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

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Cancers of the esophagus represent an important public health problem. In the United States an estimated 14,520 new cases were diagnosed in the year 2005, and 13,570 deaths resulted from the disease.¹ The mortality rate approximates that of pancreatic cancer and is more than four times that of rectal cancer.² In excess of 90% of individuals diagnosed with an incident cancer of the esophagus die within five years of diagnosis, underlining the need for strategies to prevent this disease.³

Unfortunately, the measures needed for primary prevention are not as clear-cut as they seemed even a half a generation ago. For squamous cell carcinoma, by far the dominant type of esophageal cancer in the United States until the mid-1990s, conventional epidemiologic evidence indicates that tobacco and alcohol account for the vast majority of variability in incidence of this cancer.^{4,5} However, most of these studies were conducted in European American populations. For those

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populations at highest risk of developing this disease (e.g., African Americans, who tend to participate at a much lower rate in epidemiologic studies), tobacco and alcohol use explains much less of the variability.^{6,7} Thus, recommendations to quit or reduce smoking and drinking, while effective at preventing many other health problems, may not be as effective for preventing squamous cell carcinoma of the esophagus in African Americans (AAs) as they would be in European Americans (EAs).^{8,9}

While the epidemiology of squamous cell carcinoma has gone unresolved in AAs, a relative epidemic of adenocarcinoma of the esophagus has begun^{4,5} and it appears to be concentrated almost exclusively in EAs.^{4,6,10} The association between esophageal adenocarcinoma and gastroesophageal reflux disease (GERD) is unequivocal.¹¹ The dose- and time-response association of GERD and esophageal adenocarcinoma and its biologic plausibility suggest causality. However, the epidemiologic observations made thus far do not help identify individuals who, among those patients suffering from GERD, are likely to develop adenocarcinoma.

Descriptive Epidemiology

Esophageal cancers are relatively uncommon. However, as noted, they tend to be fatal. For example, based on the combined data of the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute and the National Program of Cancer Registries of the Centers of Disease Control and Prevention the mortality to incidence ratio for esophageal cancer is 0.92

as compared to 0.20 for breast cancer and 0.17 for prostate cancer.¹² Cancers of the esophagus account for $\approx 1.5\%$ of total cancer incidence in the US males, but they account for $\approx 1.9\%$ of incidence in AA men.¹² These cancers account for a higher percentage of cancer deaths; 3.2% and 3.4% in Black and White men, respectively. In women, esophageal cancers account for only $\approx 0.5\%$ of total cancer incidence. However, the rate is twice as high ($\approx 1.0\%$ of incidence) in AA women. As in men, esophageal cancers account for proportionally more of cancer mortality (i.e., for $\approx 1.0\%$ overall and $\approx 1.5\%$ in AA women).¹²

Esophageal cancers fall into two histologic categories. Squamous cell carcinomas, which are conventionally thought to be more strongly associated with tobacco and alcohol, tend to arise from the body of the proximal esophagus.¹³⁻¹⁵ Adenocarcinomas generally arise from the distal esophagus, near its junction with the stomach, and are strongly associated with GERD.

Esophageal cancer incidence and mortality rates among Blacks (i.e., primarily AAs) were over three times those of Whites (i.e., primarily EAs) in the late 1980's.^{16,17} This large differential emerged between 1950 and 1977, when the age-adjusted esophageal cancer incidence rate approximately doubled in AAs. Thereafter, the incidence increased slightly until leveling off in the mid 1980's.^{16,17} During the same period, the rates of squamous cell cancers remained virtually unchanged in EA, and rates of adenocarcinomas remained relatively constant in both

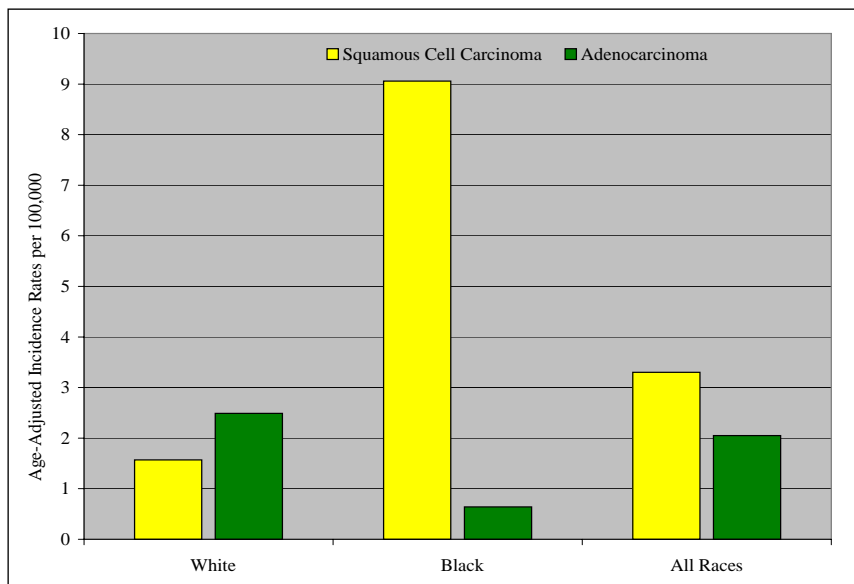


Figure 1. Esophageal Cancer Age-Adjusted Incidence Rates (1997-2002) per 100,000 in SC by Histologic Type and Race

As shown in Figure 1, in South Carolina, squamous cell esophageal cancer incidence in AAs is currently about six times higher than that observed in EAs. This racial disparity is considerably larger than the \approx four-fold difference observed nationally,^{22,23} even though AAs have much lower rates of exposure to tobacco products,^{1,24} as we will discuss in the next section.

As is true for the nation as a whole, rates of adenocarcinoma of the esophagus are higher in EAs than AAs in South Carolina (Figure 1). Men's rates are about four to eight times higher than those of women, a gender difference about as extreme as that observed for squamous cell cancers. Esophageal adenocarcinomas are thought to be less strongly associated with tobacco than is squamous cell carcinoma.^{4,6,25,26} In the United States, increasing obesity is a possible contributing factor to the rising incidence of adenocarcinoma.²⁷ One of the strongest risk factors for adenocarcinoma is GERD,⁵ the backflow of acid from the stomach into the esophagus, which irritates and sometimes damages the delicate lining on the inside of the esophagus. If this condition remains untreated in an individual, it can lead to Barrett's esophagus,

which is defined as an abnormal change in the growth of cells of the esophagus. It is generally accepted that this condition is a precursor to adenocarcinoma.^{5,28} The role of infectious agents, most notably *Helicobacter pylori*, is much less certain and more complicated.

Esophageal incidence and mortality rates are consistently at least twice as high for all types of esophageal cancer combined for AAs than for EAs.²⁹ This disproportionate cancer burden in South Carolina does not appear to be merely an issue of access to care. For example, mortality and incidence track similarly by race, indicating that incident cancers are not going undetected in AAs due to lack of care. Additionally, there is little disparity by race in stage at diagnosis of squamous cell cancers within categories of gender (Figures 2-5). Therefore, this disproportionate cancer burden does not appear to be merely an issue of decreased access to care leading to delayed diagnosis.

There do appear, however, to be some interesting disparities by gender and stage, with women (especially White women) being diagnosed at an earlier stage than their male counterparts. The very small numbers of adenocarcinomas in Blacks precludes comparisons similar to those shown in Figures 2-5 for squamous cell carcinomas. However, it does appear that the same general race-gender pattern would be seen for adenocarcinoma if the numbers were more robust.²²

Men are more likely to be diagnosed with and die from esophageal cancer, as is clearly evident in both U.S.^{12,30} and South Carolina^{29,31} data. In South Carolina from 1997 to 2002, the overall incidence rate of esophageal cancer was over four times higher in men than women [10.43 vs. 2.31 /100,000/year].²² Differences in stage at diagnosis by gender may help to explain some of this disparity.^{29,31} The racial disparity, however, is not as large (4.45/100,000 in EA vs. 10.84/100,000 in AA); in large part due to large increases in adenocarcinoma in EAs.

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As expected, mortality rates follow essentially the same pattern as incidence, but are more extreme. In South Carolina, from 1999 to 2004, the overall mortality rate of esophageal cancer was over four-and-half times higher in men than women (9.01 vs. 1.99/100,000).²² Again, stage at diagnosis by gender may help to explain some of this disparity.^{29,31} The racial disparity, however, is not as large (3.96/100,000 in EA vs. 8.64/100,000 in AA). Gender differences within race followed a similar pattern; i.e., were similar in relative terms (7.12/100,000 in White men vs. 1.49 in White women; and 16.05/100,000 in Black men vs. 3.41 in Black women).

In addition to overall statewide differences by race, we also looked carefully at the 46 counties to see if there might be smaller foci of racial differences in rates. In order to present this in the most descriptive way, we used the mapping capability of SAS/STAT[®] software, Version 9.1 so as to locate and map statistical differences in incidence and mortality rates by race for both men and women.³² The statewide rates for South Carolina Whites are used as the comparison.

As expected, we see large differences when comparing the incidence rates of squamous cell cancers in Blacks to those of Whites (see Figures 6 and 7). For men (Figure 6), all but eight counties had significantly higher rates in Blacks. The fact that the rates are higher in AAs is not surprising. What is remarkable is that the rate differences were statistically significant in such small geographical units, despite the general tendency for the 95% confidence limits to be very large with small sample sizes (which results in a lower probability of detecting a real difference). Among women (Figure 7), where the overall rates are just a fraction of those of men, statistically higher rates also were seen in twelve of the 46 counties.

Mortality rates for all esophageal cancers (i.e., all histologic types combined)

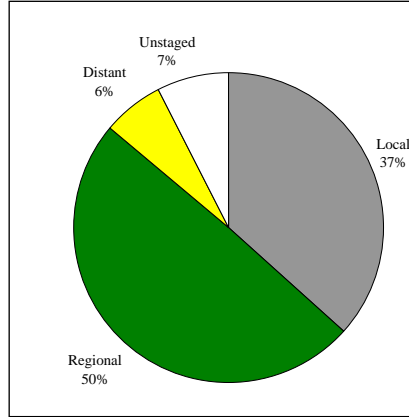


Figure 2. Esophageal Cancer Stage at Diagnosis in SC among White Men, 1997-2002 (Squamous Cell)

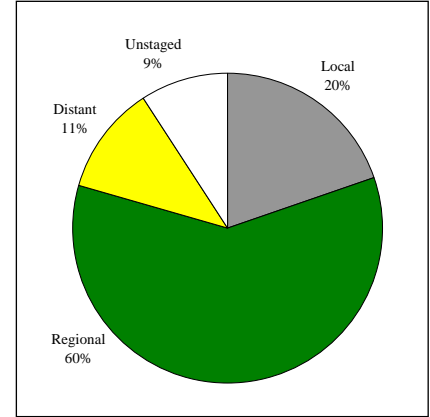


Figure 3. Esophageal Cancer Stage at Diagnosis in SC among Black Men, 1997-2002 (Squamous Cell)

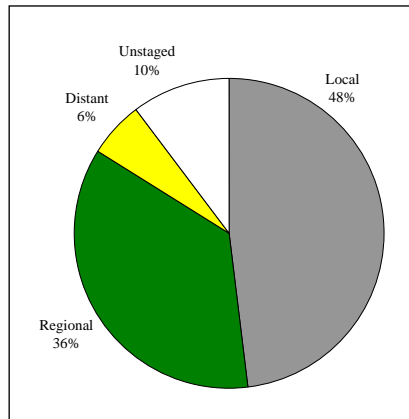


Figure 4. Esophageal Cancer Stage at Diagnosis in SC among White Women, 1997-2002 (Squamous Cell)

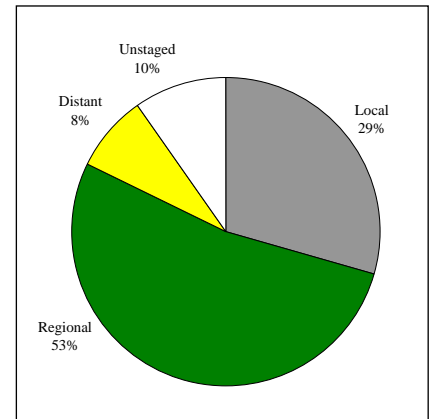


Figure 5. Esophageal Cancer Stage at Diagnosis in SC among Black Women, 1997-2002 (Squamous Cell)

are shown in Figures 8 (for men) and 9 (for women). Figure 8 shows that the very high rates of squamous cell cancers in AA men coupled with the very high lethality of this cancer results in an overall esophageal cancer death rate that is significantly higher in AA than EA men in about half (22 of 46) of South Carolina's counties. Again, owing primarily to small numbers, the pattern, though evident, was much less pronounced in AA women relative to their EA counterparts (Figure 9).

Analytic Epidemiology Studies *Squamous Cell Carcinomas*

Analytic epidemiologic studies conducted in the West, and predominantly in Europeans or EAs, indicate that tobacco smoking and the consumption of alco-

holic beverages, and especially the combination of the two, account for >95% of all squamous cell carcinomas of the esophagus.^{4,5} What is both puzzling and fascinating is that AAs drink at about the same rate as EAs, that they actually smoke less than EAs,^{16,17,33-35} and their smoking rate is especially low in South Carolina.³⁶ Despite this, their rates for this cancer are much higher^{16,17} (see Figure 1 for a depiction of rates by histologic type and race in South Carolina). So, an estimate of increased risk due to heavy consumption of alcohol or tobacco (or both) accounting for approximately 14.9 excess cases of squamous cell carcinoma per 100,000 per year in AA than EA³⁷ adds even more to the confusion. Clearly, the descriptive data on tobacco and alcohol are not explaining the elevated rates

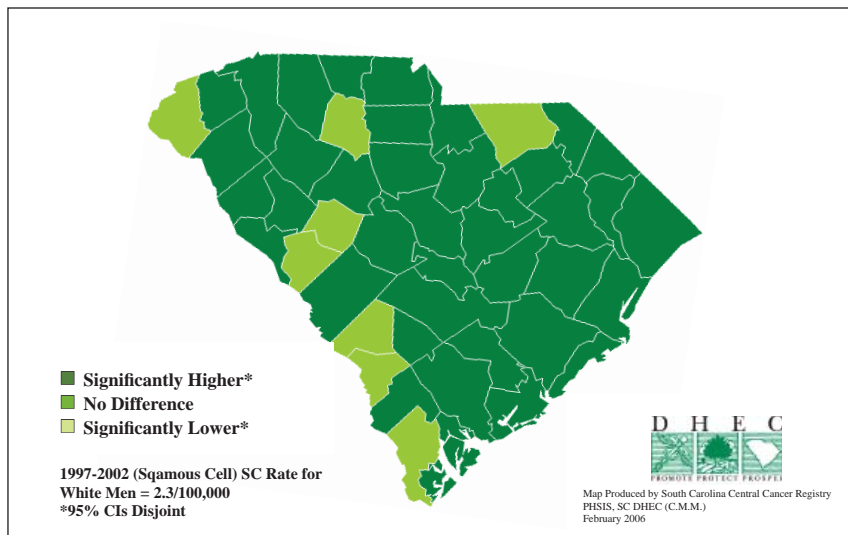


Figure 6. South Carolina Squamous Cell Esophageal Cancer: Comparison of Age-Adjusted, County-Specific Incidence Rates in Black Males vs. the Age-Adjusted, State-Average Rate in White Males (1997-2002)

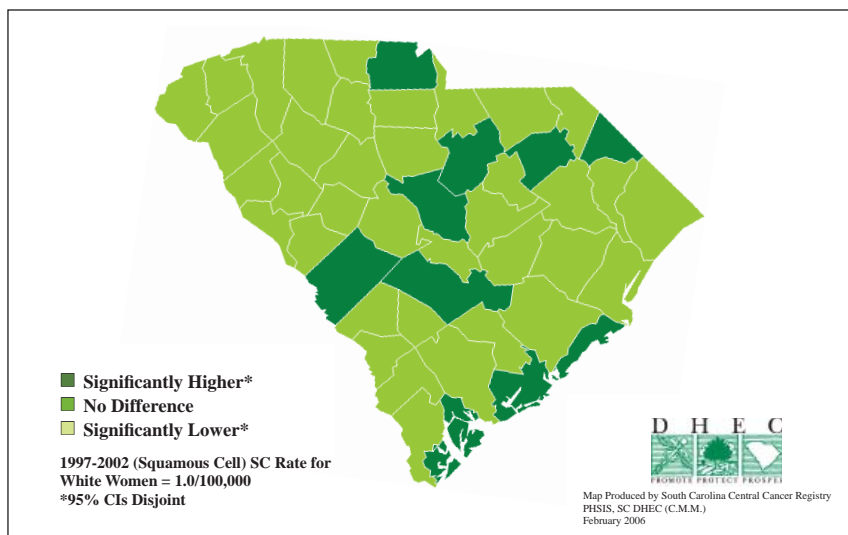


Figure 7. South Carolina Squamous Cell Esophageal Cancer: Comparison of Age-Adjusted, County-Specific Incidence Rates in Black Females vs. the Age-Adjusted, State-Average Rate in White Females (1997-2002)

of squamous cell esophageal cancers in AAs in South Carolina (and probably in the rest of the rural Southeast). In more recent work by this same group, Brown et al, it was found that, along with moderate/heavy alcohol intake and tobacco use, low income and infrequent consumption of raw fruits and vegetables explained 99% of the excess incidence among AA men.³⁸ It would be interesting to see if careful measurement of these two other categories of “risk factors” would help

to explain the anomalously high rates of squamous cell cancers of the esophagus here in South Carolina, and more generally in the American South.

Although overall rates of exposure to alcohol are not much different in AAs than EAs, differences exist in the type of alcoholic beverages consumed.³⁹⁻⁴¹ It has been found that EAs tend to consume greater amounts of beer while AAs tend to consume more wine, malt

liquors, and hard liquor. However, when they examined this issue, Brown et al. found no significant difference in risk by type of alcoholic beverage consumed. Rather, the total amount alcohol consumed played the largest role in determining risk.⁴² Given the work conducted to date, and the confusion about the role of dietary risk factors (including alcoholic beverages), future studies should focus on very careful measurement of this set of factors.

In contrast to the confusion about actual dietary exposures, we know much more about differences in the types of cigarettes smoked by AAs and EAs. It is a curious historical fact that when menthol brands were first introduced before World War II, AAs and women of all ethnicities evinced a preference for these brands.⁴³ In a classic example of the interaction between marketing and product preference, menthol brands were targeted specifically at African Americans.^{44, 45} From their introduction in the 1920s through 1955, mentholated brands represented about 3% of all cigarette sales, with AAs and women accounting for a disproportionate share of purchases.⁴³ From 1956 to the middle of the 1970s, menthol cigarettes increased in popularity.^{43,44,46} After achieving about 29% of market share in the late 1970s, their share of the market began falling in the late 1980s. They now account for just under 26% of total sales.^{9,44,47} Currently, about 75% of AA smokers use mentholated brands (vs. 23% of Whites), with three brands available only in mentholated form (Newport™, Kool™, and Salem™) accounting for 55% of total AA tobacco consumption.⁹

The close association between changes in consumption of menthol cigarettes and rates of change in esophageal cancer rates formed the basis for the hypothesis that exposure to mentholated cigarettes might explain some of the discrepancy between overall tobacco exposure and rates of esophageal cancer (and other cancers of the upper aerodigestive tract)

in AAs.^{16,17} These observations and the formulation of a hypothesis linking mentholated cigarettes to esophageal cancer led to a number of studies in the late 1980's,^{17,48,49,50,51} and is currently a focus of renewed research in South Carolina.⁵² Due to the dominance of the mentholated cigarette market by three major brands, assessment of use of menthol cigarettes has become simpler compared to the situation a couple of decades ago when many more brands were available. This circumstance will benefit future epidemiologic studies.

While smoking and alcohol are acknowledged to be the strongest risk factors for squamous cell carcinoma of the esophagus, surprisingly little is documented on other potential risk factors. Of all cancer sites, esophagus evinces the largest international variation in rates of disease.^{4,18,53,54} Until recently, most of the variation in rates of esophageal cancer could be assumed to be due to squamous cell cancers; however, that has begun to change.²⁶ Consequently, the vast majority of literature from the more "distant past" (i.e., from before the 1990s) that has not differentiated between histologic types can be assumed to reflect mainly the epidemiology of squamous cell esophageal cancers. Despite the dominant focus on tobacco and, to a lesser extent alcohol, evidence has existed for some time to suggest that there are other lifestyle-related behaviors, especially those related to diet, that may be associated with esophageal cancer risk.⁵⁵⁻⁵⁹

In general, fruits and vegetables have been shown to be inversely related to esophageal cancer.⁵⁵⁻⁵⁷ More specifically, there is some evidence that cruciferous vegetables (e.g., broccoli, cauliflower, and brussel sprouts) protect against esophageal cancer. Heterocyclic amines, by-products from charred meat, have been linked with squamous cell carcinoma.^{58,59} Selected micronutrients such as antioxidants, folate, and selenium also have shown an inverse association with squamous cell carcinoma.⁶⁰⁻⁶³ Still other

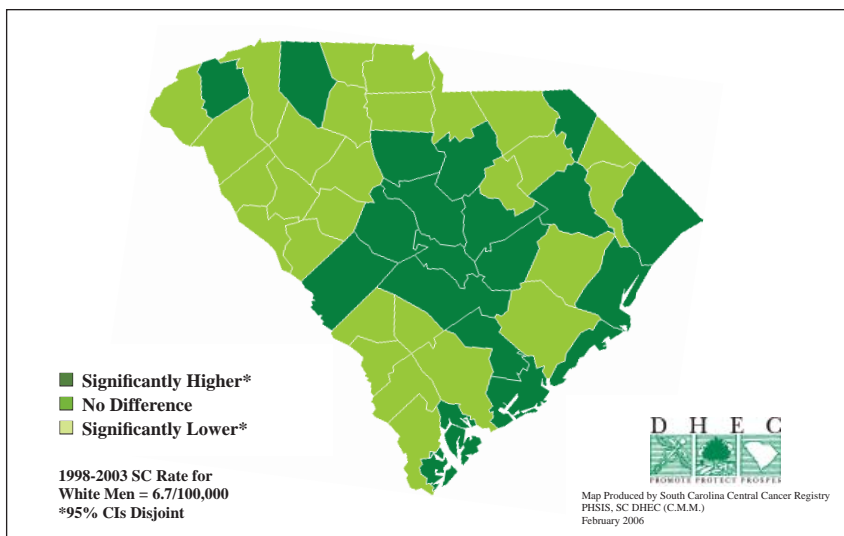


Figure 8. South Carolina County-Specific Comparisons of Black vs. White Male Age-Adjusted Esophageal Cancer Mortality Rates (1998-2003; all histologic types combined)

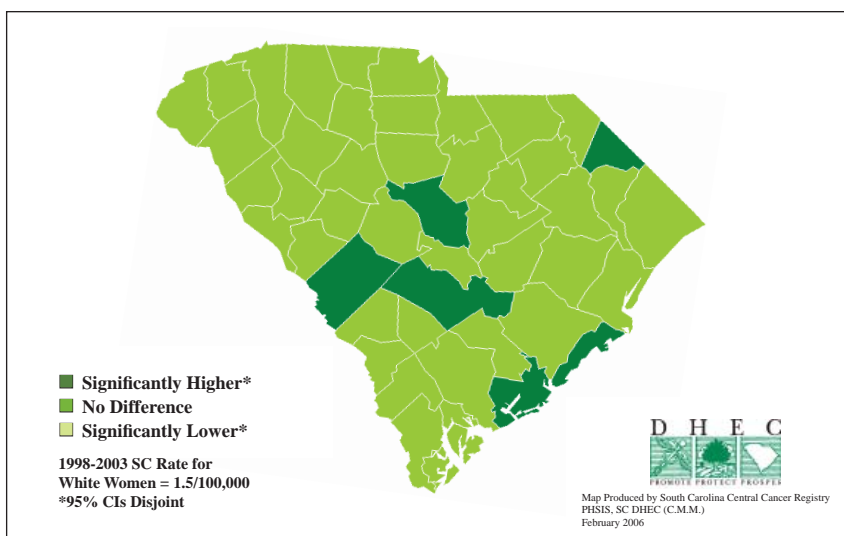


Figure 9. South Carolina Esophageal Cancer: Comparison of Age-Adjusted, County-Specific Mortality Rates for Black Females vs. the Age-Adjusted, State-Average Mortality Rate for White Females (1998-2003)

potential risk factors for squamous cell carcinoma are *Helicobacter pylori* infection (the common cause of stomach ulcers) and decreased use of non-steroidal anti-inflammatory drugs.⁶³⁻⁶⁶

African Americans in South Carolina are not the only population at unusually high risk of esophageal cancer. Some of the most intriguing data on the role of non-tobacco/non-alcohol-related risk factors comes from the Caspian Littoral (i.e.,

Azerbaijan, the Islamic Republic of Iran, Kazakhstan, Turkmenistan, the Russian Federation, and neighboring Uzbekistan). There, in alcohol- and tobacco-abstinent populations, we find some of the highest rates of esophageal cancer in the world.⁶⁷ In these regions it is customary to drink very hot beverages (usually teas) by pouring the scalding fluid onto the surface of the proximal esophagus.^{68,69} This is consistent with findings from other parts of the world,^{57,70,71} including some

interesting findings from France showing an interaction between the alcoholic content of one beverage (Calvados) and the tendency to drink it hot.⁷² Evidence of a role of thermal damage and its interaction with other factors provides a possible connection to the mentholated cigarette hypothesis because prolonged use of menthol is known to attenuate sensations of heat, thereby allowing exposures of longer duration and greater heat intensity.¹⁷ Through work conducted at the University of South Carolina, we have found that menthol appears to have additional adverse effects such as: increasing the permeability of the esophageal membrane to tobacco carcinogens, influencing the amount of the carcinogen penetrating through the membrane, and increasing the amount of carcinogens forming a reservoir within the membrane.⁵² So, the interaction among these various factors, including the direct effect of menthol, the influence of thermal damage, and the effect of dietary factors appears to be a fruitful area to explore in order to reconcile the discrepancy between the descriptive epidemiology of squamous cell cancers of the esophagus and findings from studies of humans available in the literature.

Adenocarcinomas

While squamous cell carcinoma of the esophagus is more common among AAs, adenocarcinoma is more common among EAs. It is estimated that incidence of this disease has increased on the order of 300% to 500% within the last 40 years.²⁸ Adenocarcinoma also appears to be much more common among men than women, with the latest ratios showing about seven men diagnosed to every one woman nationally;⁵ and about 8.5:1 in South Carolina.²²

It is very interesting to note that the pattern of incidence of adenocarcinoma very closely resembles that of the obesity epidemic seen in the United States, especially among individuals <50 years of age.²⁸ The risk of adenocarcinoma is increased nearly two-fold (by 179%) among those who are obese and have been diagnosed

with GERD when compared to those who are of normal weight and do not have GERD.⁵ Barrett's mucosa (specialized columnar-lined epithelium), which is strongly associated with GERD, is considered the precursor lesion to esophageal adenocarcinoma; and the progression from intestinal metaplasia to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to adenocarcinoma is a model of carcinogenesis. There are a number of molecular mechanisms involved in this progression that are under intense scientific study, including overexpression of growth factors and receptors, dysregulation of cell cycle proteins, a decrease in tumor suppressor genes (i.e., p53), an increase in telomerase, and a decrease in apoptosis.⁷³ Improved understanding of the genetic changes in the sequence from Barrett's metaplasia to adenocarcinoma will potentially provide novel methods of prevention, diagnosis, staging, and treatment.

The role of *Helicobacter pylori* is much more complicated, with indications of both increased and decreased risk.^{5,64,74} It is known that *H. pylori* infection has a profound effect on gastric acid secretion.⁷⁴ Therefore, depending on the strain of the bacteria and the anatomic location of the infection, *H. pylori* (especially cagA+ strains) may be protective against adenocarcinoma of the esophagus.^{64,74}

There is a very limited research into other risk factors for adenocarcinoma. The few studies that have been conducted on diet have shown that high intake of calories and fat are strong risk factors for this type of cancer, while fiber, lutein, niacin, vitamin B6, iron, zinc, antioxidants (vitamin C, β -carotene, α -tocopherol), and fruit and vegetable consumption appear to protect against the disease.⁵

Recommendations for Early Detection

Currently, there is no direct evidence that has validated the use of mass screening for esophageal cancer in the United

States.⁷⁵ Esophageal cancer is a rare disease and for squamous cell cancers, there is no premalignant condition for which symptoms would warrant focused screening.^{76,77} Screening for adenocarcinoma of the esophagus has been focused on the detection of Barrett's esophagus, which is associated with a risk of developing adenocarcinoma that is 30 to 60 times higher than that of the general population.¹¹ The overall absolute risk of developing an adenocarcinoma of the esophagus remains low because of the low prevalence of Barrett's esophagus and because of the slow evolution^{10,75,78} to cancer. The American College of Gastroenterology recommends that patients presenting chronic and severe GERD symptoms are more likely to have Barrett's esophagus and therefore should undergo upper endoscopy and increased surveillance.⁷⁹ Recently, a cost-utility study has suggested a once-in-a-lifetime endoscopy screening targeted at those at the highest risk – EA males over 50 years of age with symptoms of GERD.^{10,78,80}

It is recommended that patients with nondysplastic Barrett's esophagus on two consecutive endoscopies with biopsies should undergo repeat endoscopy three years after initial endoscopy.⁷⁹ If nondysplastic epithelium persists, decision analysis models would favor increasing the surveillance interval to five years, although continued one- to two-year intervals are more common. The finding of low-grade dysplasia (LGD) increases the risk of developing cancer. Repeat endoscopy should be performed in six months and if LGD persists, at one-year intervals.⁷⁹ Patients with high-grade dysplasia that has been confirmed by two experienced pathologists should be recommended to proceed with definitive surgical or endoscopic management.

Special Programs in South Carolina

The 2004-05 Review Panel of the South Carolina Research Centers of Economic Excellence awarded funding for a Center of Excellence in Gastrointestinal

Malignancy (Program Director, Carolyn E. Reed, MD). The initial focus will be on esophageal cancer. A center of excellence in esophageal cancer has been developed at the Medical University of South Carolina and includes a multidisciplinary clinic; expertise provided by the Digestive Disease Center in endoscopic ultrasonography, endomucosal resection, other ablative techniques, and palliation; a Barrett's screening program; a nutrition program; and research in the molecular profiling of esophageal cancer. This esophageal program has earned regional and national recognition. High-volume centers have been linked to better surgical outcomes.⁸¹⁻⁸³

Summary

Because of its high fatality rate and our inability to detect esophageal disease early in its development, esophageal cancer represents a significant medical and public health challenge. The mortality statistics underline the importance of focusing on prevention of these conditions as a matter of state and national public health priority. Unfortunately, the measures needed for primary prevention of these conditions do not seem as clear-cut for populations at highest risk of this disease (i.e., AAs) as for the populations represented in most epidemiologic studies.^{6,7} Our incomplete knowledge about the etiology of esophageal cancer, especially squamous cell carcinomas in AAs and adenocarcinomas in EAs, preclude developing and disseminating effective preventive measures. Clearly, the prevention and control of esophageal cancers represent a different paradigm compared to other tobacco-related cancers of the upper aerodigestive tract.

Data from a number of studies indicate that disparities exist in esophageal cancer incidence between racial groups and between geographical locations within South Carolina, and that these disparities are continuing to increase. The reasons for these disparities are only beginning to receive attention. They probably will be found to be complex and multifac-

eted. A combination of genetic factors, environmental influences (e.g., those related to diet), and the deleterious changes associated with smoking and alcohol consumption are the obvious parameters that should be the focus of initial epidemiologic data collection and assessment. Issues around dietary assessment, a major area of expertise among researchers in South Carolina, must be addressed in these studies.^{33,35,84}

Much remains to be done for us to understand how research, health care, and educational efforts in the state of South Carolina might influence the detection, care, treatment, and, ultimately, reduction in esophageal cancer incidence and mortality rates. An important step in the process will be to coordinate data-collection efforts between clinicians, researchers, and concerned community members in South Carolina. This would allow comprehensive background profiles of patients to be collected for studies ranging from those focusing on the basic biology of the disease and its etiology to those aimed at understanding the role of health services and the effect of policy. In order to design and implement the full range of research needed to understand what we can do to prevent and control esophageal cancer in our state, it is our intention to engage all of the stakeholders within South Carolina; including community members, cancer survivors, cancer care providers, researchers, and individuals at high risk of esophageal cancer. With its large proportion of rural, socioeconomically deprived African Americans, what is learned about esophageal cancer in South Carolina will have national, and perhaps international, relevance.

Acknowledgements

We would like to acknowledge:

- Funding of the South Carolina Cancer Disparities Community Network (SCDCN) through grant number 1 U01 CA114601-01 from the National Cancer Institute (Community Networks Program); and

- The South Carolina Central Cancer Registry (SCCCR) 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 SC Department of Health and Environmental Control.

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