SEER) program. SEER provides cancer incidence and survival data from population-based cancer registries, representing approximately 25% of the US population [16]. All oral cancer statistics in this report are based on SEER incidence and National Center for Health Statistics (NCHS) mortality statistics, which consisted of cancers of the oral cavity, pharynx and lip [17]. Oral cancer mortality rates between 1975 and 2005 were also obtained from SEER for each year, age-adjusted to the year 2000 standard US population. Deaths qualified for inclusion
in SEER oral cavity and pharyngeal cancer if the underlying cause of death was specific for head and neck cancers [18]. The overall mortality trends over time were calculated and graphed based on available data from 1981-2005.

Annual percent change (APC) for selected US states: Recent trend data in death rates from oral cancer in individual US states were calculated by the National Cancer Institute (NCI) SEER*Stat using data provided by the National Vital Statistics System public use data file (SEER) and from the State Cancer Registries using the Joinpoint Regression program and are expressed as the annual percent change (APC) over the reported trend period (1999-2003, for example) for selected US states. These states included Nevada (NV), North Carolina (NC), Iowa (IA), Ohio (OH), Maine (ME), Idaho (ID), North Dakota (ND), Wyoming (WY), Arizona (AZ), California (CA), Oregon (OR) and Utah (UT). Trends calculated using the Joinpoint Regression statistical software program model the natural logarithm of the rates, identifying years at which any given trend changes, connecting these years graphically by a series of straight line segments [19,20]. Current annual death rates of oral cancers from individual US states were similarly obtained and the most recent data available (2003, 2004 or 2005) at the time of article preparation were reported.

Risk factor data: Behavioral Risk Factor Surveillance System (BRFSS): Historical risk behavior data for tobacco use from selected US states were obtained from the Behavioral Risk Factor Surveillance System (BRFSS). BRFSS is among the largest health surveillance and survey systems, responsible for tracking data monthly and reporting health conditions and risk behaviors from all US states, the District of Columbia, Puerto Rico, the U.S. Virgin Islands, and Guam, since 1984 [21]. BRFSS is part of the National Center for Chronic Disease Prevention and Health Promotion, sponsored by the Centers for Disease Control and Prevention (CDC). Data included
four level smoking status  (Smoke Every Day; Smoke Some Days; Former Smoker; Never Smoked), and adults who are current smokers. Temporal data files were available for all states after 2001, and from selected states dating from 1984.

*Initial Outcomes Index (IOI) and Strength of Tobacco Control (SoTC):* State-specific data and rankings that form the US State Tobacco Control Initial Outcomes Index (IOI) were obtained from a previous report [22]. Measures used to generate the IOI index included smoking prevalence, computed as the percentage of current smokers who indicated at the time of the survey they smoked either every day or some days, per capita cigarette consumption, computed using total number of packs removed and sold in any given month divided by the US Bureau of Census estimates for state population aged 18 years or older at the time of the survey, weighted averages for cigarette prices during the time period analyzed, and the prevalence of workplace and home smoking bans. For the index factors (cigarette price per pack, workplace smoking bans among ever smokers and home smoking bans among ever smokers) z scores were calculated and summed to form a tobacco control IOI, which was correlated with adult smoking prevalence and the point estimate of per capita cigarette consumption. Similarly, state-specific data and rankings from 1999-2000 form the standardized Strength of Tobacco Control (SoTC) index, which were also obtained from previous reports [23, 24]. Positive IOI or SoTC index scores indicate relatively robust state tobacco controls, including smoking bans, and generally reflect higher cigarette prices and taxes, while negative index scores indicate states with weaker tobacco controls, fewer smoking bans and comparatively lower cigarette prices and taxes.

Results
Surveillance Epidemiology and End Results (SEER): Oral cancer rates in those selected states with previously identified increasing APC [9] were recalculated and updated to reveal any changes to the previous trends observed (Figure 1). This re-analysis confirmed the previous report that oral cancer rates have been decreasing in most US states, however a small subset of states have experienced recent increases in rates of death from oral cancer (Fig. 1B). This data revision also confirmed the previous report that mortality in the state with the highest APC in oral cancer deaths, Nevada, was decreasing for many years (1981-1995) (Fig. 1A). However, the distinct reversal and subsequent upward trend in deaths from oral cancer in Nevada was found to have begun earlier (1995-2005) than previously noted (1998-2004), providing further confirmation this upward trend appears not only to be continuing (2004-2005), but may also be increasing. In addition, this analysis confirmed these observed increases were not among females or minorities, but instead were restricted primarily to white males.

To determine if these trends were restricted to these particular states or if they are part of a larger regional increase, oral cancer rates for US states with contiguous geographic borders to Nevada were analyzed to determine any demonstrable changes (Fig 1B). This analysis revealed the majority of states sharing a contiguous border with Nevada, including Arizona, California, Oregon and Utah, have all experienced decreasing rates of oral cancer deaths, similar to the national US trend. The only state bordering Nevada found to have a positive oral cancer APC was Idaho, a state previously identified as one of the subset of US states with increasing rates of death from oral cancer [9].

Behavioral Risk Factor Surveillance System (BRFSS): Epidemiologic evidence has previously demonstrated oral cancer incidence and mortality rates are
correlated strongly with two major risk factors, tobacco use – consisting primarily of smoking, and to a lesser extent, heavy alcohol use [10]. To assess the potential relationship between tobacco use, the primary risk factor for oral cancer, and the subset of US states with increasing oral cancer rates, data regarding tobacco use and smoking prevalence in these states was obtained from the Behavioral Risk Factor Surveillance System (BRFSS). Analysis of these data demonstrated that the majority (7/8) of those states with elevated oral cancer APC also had current smoking rates (2007, most current available data) at or above the national average (Table 1). Moreover, all of the states sharing a contiguous border with Nevada, mainly with decreasing rates of oral cancer, were found to have current smoking rates at or below the national average.

Initial Outcomes Index (IOI): Although current smoking rates may indicate state-specific usage for tobacco based on price, availability or other social and economic factors, current oral cancer mortality rates are generally the result of previous smoking prevalence [10]. Recent public health efforts have focused on developing comprehensive, state-specific measures of previous tobacco use through development of a comprehensive index that measured and ranked all US states according to multiple factors, including per capita tobacco consumption, cigarette prices, as well as workplace and home smoking bans. One such comprehensive index or measure of previous smoking prevalence and tobacco control, known as the initial outcomes index (IOI), ranked all US states for these various factors between 1992 and 1993. Analysis of the IOI index data revealed the majority of states with increasing oral cancer APC also earned IOI scores in the LOW or MODERATE categories (6/8), mainly the result of higher rates of smoking and lower rates of tobacco control, such as lower cigarette prices and fewer smoking bans (Table 1). Conversely, all of the
states sharing a contiguous border with Nevada, mainly those with decreasing oral cancer rates, earned IOI scores of HIGH – suggesting these states had lower smoking rates and higher overall tobacco controls, including higher cigarette prices and more extensive smoking bans.

**Strength of Tobacco Control (SoTC):** Another comprehensive measure of previous state tobacco usage, known as the strength of tobacco control (SoTC), was subsequently developed by public health officials to rank and compare all US states in 1999 and 2000, similar to the IOI. Once again, an analysis of the SoTC index data revealed the majority of states with increasing oral cancer APC earned negative SoTC scores, with Nevada scoring the lowest (-1.42), suggesting that tobacco control in these states remained comparatively weak and less than the national mean index (mean=0.0, STD=1.20) (Table 1). In contrast, all of the states sharing a contiguous border with Nevada had positive SoTC index scores. When combined in this manner, these data provide compelling evidence that the current smoking prevalence in states with elevated oral cancer rates may have long-standing, historical trends of tobacco use and control that may explain, in part, these anomalous state-specific increases in oral cancer.

Although the rates of oral cancer incidence and mortality have declined over the past thirty years, a reversal of these trends has recently emerged during the short-term, which may signify an important change in the epidemiology of this cancer. The IOI, SoTC, as well as current smoking rates provide important information regarding the overall prevalence of tobacco use at specific time points, indicating potential geographic areas that may suffer from tobacco-induced diseases, including oral cancer. A more detailed examination of the changes in short-term trends of tobacco usage rates or smoking prevalence within these states was necessary to explore these
potential interactions and effects. Based upon this information, data from BRFSS regarding annual smoking prevalence for states with elevated oral cancer APC and states with a contiguous border to Nevada were assessed to reveal any significant changes (Figure 2).

Detailed analysis of this data revealed that most states with elevated oral cancer APC were found to have increases in the prevalence of smoking during the initial, short-term time period examined (1995 – 2000) (Fig. 2A). In addition, most states sharing a contiguous border with Nevada were found to have decreases in the prevalence of smoking over this same time period, with the notable exception of Idaho. To evaluate how these short-term changes in smoking rates may have changed over time, BRFSS smoking prevalence data for all available years (1995-2007) from the individual state with the highest oral cancer APC, Nevada, were obtained and plotted to reveal any significant trends (Fig. 2B). This analysis demonstrated that although smoking rates in Nevada were initially increasing between 1995 and 1999, these rates have begun a more recent year-by-year decline – although they remain above the national average.

To determine any changes in smoking prevalence occurring in the states examined so far, BRFSS data for all available years (1995-2007) were obtained and short-term changes in smoking rates were evaluated to uncover any significant trends (Table 2). This analysis revealed that all of the states identified with elevated oral cancer APC also experienced an increase in smoking trends during one or more of the first four time intervals examined (1995-2000, 1996-2001, 1997-2002, 1998-2003). Furthermore, all of the states sharing a contiguous border with Nevada experienced only decreasing rates of smoking during these same intervals, with the exception of Idaho (Table 2). Moreover, these data revealed an important shift and reversal in
smoking trends among the states with elevated oral cancer APC during the 1999-2004 interval. This reversal signified a dramatic decrease for each of these states, which has continued during all subsequent intervals (2000-2005, 2001-2006, 2002-2007), albeit by differing percentages.

To further examine the changes in smoking prevalence over time from those states with elevated oral cancer APC, BRFSS data for each year were collected and graphed (Figure 3). The year-by-year plot of individual states with elevated oral cancer rates demonstrated that although some initial increases were observed in each state, most states developed a general, decreasing trend that became evident between 1999 and 2001 (Fig. 3A). Plotting the smoking prevalence trends from Table 2 to visualize the changes over five-year intervals revealed the dramatic shift from mainly positive trends, or increases in reported state-wide smoking during the first four time intervals to negative trends, or net decreases in smoking during all subsequent time intervals (Fig. 3B).

A similar examination of changes in smoking rates over time was performed using BRFSS data from those states sharing a contiguous border with Nevada to reveal any significant changes in trends and for comparison with those states experiencing elevated oral cancer APC (Figure 4). In detail, the year-by-year plot of smoking trends from these states revealed that most experienced year-by-year decreases for the vast majority of years examined, with the notable exception of Nevada itself (Fig. 4A). A plot of the changes in smoking trends for each time period from Table 2 revealed that all of these states experienced declining rates of smoking during all intervals examined (1995-2000, 1996-2001, 1997-2002, 1998-2003, 1999-2004, 2000-2005, 2001-2006, 2002-2007), with the notable exceptions of Nevada and Idaho (Fig. 4B).
Discussion

The overall rates of cancer incidence and mortality have declined within the US in recent decades, but are not uniform or consistent within this population [1-4]. Although strong evidence has shown increased rates among minority groups and women during this same period [5-7], recent evidence has suggested rates are also increasing within particular US states, creating additional health disparities [13]. This study re-examined those data and confirmed that oral cancer rates have increased within this small subset of US states. Moreover, further analysis verified that these trends are not part of larger, regional increases in oral cancer nor are they linked with the previously observed increases among females and minorities, but instead represent state-specific phenomenon with geographic specificity.

Oral cancer has been linked primarily to tobacco use and smoking [10], therefore, this study sought to analyze comprehensive state demographic and behavioral data necessary to reveal the current and historical trends of tobacco use and smoking in these specific states. Although it was expected, and confirmed, that states with higher rates of oral cancer had comparatively higher rates of current, as well as former, smokers than other states, this study exposed more recent, short-term trends that suggest these smoking rates have more recently reversed and are now steadily decreasing over time. Because oral cancer incidence and mortality are generally the result of previous smoking prevalence, this reversal may signify that oral cancer rates within this subset of US states will also begin to decline, although previous observations suggest a lag time of many years [6,7,10,11].

Although epidemiologic studies of demographic and behavioral characteristics provide invaluable methods for identifying subgroups with increased risk for oral cancer within larger populations, this study provides strong evidence of other
potential variables, including state-specific indexes of policies and pricing structures for tobacco, that may create “geographic pockets” of increased risk, even among the general population. In addition, the inclusion of workplace and home smoking bans as integral components of the IOI and SoTC indexes may suggest these data have the potential to provide more nuanced and comprehensive measures of state-specific smoking activity and risk than the more commonly reported measures of current adult smokers or per capita cigarette consumption. However, despite recent increases in the number of workplace smoking bans passed in several of these states, the role of second-hand smoke in the work or home environment may represent additional factors that further complicate and exacerbate the effects of tobacco use within these areas [25,26].

Aside from the confounding effects of second-hand smoke, several additional limitations of this study should be noted. For example, some of these states have seen dramatic shifts in population, including a rapid influx of both casino and construction workers in Nevada, which were coupled with an influx of retired and elderly seeking affordable housing in warmer climates [27]. Although the survey and sampling of populations through the CDC, BRFSS and SEER should account for these shifts in population demographics, the possibility remains that these shifts could have skewed the data sampling, which may have resulted in the inaccurate representation of current or former smokers in each state - thereby influencing the outcome of these analyses.

In addition, other potential risk factors for oral cancer have also recently been identified and these underlying medical conditions may have some effects on the different rates observed. For example, immune suppression and immune modulation due to infection with the human immunodeficiency virus (HIV), or by pharmacologic
means to prevent rejection of tissue, have increased in prevalence within the US during these same time periods, although their recognized influences on the development of oral cancers have been the subject of relatively fewer epidemiologic investigations [28,29]. Additional evidence that other infectious agents, such as human papillomavirus (HPV), may increase the risk of developing oral cancer and contribute to its progression has also been accumulating [30-33]. Because few data specific to oral HPV prevalence or infection rates are currently available [34], assessing the potential association with increasing rates of oral cancer has remained elusive.

Finally, additional studies examining other modulating factors for oral cancer development have identified potential risk factors that may also influence overall rates, incidence, and mortality. Some studies have demonstrated an inverse relationship between the consumption of fruits or vegetables and oral cancer risk, indicating that dose-dependent reductions in oral cancer risk are possible with each additional serving of fruits or vegetables consumed [35-38]. Moreover, recent epidemiologic evidence has demonstrated that serum and tissue folate levels, highly correlated with fruit and vegetable consumption, may be inhibited by tobacco or alcohol use - known primarily for their direct and indirect carcinogenic effects rather than their modulating effects on micronutrient absorption [39-41]. Although preliminary epidemiologic studies have found inconclusive, and seemingly contradictory, effects of folate status on oral cancer risk [42,43], no studies to date have directly examined the association between folate status and state-specific or demographic increases in oral cancers.
Conclusion

Due to the rising costs of health care in the US and the limited resources available for health prevention efforts, it is essential to organize and direct more effective efforts by public health officials and epidemiologists, as well as funding from local, state and federal governments, to reduce and eliminate identified health disparities. This study provides evidence of state-specific increases in oral cancer that are not associated with the increases previously observed among females and minorities, thereby providing new insights regarding potential methods to identify changes in relevant trends in geographic areas which may experience increases in tobacco-induced diseases in the future. As state and local public health professionals strive to formulate effective prevention and education programs for their residents, understanding the relationships between cause and effect, as well as the primary or secondary factors that more accurately indicate the potential for increased risk, becomes more imperative.

Acknowledgements

KK would like to acknowledge the American Cancer Society for previous grant support and also the Departments of Biomedical Sciences and Occupational and Environmental Health in the Schools of Dental Medicine and Public Health, respectively. KK would also like to thank Chandler Marrs, Laurel Pritchard and Kenneth Fernandez for their invaluable assistance with this manuscript.

Declaration of Competing Interests

The authors declare that they have no competing interests.
References

16. National Cancer Institute, Surveillance, Epidemiology and End Results Database (NCI-SEER) [http://seer.cancer.gov/about/]


to oral and pharyngeal cancer. *Cancer Res.* 1998, 489:
Figures

Figure 1 – Analysis of state-specific oral cancer mortality data: Historical trends (1981-2005) of mortality from oral cancer were sorted by race and ethnicity using NCI SEER*Stat (National Cancer Institute Surveillance Epidemiology and End Results) and regression lines calculated using the Joinpoint Regression Program. A) Oral cancer deaths in Nevada were initially declining, but exhibited a distinct, sustained upward trend among white males beginning in 1995. B) US states previously identified with short-term increases in oral cancer rates were confirmed as NV, NC, IA, OH, ME, ID, ND and WY, while states sharing a contiguous border with Nevada generally experienced declining trends.

Figure 2 – Analysis of smoking trends in specific US states: A) Analysis of the annual percent change (APC) or change in smoking trends (1995-2000) from states with elevated oral cancer rates demonstrated these states experienced positive, increasing rates of smoking prevalence, while states sharing a contiguous border with Nevada experienced simultaneous negative or declining rates of smoking, with the exception of Idaho. B) Graphing the smoking prevalence in Nevada revealed a year-by-year increasing trend which peaked in 1999 and subsequently began a steady, sustained decline over successive years.
Figure 3 – Analysis of annual smoking prevalence data in states with elevated oral cancer APC: A) A plot of annual data regarding state smoking prevalence demonstrates some initial variability among varying states, following by a more general declining trend beginning between 1999 and 2001. B) Graphing the trend or five-year annual percent change (APC) from these states revealed the more general trend of variability during the initial time periods (1995-2000 through 1998-2003), that was followed by more general declining trends in subsequent periods (1999-2004 through 2002-2007).

Figure 4 – Analysis of annual smoking prevalence data in states sharing a contiguous border with Nevada: A) A plot of annual data regarding state smoking prevalence demonstrates a general declining trend for all states during the entire period of available data, with the exception of Nevada, initially. B) Graphing the trend or five-year annual percent change (APC) from these states revealed the general declining trends in all periods (1995-2000 through 2002-2007), with the notable exceptions of Nevada and Idaho.
### Table 1. Comparison of smoking rates and tobacco control in selected US states

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Table legend: NV (Nevada), NC (North Carolina), IA (Iowa), OH (Ohio), ME (Maine), ID (Idaho), ND (North Dakota), WY (Wyoming), AZ (Arizona), CA (California), OR (Oregon), UT (Utah).
Table 2. Comparison of smoking trends in selected US states

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Contiguous border states (NV):

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Table legend: NV (Nevada), NC (North Carolina), IA (Iowa), OH (Ohio), ME (Maine), ID (Idaho), ND (North Dakota), WY (Wyoming), AZ (Arizona), CA (California), OR (Oregon), UT (Utah).
CHAPTER 3

POTENTIAL EFFECTS OF DIETARY FOLATE SUPPLEMENTATION ON ORAL CARCINOGENESIS, DEVELOPMENT AND PROGRESSION

This chapter has been accepted for publication in the peer-reviewed scientific journal Journal of Dietary Supplements and is presented in the style of that journal. The complete citation is:


Abstract

Folates are associated with a variety of human health benefits, while folate deficiency has been identified as a potential risk factor for many health problems and cancers, due to its role in dysregulation of DNA synthesis, repair and methylation. The US Food and Drug Administration adopted requirements for folate fortification in some food products, which has resulted in an increase in mean dietary folate intake and a concomitant reduction in the incidence of adverse health effects associated with folate deficiency. This includes a significant reduction in the incidence of folate deficiency-associated birth defects, such as spina bifida.

Although dietary folate supplementation protects normal, non-neoplastic cells from turning cancerous by preventing folate deficiency, more recent evidence suggests that folate supplementation may also contribute to some negative health effects. For example, recent studies found that dietary folate supplementation resulted in the increasing rate at which some slow-developing, early-stage colon cancers proliferate. The role of folate supplementation, and its effects on already developing colorectal cancers, now raises the question of whether folate might play a similar and significant role in the growth and proliferation of other slow-developing, early-stage cancers.
Another group of slow-developing cancers, oral cancer, may take many years or decades to develop and are often undetected and undiagnosed until later stages. However, no studies to date have adequately examined the potential ability of folate supplementation to alter the proliferative phenotype of established oral cancers, although growing epidemiologic evidence now suggests this may be a distinct possibility. The relatively long time horizon for development of oral cancers provides an opportunity for folate supplementation to act as a potential modulator of oral tumor growth and development.

In addition, many other factors are known to modulate cellular responses to micronutrients and dietary supplements, such as folate. For example, high-risk human papillomavirus (HPV) infection has been proven to modulate proliferative phenotypes of many cancers to folate supplementation. Recent studies of HPV infection in a significant fraction of oral cancers now confirm HPV alters growth and development within this subset of oral cancers. These discoveries add further support that the relationships between HPV infection, folate supplementation and oral cancer growth should be thoroughly examined. These data are critical and necessary components for understanding the impact of dietary folate supplementation and for directing more targeted and focused clinical and translational research in the prevention and treatment of oral cancers.

Discussion

Folic acid: Folates are associated with a variety of human health benefits, can be found in a wide assortment of foods, and are highly concentrated in certain dietary vegetables, grain products and some fruit juices [1]. Many important cellular functions involve folate-dependent processes, including amino acid metabolism and the formation of S-adenosylmethionine, the primary methyl donor for DNA
methylation reactions [2]. Folate deficiencies, resulting from low consumption of fruits and vegetables, strongly correlate with increased incidence of neural-tube defects, many cancers, hyperhomocysteinemia and vascular disease [3-5].

**Folate deficiency:** Folate deficiency has been identified as a potential risk factor for head and neck cancers, and oral cancers more specifically, due to its primary role in dysregulation of DNA synthesis, repair and DNA methylation associated with carcinogenesis [6]. The source of some folate deficiencies can be traced to a common DNA polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene, which encodes the enzyme responsible for producing the circulating form of folate [7, 8]. Other research has demonstrated that insufficient dietary folate intake, and poor diet in general, may be responsible for as much as 10-15% of all cases of oral cancer [9, 10]. In addition, other significant behavioral risk factors for oral cancer, such as tobacco and alcohol use, have been demonstrated to interfere with folate absorption, as well as increasing the rate of folate excretion by the kidney, thereby lowering folate concentrations in serum and tissues [11-13].

**Folate supplementation:** In an effort to reduce poor health outcomes associated with dietary folate deficiency, and to reduce incidence of neural tube defects, the US Food and Drug Administration (FDA) adopted requirements for folate fortification of all enriched cereal grain products beginning in 1996 [14]. USDA fortification guidelines specified each serving should contain at least 25% of the USDA recommended daily intake (RDI) of 400 micrograms per day (100 micrograms per serving). Nutrition scientists and epidemiologists, using data from the National Health and Nutritional Examination Survey (NHANES), demonstrated folate fortification and supplementation in the US has resulted in higher mean dietary folate intake, increasing from 275 to 351 micrograms per day. This correlates with a
significant rise in folate concentrations measured in serum, as well as erythrocytes and tissues, increasing from 11.4 nmol/L to 26.9 nmol/L and 375 nmol/L to 590 nmol/L, respectively [15]. The Centers for Disease Control and Prevention (CDC) attributes the 26% reduction in the incidence of neural tube defects in the US to these measures [16].

Folate toxicology: Although numerous health benefits are derived from mandatory folate supplementation, this policy can also create conditions of nutritional excess (hyperfolatemia) in some individuals, eliciting adverse clinical effects. Folate concentrations within the normal physiologic range provide health benefits, however concentrations falling outside of this range, including deficiency (hypofolatemia) or excess (hyperfolatemia), can elicit strong adverse effects - the classic hormetic dose-response relationship [17]. Inadvertent, but excessive, folate intake and higher folate serum levels above 400 micrograms per day are now known to clinically ‘mask’ megaloblastic anemia, caused by vitamin B12 deficiency [18]. In addition, hyper supplementation of folate above these levels, extending to more than five milligrams per day, also causes neurologic damage in patients with undiagnosed pernicious anemia [19]. Recent studies and epidemiologic reviews now suggest that mandatory folic acid fortification may, in some cases, increase the risk of some cancers – due in part to this hormetic dose-response relationship but which may not be restricted to conditions involving hyper- and hypofolatemia [20, 21].

Folate and cancer: These seemingly contradictory findings may be explained by the dual roles of folate; the dose of folate supplementation determines the hormetic dose-response effects, while the timing of folate administration may influence a non-hormetic response within the normal physiologic range. While adequate folate status seems to protect normal, non-neoplastic cells from turning cancerous, normal levels
of folate also seem to increase the rate and speed at which cancerous cells grow. Conversely, folate depletion impairs existing cancers from growing, but can also simultaneously increase the risk of forming new cancers at other sites or tissues. Although treatment of folate deficiency with supplementation is an effective strategy to prevent oncogenesis, folate supplementation has an opposite effect on any existing or early-stage cancers or neoplasms [21, 22]. Cancers, by definition, are composed of rapidly dividing cells, thereby exhibiting an increased need for folate. Consequently anti-folate therapy has been used successfully to inhibit the growth of many tumors and metastatic cancers [23, 24].

**Oral cancer and folate:** Oral carcinogenesis is a process that typically involves many separate, inter-related risks and corresponding mechanisms of transformation [25, 26]. This process may take many years or decades to become clinically apparent, thereby providing a window of opportunity for folate supplementation to modulate tumor growth and development. Epidemiologic evidence has demonstrated the major risk factors for developing oral cancer are the use of tobacco and alcohol, known for their direct and indirect carcinogenic effects [27, 28]. However, these risk factors are also known for their ability to decrease serum and tissue folate levels [11-13]. Although some preliminary work and epidemiologic studies have found inconclusive, and seemingly contradictory, effects of MTHFR mutation and folate status on oral cancer risk, no studies to date have directly examined the effects of folate on existing or established oral cancers [8, 29].

**Folate and p53 expression:** Most recently it has been shown that the effect of folate status differs significantly according to the p53 expression profile of the particular tumor [30]. Folate intake confers a protective effect against tumors that over-express p53, but has no effect on tumors that exhibit wild type p53 expression.
Interestingly, many of the earliest detectable events in oral carcinogenesis include disruptions to growth inhibitory or tumor suppression signals, most commonly involving proteins regulating the G1/S transition of the cell cycle – including p53, as well as Rb, bcl-2, and p16 [31-33].

This intracellular dysregulation is facilitated in part by tobacco carcinogens, including polycyclic aromatic hydrocarbons (PAH) and nicotine-derived nitrosamines (NDN), which mediate oral carcinogenesis by activating DNA methyltransferases. These enzymes preferentially methylate CpG-rich DNA sequences found in exons 248 and 273 of the p53 tumor suppressor gene, causing the transcriptional deregulation and subsequent mutation during DNA replication [34, 35]. p53 deregulation then reduces the expression of other growth inhibitory regulators, such as p21 and bcl-2. These regulators function to prevent the inactivation of the tumor suppressor Rb and to induce apoptosis [36, 37]. PAH and NDN also induce deregulation of p16, an inhibitor of cyclin CDKs, and p14/p29. p14/p29 functions to inactivate mdm-2, which in turn down-regulates the p53 tumor suppressor [38], further complicating the potential effects and inter-relationships between folate supplementation and oral cancer development. Based upon this information, the relationship between p53 expression, folate and oral carcinogenesis becomes clearly more complex than mere dysregulation of G1/S cell cycle mediators.

Oral cancer and HPV: Although there is consensus among epidemiologists that most oral cancers originate from the deleterious effects of tobacco use and alcohol, recent evidence has demonstrated that human papillomavirus (HPV) infection is also a separate, independent risk factor for developing oral cancer [39, 40]. The human papillomaviruses are a family of dozens of related viruses that are involved in the development of warts and some cancers, more specifically cervical cancers [41].
HPV oncoproteins disrupt the function of known tumor suppressor genes, leading to the production of transcription factors that ultimately drive cell proliferation, transformation and carcinogenesis [42-44].

Recent evidence indicates the HPV types that cause cervical cancer are also found in a subset of oral cancers (30%) and are now thought to contribute to carcinogenesis in the oral cavity by mechanisms similar to those involved with the development of cervical cancers [39, 45, 46]. More specifically, the HPV oncoproteins, E6 and E7, produce ‘mdm-2-like’ proteins which bind to p53 and disrupt the tumor suppressor functions. These oncoproteins also affect other associated tumor suppressors, including Rb and bcl-2, ultimately driving cell proliferation, transformation and carcinogenesis [47].

*HPV, folate and carcinogenic progression:* Although great scientific emphasis has been placed upon HPV as the primary cause of cervical cancers and its involvement in carcinogenic progression of other cancers [41], less attention has been focused on the secondary factors that are associated with progression from subclinical HPV infection to invasive carcinoma. Among the secondary factors that limit virus production and carcinogenic progression is CpG methylation of the HPV genome [48-50]. Several studies now confirm that CpG site-specific methylation of HPV DNA, mediated in part by folate availability, is sufficient to suppress neoplastic progression [51-54]. In contrast, demethylation or hypomethylation of HPV-DNA sequences is required for transformation, revealing the importance of preferential DNA methylation at CpG sites in the HPV long control region (LCR) between L1 and E6 HPV genes, in addition to the tumor suppressor sites in p53 exons 248 and 273 that were already discussed [55]. Because HPV has the potential to initiate oncogenesis, and also to modulate oral cancer growth and folate plays a central role in mediating
the availability of methyl groups for CpG-specific DNA methylation (modulating both p53 and HPV mRNA expression) – a thorough investigation of these interconnected and inter-related mechanisms in oral cancers must be undertaken.

Figure 1. Overview of selected environmental influences and genetic pathways in oral cancers that may be affected by folate supplementation.

Summary

The role of folate supplementation, and its effects on already developing colorectal and breast cancers, now raises the question of whether folate might play a similar and significant role in the growth and proliferation of already developing oral cancers. To date, no studies have examined the potential ability of folate to alter the proliferative phenotype of established oral cancers, although growing epidemiologic evidence now suggests this may be a distinct possibility. Moreover, the interconnected role of HPV infection, and its association with the growth and development of a subset of oral cancers, has not been explored with relation to folate supplementation or folate status. These data are critical and necessary components needed in order to establish clinical and translational research in this area. The
ultimate goal is to provide new clinical treatments and diagnostic criteria for the approximately 45,000 new patients diagnosed with oral cancer in the US each year, who face a 40% five-year survival rate that has not changed significantly in many decades [56].

References


CHAPTER 4

GENERAL DISCUSSION

In this study, I sought to determine the temporal and geographic patterns of oral cancer morbidity and mortality within the US population. Using well-established methods for epidemiologic research, I found a geographic and temporal pattern of increased oral cancer rates in a select subset of US states, including Nevada. These published results demonstrate that oral cancer rates within specific geographic locations of the US have been, and are currently, increasing. These results clearly demonstrated an important public health problem that exists within this state population.

Based upon these results, I hypothesized that these observed increases were associated with state-specific exposures of this population to the primary risk factor for oral cancer development, tobacco use. I attempted to analyze the use of tobacco within Nevada, as well as the neighboring states and found that rates of smoking and tobacco use were higher in this state than in neighboring states, as well as in comparison to national averages. However, further research showed that these rates were also intricately linked to other factors that influence cigarette and tobacco consumption. These included cigarette pricing and taxes, which were found to be significantly lower than in other regional states, such as Arizona, California and Utah. Moreover, the rates of smoking and tobacco use in Nevada, although historically higher than neighboring states have recently begun to decline. This finding suggests that oral cancer rates may soon begin to decline within this population in the next ten to fifteen years, although significant input from public health officials will be required to avoid further health disparities.
The analysis of oral cancer primary risk factors provided the opportunity to consider additional, secondary factors that may also be environmental mediators of oral cancer risk. Based upon research from the evidence base I found that specific nutritional and dietary changes within the US correlate strongly with the onset of the oral cancer increases observed in Nevada. Specifically, the introduction of folate supplementation into the US food supply was strongly associated with the increased incidence and mortality from oral cancers in Nevada. Furthermore, other studies have found that folate supplementation has increased the incidence and mortality from other slow growing cancers, such as colorectal cancer. These discoveries are so recent that virtually no research has explored the possibility that folate supplementation may have influenced oral cancer rates in conjunction with other factors, such as higher rates of smoking due to state-specific taxing and policies.

Recommendations

_Foster Interdisciplinary Research:_ Because cancer remains a leading cause of morbidity and mortality within the US and contributes substantially to the burden of rising healthcare costs, it is critical that biomedical research scientists become familiar with methods of public health investigation and epidemiologic research. Moreover, it is important for public health professionals to collaborate with, and integrate, their efforts with biomedical research scientists. This study incorporated the basic biomedical research focus of my laboratory, oral cancer growth and development, with the important elucidation of an increasing public health problem and health disparity in Nevada.

_Encourage Curricular Integration:_ It is my recommendation that public health professionals and educators incorporate these findings into health programs, curricula, and public service announcements in order to better serve the population of Nevada.
The School of Dental Medicine has found great success with integrating research into the basic science and biomedical curriculum for doctoral-level students and it is my hope that these established collaborative efforts will result in long-term collaboration and participation between the School of Community Health Sciences and the School of Dental Medicine.

**Mentoring:** In addition, it is my recommendation that future students explore other aspects of oral cancer risk and epidemiology and to use this work as a foundation from which to explore other important aspects of public health efforts in this area. For example, an on-going research focus of my laboratory research will be to explore the relationship between folate administration and supplementation with oral cancer growth and proliferation. These studies can easily be linked with MPH research projects that examine these correlations within the patient population at the School of Dental Medicine, providing an additional avenue for interdisciplinary research and collaboration.
APPENDIX
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KINGSLEY K, Koontz G, Plopper GE. The globular domains of human and rat laminin-5 alpha3-subunits may contain similar and distinct alpha3 beta1


Thesis Title:
Oral Cancer in Nevada: A Public Health Perspective

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