
Colorectal Cancer Disparities in South Carolina: Descriptive Epidemiology, Screening, Special Programs, and Future Direction

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Colorectal cancer (CRC) is one of the most common and deadliest forms of cancer in the United States (US). According to the National Cancer Institute, CRC—cancer that affects the colon or large intestine, or the rectum, or both at once—is the second leading cause of cancer-related death and the fourth most commonly diagnosed form of cancer in South Carolina. The American Cancer Society (ACS) predicts that 2,370 new cases of CRC will arise in South Carolina in 2006 and 880 deaths will occur from the disease.¹

Unlike lung cancer, there are screening strategies capable of preventing most, if not all, colorectal malignancies.²⁻⁵ CRC screening methods include: fecal occult blood testing (FOBT), sigmoidoscopy, colonoscopy, and the double barium contrast enema. Using these technologies, we have the ability to recognize premalignancies long before they become deadly. Furthermore, promising new screening procedures are currently being developed including fecal DNA testing, computer-

ized tomography (virtual colonoscopy), and videocapsule endoscopy. Of the currently available techniques, colonoscopy is generally considered the gold standard for CRC screening and early detection. This procedure is not without risk (perforation of the colon, intraluminal bleeding), and the costs can be prohibitive (approximately \$1,000 to \$3,000 per procedure). The risk of colon perforation during colonoscopy, however (1 in 2,000 to 1 in 5,000), is much lower than the lifetime risk of colon cancer diagnosis (approximately 1 in 17). Other limitations include the need for sedation and a fairly involved preparation protocol, which can be a barrier to compliance. These limitations are offset by the advantages of colonoscopy, which include full visualization of the colon and the ability to administer therapy (e.g., polyp excision) during the procedure. Polyps are growths of tissue in the colon that can be either benign or malignant when detected during a colonoscopy. These can be safely and easily removed during colonoscopy years before developing into invasive CRC, thereby facilitating primary CRC prevention. In colorectal cancer associated with inflammatory bowel disease, precancerous ulcerative and dysplastic lesions also can be monitored during colonoscopy. Reducing the mortality rate from colorectal cancer means detecting and either removing or otherwise regressing polyps or dysplastic lesions as early as possible, and treating any invasive cancer in its earliest stages. Treatment options include surgery, radiation therapy, or chemotherapy (5-fluorouracil, capecitabine, irinotecan, oxaliplatin). Recently, promising monoclonal antibody therapies targeting epidermal growth factor receptor (e.g., cetuximab)

or vascular endothelial growth factor (e.g., bevacizumab) have been initiated. Several promising prevention strategies are also being investigated.

Epidemiology of Colorectal Cancer

As with other cancers, age is a major CRC risk factor. Around 90% of incident colorectal cancer occurs in individuals over 50 years of age. Certain populations are at greater risk for CRC due to genetics and heredity. A family history of CRC accounts for approximately 25% of cases, which suggests a role for an inherited genetic trait, common exposures among family members, or a combination of these factors.⁶ Hereditary CRC has two forms that have been well-described. Approximately 5% to 6% of cases occur due to germline mutations in the APC gene (familial adenomatous polyposis or FAP) or in the DNA mismatch repair genes (hereditary nonpolyposis colorectal cancer or HNPCC). Approximately 75% of CRC cases are sporadic (i.e., without evidence for inheritance) and as much as 85% to 90% of sporadic tumors have had acquired (somatic) alterations in APC, which illustrates the importance of this tumor suppressor gene in CRC etiology.⁷ Even after controlling for the effects of stage at diagnosis, comorbidities, and socioeconomic status, African Americans (AAs) have been more likely than European Americans (EAs) to die from CRC.⁸ Genetic differences may at least partially explain these observations. Differences in mismatch repair genes among AA populations have been observed in comparison with EAs,^{9,10} although more research is required to identify specific genetic factors that may explain racial differences in

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CRC mortality. Genetic mutations pertinent to CRC are detectable in fecal DNA obtained from exfoliated epithelial cells in the stool. In a recent cohort of 4,404 asymptomatic individuals 50 years old or older, a panel of 21 fecal DNA mutations was approximately three times more sensitive than FOBT in detecting invasive CRC or dysplastic polyps.¹¹ Although encouraging, more work is needed to improve the accuracy and accessibility of fecal DNA testing.^{11,12}

Contrasts among international rates of disease may provide clues as to non-genetic causes of CRC and point towards effective prevention strategies. As with other cancers associated with affluence, such as breast and prostate, there are marked international variations in the incidence and mortality rates of colorectal cancer (CRC).^{13,16-19} High-risk areas include most regions in North America, Western Europe, and Australia, which account for over 555,000 cases, or 63% of new cases diagnosed worldwide in 1996.¹⁹ Low-risk areas include most places in South America, Asia, and Africa. These geographic differences suggest that environmental factors likely play an important role in CRC etiology. Ecologic studies have revealed associations between CRC rates and per capita consumption of meat, fat (positive correlations), and dietary fiber (negative correlation).^{13,16} The incidence in certain low risk areas is now rising as these areas become more industrialized and adopt more Western-type diets. Furthermore, the rates of colorectal cancer in migrants from low to high-incidence countries tend to increase towards the rates of host countries.²⁰ For example, CRC incidence in Japan has traditionally been low. However, Japanese individuals in the US have higher CRC rates than those of US whites, and the rates for Japanese individuals living in Hawaii or Los Angeles are among the highest in the world.^{13,17} These results further support an environmental component to CRC risk and also indicate that CRC rates are responsive to changes in lifestyle, which can be used to inform potential intervention and preven-

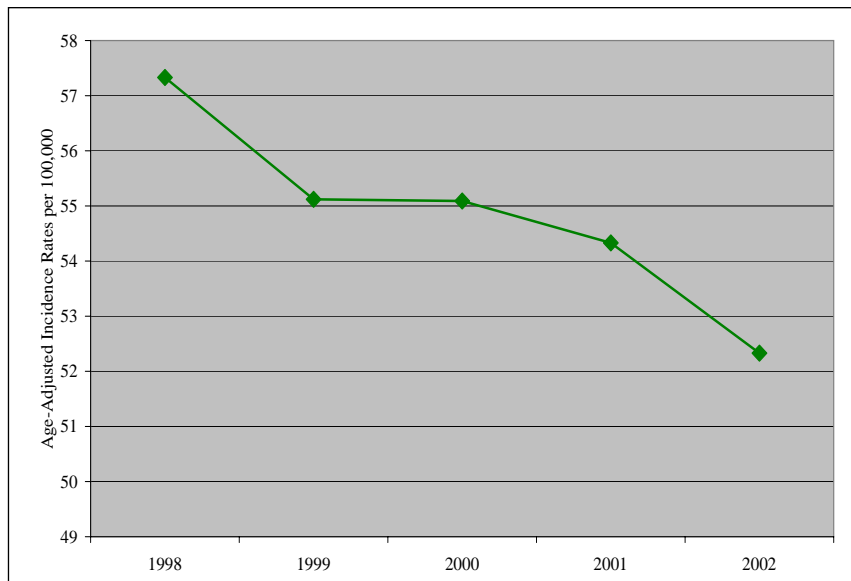


Figure 1. Age-Adjusted Incidence (1998-2002) Rate by Year of Diagnosis in SC

tion strategies. Epidemiologic evidence therefore supports a role for non-genetic factors, especially lifestyle (e.g., dietary) factors, in the pathogenesis of CRC.

The modifiable risk factors for CRC include: too little physical activity (including the lack of intentional or occupational physical exercise); nonsteroidal anti-inflammatory drugs (NSAIDs); calcium; a diet high in saturated fat and low in fiber from a variety of fruit, vegetable and grain sources; obesity; and smoking cigarettes. Dietary and physical activity factors likely play an important role in CRC risk, even if analytic epidemiologic studies have not provided conclusive evidence. We discussed many of the methodologic reasons for this back in the 1980s²¹ and work conducted in the interim has confirmed this.²² Several studies suggest that occupational physical inactivity is a risk factor for colon cancer but not for rectal cancer.^{23,24} Cigarette smokers are 30 to 40 percent more likely to die of colorectal cancer than nonsmokers. It should be noted, however, that tobacco use often clusters with a variety of other known risk factors thought to be related to disease risk.²⁵⁻²⁷ Unfortunately, the contribution of well-established modifiable lifestyle factors is small. However, aspirin

and other NSAIDs and calcium have all shown a significant reduction in colorectal cancers.

Colorectal tumors may arise from sites of chronic, asymptomatic inflammation, the body's natural response to infection. In general, diet is a powerful determinant of inflammation and diets in the West tend to be pro-inflammatory while those in other parts of the world that have higher concentrations of phytochemicals and lower levels of fat, particularly the ω -6 polyunsaturated and saturated fatty acids, which is expected to exert anti-inflammatory effects.²⁸⁻³² A recent study associated lifestyle risk factors for colorectal cancer and fecal calprotectin, a marker of gastrointestinal inflammation, colon adenomas, and carcinomas in a random sample of 320 individuals at average risk for colorectal cancer.³³ Identified risk factors include age, fiber intake, obesity, and lack of physical activity. Significant inverse associations were found with fiber and vegetable consumption. Findings from this particular study reinforce the idea that low-level gastrointestinal inflammation may be one of the missing links between diet/lifestyle and risk for colorectal cancer.

Consistent with the inflammation hypotheses, chronic inflammatory and symp-

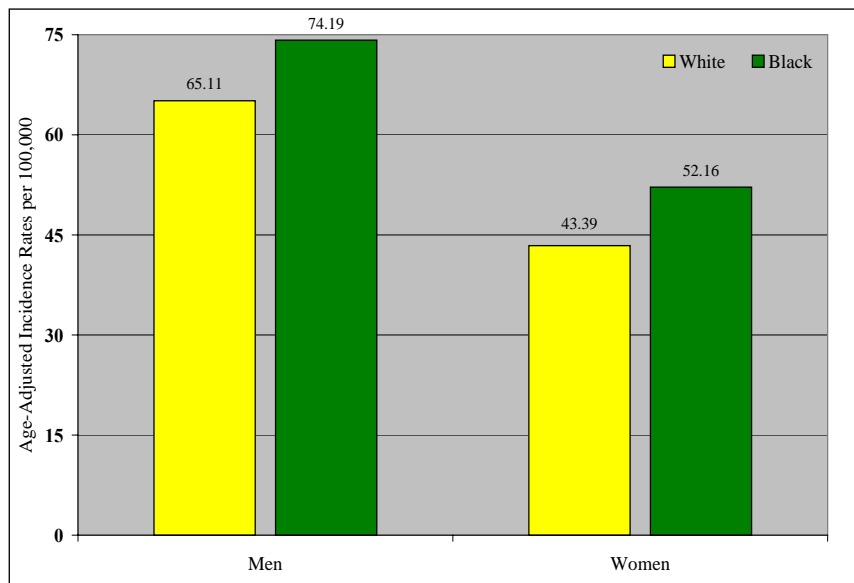


Figure 2. Colorectal Cancer Age-Adjusted Incidence (1998-2002) Rates per 100,000 by Gender & Race in SC

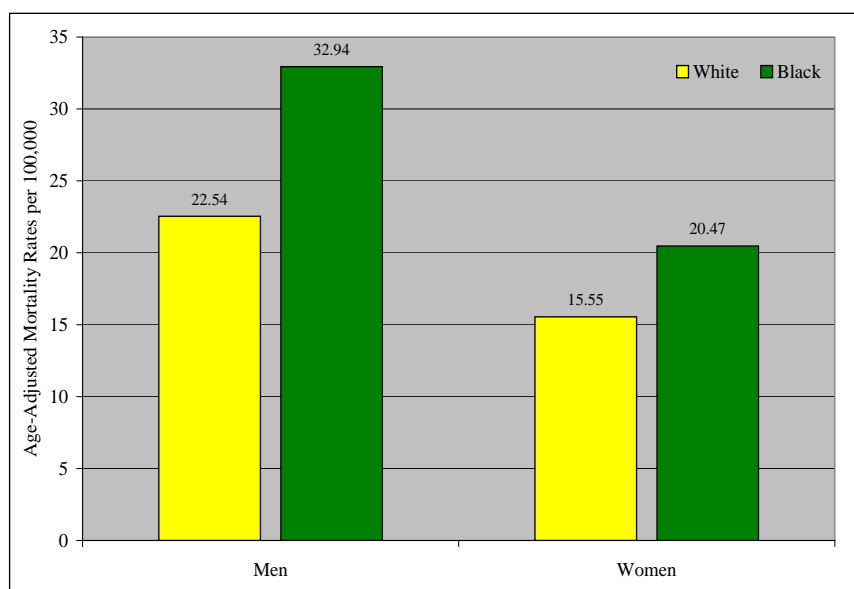


Figure 3. Colorectal Cancer Age-Adjusted Mortality (2000-2004) Rates per 100,000 by Gender & Race in SC

omatic conditions such as ulcerative colitis are strongly associated with increased carcinogenesis of the colon. At the population level, ulcerative colitis and Crohn's disease, collectively known as inflammatory bowel disease (IBD), are chronic inflammatory conditions that are associated with increased risk for colorectal cancer. Similarities in the biological and molecular mechanisms between IBD-associated and sporadic colorectal cancers have led

to speculation that sporadic cancers in non-IBD patients may be a result of constant low level inflammation of the bowel, and that this may arise from interactions between the bacterial flora and the colonic mucosa.³⁴

Several human trials have found NSAIDs such as celecoxib,³⁵ sulindac³⁶ and aspirin^{37,38} to reduce the risk for colorectal cancer by blocking the activity of the cy-

cloxygenases (COX 1 and 2) and thereby preventing polyp recurrence among people with a history of this condition. In humans, levels of COX-2 are increased in 40% of colorectal adenomas and in 90% of colorectal cancers, relative to non-tumor colonic mucosa.³⁹ Because of cardiovascular disease risks recently observed in clinical trials, the specific COX-2 inhibitors are not currently recommended for the treatment of IBD or the prevention of colorectal cancer associated with IBD. Studies have shown COX-2 inhibition can also exacerbate colitis.⁴⁰⁻⁴²

With regard to other CRC prevention strategies, several other clinical trials targeting dietary modification or nutritional supplements have yielded disappointing results, despite the existence of reasonably compelling epidemiologic evidence. These studies have typically focused on reduced polyp formation or recurrence as a surrogate for CRC risk reduction. For example, the protective effect of dietary fiber intake on CRC risk and polyp formation was supported by results from two large cohort studies completed recently^{43,44} and by numerous case-control investigations.^{45,46} However, these findings were not supported in other cohorts, or among several clinical trials.⁴⁶⁻⁴⁸ The reason for this inconsistency may be due to confounding by folate intake or other lifestyle factors that accompany a high fiber diet.⁴⁸ Other trials that evaluated nutritional supplements such as vitamins C and E, or beta carotene failed to elicit consistent protective effects with these agents, or even suggested detrimental effects.⁴⁹ However, calcium supplementation has demonstrated some promise in reducing colorectal adenoma formation, particularly when combined with elevated vitamin D levels, and studies evaluating the beneficial effects of folate are in progress.⁴⁹ These observations emphasize the need for clinical trials to confirm associations identified through analytical epidemiologic studies. Several intriguing new trials are employing a combination of agents in an attempt to reduce single agent toxicity and/or to target comple-

mentary or redundant molecular signal transduction pathways.⁴⁹

Variations in CRC incidence and mortality can provide etiologic clues and suggestions for applying resources for prevention efforts including screening. In both the US as well as in South Carolina (Figure 1),⁵⁰ incidence rates have been decreasing (1998-2002), which may be due to improved treatments or to an increase in screening exams and polyp removal, which prevents polyps from turning into cancer.⁵¹ As screening colonoscopy becomes more widely accepted and as better screening techniques become available in the years ahead (e.g., fecal DNA testing, virtual colonoscopy, videocapsule endoscopy), the current trends of decreasing incidence may be expected to moderate somewhat or even increase due to the increased detection of CRC cases. CRC mortality rates, however, would be expected to decrease over time since cancers detected at earlier stages are more treatable, thus yielding better survival rates.³³

In South Carolina, incidence rates for colorectal cancer are slightly greater among AAs than among EAs for both men and women (Figure 2). AA men have an 8% greater incidence rate compared to EA men and AA women have a 16% greater incidence rate than EA women. Similarly AA men and women have higher mortality rates than EA's (Figure 3). The most striking disparity is among men; AA men have a 46% higher mortality rate than EA men,⁴¹ a differential that is over five times that of incidence.

Although AA are more likely to be diagnosed with and die from CRC when we compare South Carolina county-specific age-adjusted incidence rates to the average U.S. rates for each race, it is clear that, for several counties in SC, EA men have much higher rates of CRC than the U.S. average (Figures 4 and 5). However, this is not true for mortality. Overall, SC county age-adjusted mortality rates for EA or AA are not significantly higher than CRC rates for the US⁵⁰ (Figures 6 and 7).

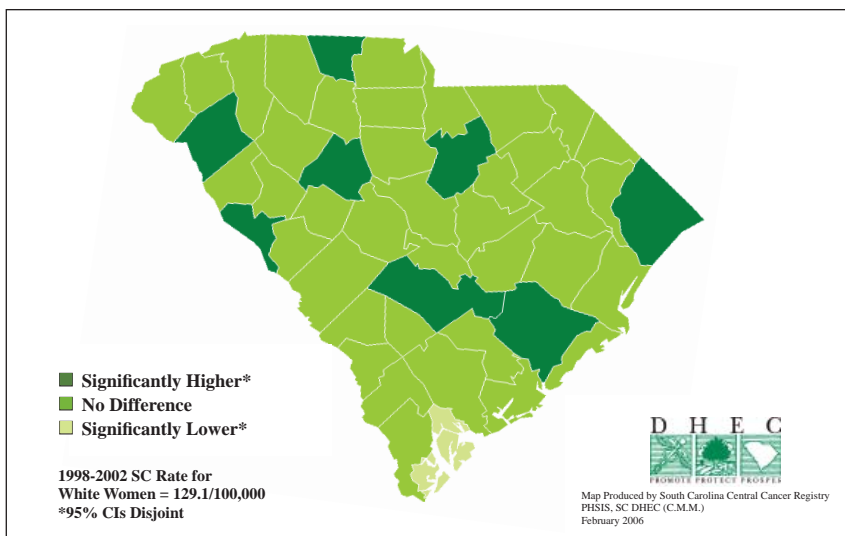


Figure 4: South Carolina Colorectal Cancer: Comparison of Age-Adjusted Rates, County-Specific Incidence Rates per 100,000 (1998-2002) in White Males, Compared to the US Rate among White Males (2002)

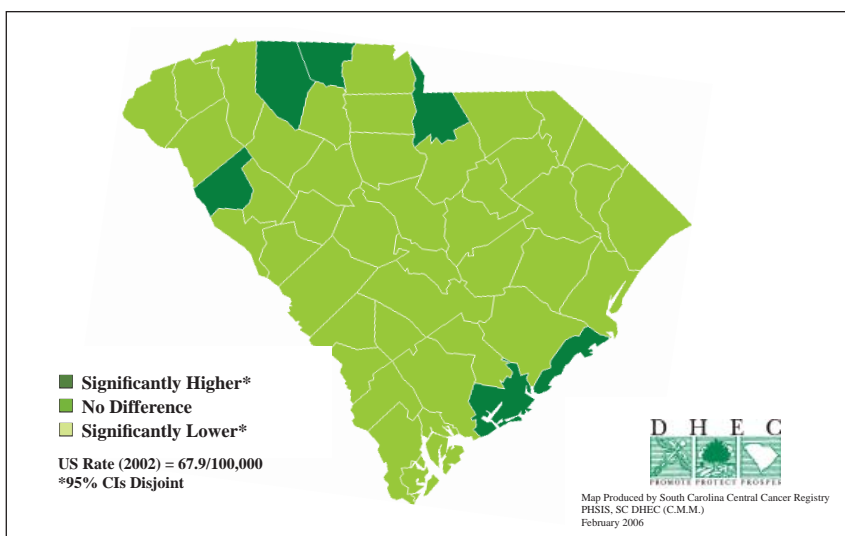


Figure 5: South Carolina Colorectal Cancer: Comparison of Age-Adjusted Rates, County-Specific Incidence Rates per 100,000 (1998-2002) in Black Males, Compared to the US Rate among Black Males (2002)

CRC Screening and Special Programs in South Carolina

Screening plays a vital role in facilitating early cancer detection, effective treatment, and increased survival. The signs and symptoms of CRC are typically only apparent when disease is more advanced and less curable. They are also relatively uncommon with adenomatous polyps, making these lesions difficult if not impossible to detect clinically. These phenomena provide a rationale for mass

screening of the general asymptomatic population for prevention and early detection of CRC.⁵⁰ An estimated fifty-percent of colorectal cancer deaths can be prevented by removing polyps before they become cancerous. Unfortunately, only half of South Carolinians over the age of 50 years report ever having had a colonoscopy or sigmoidoscopy (SC BRFS). We have great strides to make in getting South Carolinians screened for CRC. It is astounding that only 34.7% of South

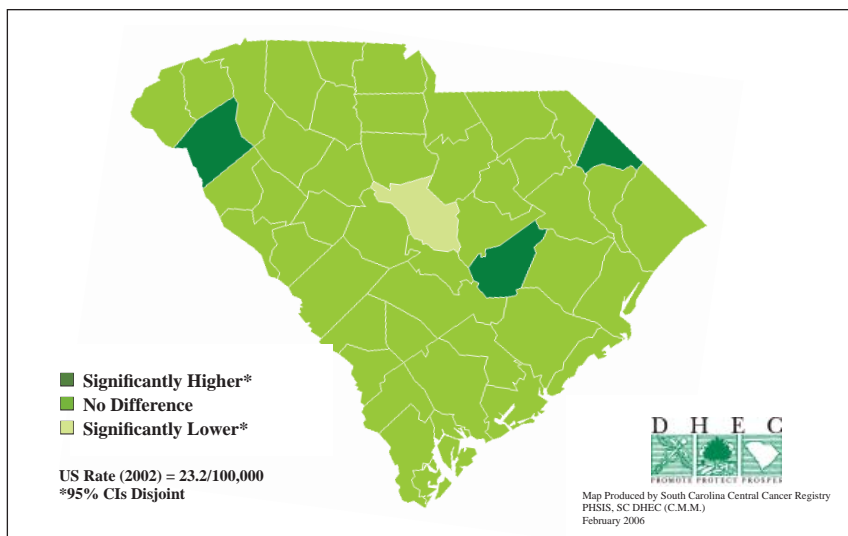


Figure 6: South Carolina Colorectal Cancer: Comparison of Age-Adjusted Rates, County-Specific Mortality Rates per 100,000 (1999-2003) in White Males, Compared to the U.S. Rate Among White Males (2002)

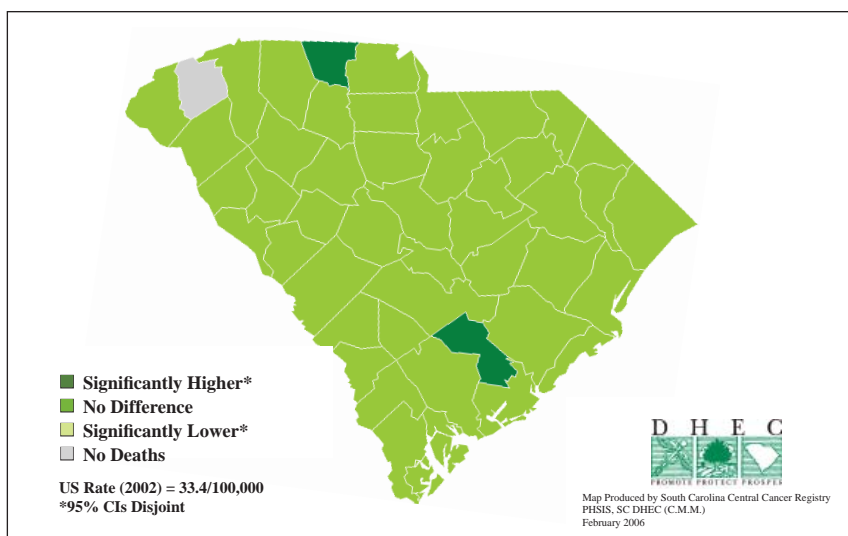


Figure 7: South Carolina Colorectal Cancer: Comparison of Age-Adjusted Rates, County-Specific Mortality Rates per 100,000 (1999-2003) in Black Males, Compared to the U.S. Rate Among Black Males (2002)

Carolinians are diagnosed at early stages where the five-year survival rate is up to 96%. Survival rates drop to 10% once the cancer has spread to distant sites.²⁵ Clearly, colorectal cancer is a deadly disease and screening can save lives.

Surviving colorectal cancer depends critically on the stage at which the disease is diagnosed. The five-year survival rate is 87% to 96% if the disease is diagnosed at early stages (I or II), as opposed to just

5% at advanced stage (IV). Among invasive cases of colorectal cancer in SC, 35% are diagnosed at local stages while 40% of cases are diagnosed at regional stages and 17% at distant stages.⁵⁰ Although there are few differences in CRC stage at diagnosis by either race or gender in SC, a slightly greater proportion of AA men and women tend to present with distant disease compared with EAs (Figures 8-11). Rates of metastatic disease among South Carolinians tend to be slightly

lower than U.S. rates, which indicate that 25% of AAs are diagnosed with metastatic disease compared to 20% of EAs.⁵² Examining the patterns of colon cancer stage by anatomic subsite may reflect differences in screening practices among AAs and EAs. In a large national study of aggregated cancer registry data among CRC patients aged 50 years and older, localized disease was more common in the distal colorectum (41.5%) compared to the descending (37.0%) or proximal colon (31.9%).⁵³ AAs were more likely than EAs to be diagnosed with metastatic disease across all anatomic subsites, and were 15% to 19% more likely than EAs to have tumors in the proximal colon where metastatic disease occurs more frequently. These results may reflect a greater prevalence of screening sigmoidoscopy among AAs, since those procedures do not visualize the proximal colon and may therefore leave some tumors undetected.⁵³

Factors in the U.S. that contribute to racial differences in screening include: access to health care, inadequate screening compliance, education level, income, cultural differences, and health insurance coverage.⁵³ South Carolina is currently involved in a survey of endoscopic capacity (SECAP), an initiative sponsored by the Centers for Disease Control that will estimate the number of average risk South Carolinians who still need to be screened by race/ethnicity, gender, insurance status and poverty level. Results regarding the capacity to conduct additional screening colonoscopies in our state will be available later this year. This information is an essential first step in ensuring that resources for early detection are concordant with need.

Based on SECAP estimates, it is not surprising that South Carolinians who are uninsured are much less likely to be screened than those with insurance, irrespective of poverty level. Among individuals whose incomes are at least 250% of poverty level and uninsured, 30.5% have been screened for CRC while 56.2% of those with insurance are estimated to have been

screened. Among those whose incomes are greater than 250% of poverty level and without insurance only 39.8% were estimated to be screened while 62.4% of those insured were screened. Clearly, the implications for screening our uninsured population are huge.

Among the efforts to reduce the toll of colorectal cancer in South Carolina, two programs stand out as potential models for addressing barriers to effective screening. To elevate colonoscopy to the level of mammography for breast cancer screening (80% compliance), we need to quadruple the state's screening rate. The incremental cost per year of life saved is \$6,600 for colonoscopy every ten years compared to \$22,000 for breast, \$160,000 for heart transplant, or \$250,000 for cervical cancer screening. We must also strike a balance between education of the public on the virtues of colonoscopy with the capacity to perform the procedures. "Seeking Cecums" provides training to extend the capabilities of primary care physicians trained to perform sigmoidoscopy to perform full colonoscopy. To date, fifty graduates are providing over 7,500 procedures annually in the Midlands regions of the state. This is equivalent to the patient volume of ten gastroenterologists. This increased access is particularly valuable considering the closure in 2003 of the USC School of Medicine fellowship in gastroenterology, which produced two or three graduates each year. Thus far, 50% of the physician graduates of the "Seeking Cecums" program are African Americans (AA), providing significant inroads in the battle against health disparities.

The second innovative program is a faith-based initiative of the Carolina Community-Based Health Support Network. This community outreach effort provides educational and financial support to provide colonoscopy screenings. The 1,000 participants have revealed an extraordinarily high polyp rate that is over double the national colonoscopy average (64% vs. 32%). Factors contributing to this observation include the high proportion of sub-

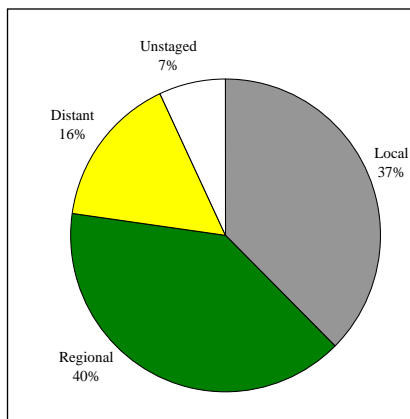


Figure 8. Colorectal Cancer Stage at Diagnosis in SC among White Men, 1998-2002

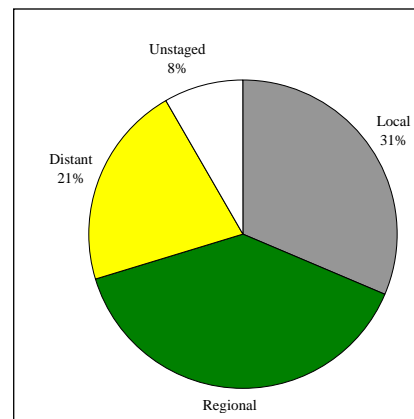


Figure 9. Colorectal Cancer Stage at Diagnosis in SC among Black Men, 1998-2002

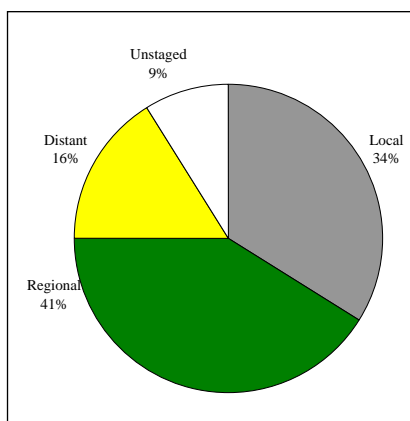


Figure 10. Colorectal Cancer Stage at Diagnosis in SC among White Women, 1998-2002

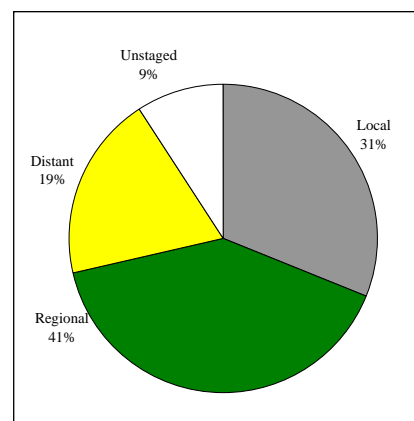


Figure 11. Colorectal Cancer Stage at Diagnosis in SC among Black Women, 1998-2002

jects with no prior screening (88%) and a predominance of AA (92%) screenees. This group will serve as the basis for a long-term investigation of the program's impact on incidence and mortality of colorectal cancer, but it will be ten years before the results are forthcoming.

Screening Recommendations

Guidelines for screening vary. Table 1 outlines current screening recommendations by medical organizations and the American Cancer Society.

Summary and Future Directions

Through a comprehensive examination of CRC in South Carolina, several recommendations for more research have been identified. Currently, some areas of the state

cite low health literacy as a major barrier to screening and risk assessment for CRC. For example, in the Pee Dee area of South Carolina, workers at McLeod Medical Center have begun to address community needs related to health literacy. The staff have begun to identify 'natural helpers' in the community and started to outreach to the people by collaborating with local churches to spread health information. This model has worked well to inform the public about several other diseases (i.e., diabetes, heart disease), but additional work needs to be implemented for CRC health education. Bridging the literacy gap through community outreach programs will lead to increased health awareness, provide a means to help individuals with informed decision-making, and improve clinical outcomes related to CRC.

Table 1. Colorectal cancer screening guidelines for average risk individuals

American Academy of Family Physicians	No published standards or guidelines for low-risk patients
American Cancer Society	After age 50, annual fecal occult blood test (FOBT)* or fecal immunochemical test (FIT) and one of the following: <ul style="list-style-type: none"> • Flexible sigmoidoscopy • Flexible sigmoidoscopy • yearly FOBT* or FIT plus flexible sigmoidoscopy every 5 years** • double-contrast barium enema every 5 years • colonoscopy every 10 years
American College of Gastroenterologists	After age 45, African-Americans; colonoscopy every 10 years, After age 50, for other races colonoscopy every 10 years
American College of Oncology Surgeons	After age 50, annual FOBT (DRE should accompany pelvic examination); sigmoidoscopy every 3 to 5 years
American Medical Association	Annual FOBT beginning at age 50, and flexible sigmoidoscopy every 3 to 5 years beginning at age 50
American Gastroenterological Association	Colonoscopy every 10 years, or double-contrast barium enema every 5 years
Canadian Task force on Preventive Health Care	After age 50, Annual FOBT
United States Preventive Services Task Force	After age 50, yearly FOBT and/or sigmoidoscopy

* for FOBT the take home multiple sample method should be used

** The combination of yearly FOBT or FIT plus sigmoidoscopy every 5 years is preferred over either of these options alone

As with other cancer sites, studies are needed to understand the unique patterns of incidence and mortality observed in South Carolina. Linking etiologic research with the obvious need to increase screening for primary prevention is one possible approach. For example, a program to increase colonoscopy screening in underserved regions will lead to identification of people with polyps and those free of these lesions. With this information it would then be possible to conduct a case-control study to identify factors that help distinguish cases (i.e., those with precancerous lesions) from controls (i.e., lesion-free individuals). Cases could then be followed to determine what factors predispose to future lesions. ‘Host factors’ such as diet and exercise could be studied, in both the case-control and follow-up studies. It also

would be possible to test whether promising biomarkers predict future risk for colorectal cancer. In this way, we would be able to combine what otherwise might be simply a service project with work having both an epidemiological and a biological focus. Research of this type may lead to the identification of target groups, further definition of risk behaviors, and establishment of additional protocols for more efficient population-based screening. Genetic susceptibility markers could also be used in these settings to identify high risk individuals who can be referred for heightened surveillance and enrolled in CRC prevention programs. In addition, culturally appropriate chemopreventive and lifestyle intervention programs are needed to reduce the CRC disease burden, particularly those that combine

approaches by targeting complementary disease processes.

Currently, the costs associated with screening for colorectal cancer present a clear barrier to individuals being screened, particularly for colonoscopy. Still, it is known that treating a person with late-stage cancer is very expensive. Therefore working out the health economics of colorectal screening to prevent or downstage colorectal cancer is crucial to informed policy decision-making. This would entail collecting and analyzing the cost-benefit and cost-effectiveness data related to early primary and secondary prevention.

Colorectal cancer is one of only a few cancers for which screening addresses both primary prevention (i.e., the prevention of an incident cancer from occurring in the first place) and secondary prevention (i.e., to downstage the cancer at the time of diagnosis). As such, it has the potential for immediate public health impact. Also, by intervening early in the natural history of the disease, it allows us the opportunity to understand the biology of the process in order to move effective prevention strategies even earlier in the process of carcinogenesis and malignant transformation.

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