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Disparities in Colorectal Cancer: Measuring Spatial Accessibility, Screening, and Surveillance Outcomes in South Carolina

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DISPARITIES IN COLORECTAL CANCER: MEASURING SPATIAL ACCESSIBILITY, SCREENING, AND SURVEILLANCE OUTCOMES IN SOUTH CAROLINA

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DEDICATION

This degree is dedicated to my late mother, Lenora Hinton Josey. It was her dream that my sister and I strive for higher education and excel in every endeavor. Thanks to her leadership and sacrifices, I will be the first PhD in my family. This degree is also dedicated to my sister, Delora M. Sutton. Thank you for your constant upliftment and support!

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ABSTRACT

The purpose of this dissertation project is to add to the growing literature about the multi-faceted aspects of colorectal cancer (CRC) prevention and related disparities. We focused on the spatial distribution of facilities performing screening services to identify areas that underutilize colonoscopy screening. Next, we examined how the food and physical activity environment affects precursors of CRC by considering plausible pathways. Finally, we explored if access to health insurance reduced the racial disparity of receiving a timely surveillance colonoscopy after a CRC diagnosis.

We utilized the SC Ambulatory Surgery Discharge Database, an all-payer, population-based outpatient dataset with colonoscopy records from 2000 – 2014. To identify individuals with a personal history of CRC, we used the SC Central Cancer Registry. We used the Colorectal Cancer Prevention Network screening cohort of low-income, uninsured adults in SC to study colorectal polyps. We paired these unique datasets with innovative analysis methods like two-stage Bayesian hierarchical logistic regression, causal mediation analysis, and loglinear regression.

We were able to create catchment areas (CAs) for all facilities in SC performing screening colonoscopies and found that only a small proportion of ZIP codes were not included in any CA. Aspects of the food and physical activity environment had a direct, protective effect on having high-risk colorectal polyps. Finally, we found that over time, increased access to health insurance helped to diminish the racial disparity in receiving a timely surveillance colonoscopy.

Overall, this dissertation was able to address gaps in the literature, particularly providing risk and prevalence estimates for the state of South Carolina (SC). This work lays the foundation for addressing screening and surveillance capacity in SC and understanding the individual role within unhealthy environments.

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LIST OF ABBREVIATIONS

ADR ..... Adenoma detection rate

ASD..... Ambulatory Surgery Database

CA ..... Catchment area

CIMP..... CpG island methylator phenotype

CCPN ..... Colorectal Cancer Prevention Network

CRC..... Colorectal cancer

CRS ..... Colorectal surgeon

FAP ..... Familial Adenomatous Polyposis

GE ..... Gastroenterologist

GS ..... General surgeon

LS ..... Lynch syndrome

MSI ..... Microsatellite instability

OEI ..... Obesogenic environment index

PDR..... Polyp detection rate

PCCRC..... Postcolonoscopy colorectal cancer

PCP ..... Primary Care Physician

SC..... South Carolina

SCCCR..... South Carolina Central Cancer Registry

U.S. ..... United States

CHAPTER 1

INTRODUCTION

Colorectal cancer (CRC) is cancer of the large intestine (colon) or rectum; it is considered a disease of the developed world.[1] Overall, men and women in the United States have approximately a 5% lifetime risk of developing colorectal cancer[2], and it is the third most common cancer, affecting mostly adults over 50 years old. For 2017, the American Cancer Society estimated that 67,800 deaths were attributable to CRC.[3] More specifically, CRC was estimated to be the second leading cause of cancer death in the United States (U.S.) and South Carolina (SC) for the same year.

CRC is largely preventable through primary and secondary prevention methods and reduce the risk of CRC through maintaining a healthy lifestyle, which include a healthy diet (5-8%), physical activity (16%), not smoking (12%), and regular screenings (63%).[1,4–6] Screening has become more affordable over the last two decades due to Medicare's determination to cover colonoscopy for average-risk individuals in 2001 and the more recent Affordable Care Act making screening available to nearly all insured average-risk individuals with no out-of-pocket costs, yet only 67.6% of eligible adults have received any type of screening.[7] Research has shown that the barriers to CRC screening include lack of awareness, affordability, distance to a screening facility, lack of symptoms, and views of cancer fatality.[8–10]

CRC survival is relatively high compared to other cancers, but dependent on numerous factors. The five-year survival is 65% overall, and ranges from 14% to 90% for

distant and localized stage, respectively.[3] Research on survival and recurrence after a CRC diagnosis is limited, and somewhat inconclusive.[11] However, it is suggested that primary prevention methods like reduced processed food consumption and physical activity reduce recurrence after a CRC diagnosis as well.[12,13] In addition, consistent surveillance is recommended to prevent CRC recurrence. Colonoscopy is primarily recommended, however the method and intervals of testing vary by family history, polyp size, age, and location of the tumor.[14,15] Factors preventing prolonged survival include financial burden[16,17] and lack of social support[18,19].

1.1 Statement of the Problem

Over the last two decades, there has been an overall decrease in CRC mortality in the U.S. population.[3] This may be due to increased CRC screening and improved treatment. While any reduction in CRC morbidity or mortality is considered a victory, certain populations are still at a disadvantage compared to others. There are consistent disparities in CRC outcomes between Black and White Americans,[4,20] lower and upper SES,[21] and rural and urban Americans[22,23]. Compared to Whites, African Americans are more likely to be diagnosed with and die from CRC.[3,24] This could be due to less understanding about screening and lower screening rates, even when there is a known family history of the disease.[24,25] African Americans are also more likely to be diagnosed at later stages, which is directly related to survival.[25–27] In addition, individuals of lower socioeconomic status have a higher risk of CRC incidence and mortality.[25,28] This disparity is not always mitigated by insurance.[29–31] Finally, compared to those residing in

urban areas, rural residents are less likely to receive screening, have higher CRC incidence rates, and later stages at diagnosis.[22,23,32,33]

Progress in reducing colorectal cancer death rates and disparities can be accelerated by improving access to screening/surveillance, and providing high-quality, timely treatment in all populations.[20] Particularly in South Carolina, there is large intersectionality of African American living in rural areas compared to the national distribution[34], and due to the lack of Medicaid expansion, high rate of no insurance, and large minority representation, these disparities may be compounded. Similar disparities are noted for prevention opportunities like access to affordable healthy food outlets.[35,36] Across the U.S., predominately rural, low income, or ethnic minority communities have less access to quality food and supermarkets,[37] which is directly related to chronic diseases like CRC.

1.2 Purpose & Aims

The purpose of this project is to investigate disparities in travel patterns of CRC screening (Paper 1), obesogenic environmental effects on CRC screening outcomes (Paper 2), and adherence to post CRC diagnosis surveillance (Paper 3) in SC.

Aim I: To determine the catchment areas of facilities performing screening colonoscopies and the associated travel patterns of their patients in South Carolina.

The purpose of this project is to illustrate and describe the catchment areas (CA; i.e. service area) of facilities in SC providing screening colonoscopies from 2010 – 2014. Catchment area analyses help describe the types of people that are more likely utilize a service in specific locations. Using data from the population-based SC Outpatient

Ambulatory Discharge database, we will construct CAs and examine travel patterns of age-eligible adults seeking a screening colonoscopy. The following research questions will be answered within this aim:

1. What is the greatest distance that patients are willing to travel? How does it differ by patient rurality?
2. What are the characteristics of patients inside and outside of the catchment areas?

Aim II: To determine the relationship between the obesogenic environment and the presence of colorectal polyps among patients screened for CRC. Poor access to recreational opportunities and healthy food outlets can be barriers to living a healthy lifestyle, and are more pervasive in low-income and rural neighborhoods.[38,39] Although the environment is a social determinant of health, its role in CRC has not been clearly established, as studies have produced mixed results.[40–42] Using a low-income, uninsured screening cohort from the Colorectal Cancer Prevention Network sponsored by the University of South Carolina, we propose to:

1. Examine the pathways between the obesogenic environment and the presence of CRC polyps.
2. To explore whether the association of the obesogenic environment on the presence CRC polyp(s) differs by polyp type (any and high-risk).

Hypotheses:

1. The pathway between the obesogenic environment and having a polyp is mostly mediated through obesity.
2. The direct pathway (not through individual-level obesity) has a stronger effect on high-risk polyps than the general class of polyps.

Aim III: To determine if racial disparities in CRC surveillance adherence diminish over time with increased access to health care as measured by insurance coverage. CRC survivors are at an increased risk of CRC recurrence. After a cancer diagnosis and treatment, there are several steps that a survivor can take to protect their quality of life; surveillance is a key step. A surveillance colonoscopy is recommended one year after a colorectal cancer (CRC) diagnosis and treatment to detect early signs of recurrent cancer.[43] Adherence to this recommendation varies widely, and uptake is suboptimal among minority populations.[44] Using data from the SC Outpatient Ambulatory database linked to the SC Central Cancer Registry, we propose to:

1. Describe surveillance uptake overtime in SC among patients diagnosed with CRC.
2. To examine racial disparities in adherence to surveillance by age group over time.

Hypothesis: The disparity between older (≥ 65) African American and White patients is significantly reduced for colorectal cancer surveillance adherence due to increased access to health care through insurance.

1.3 Significance & Rationale

In 2014, the National Colorectal Cancer Roundtable announced an initiative to screen 80% of age-eligible adults by 2018. In the same year, approximately 68% of SC adults aged 50 and over were up-to-date on any CRC screening.[45] Population screening is imperative in reducing the incidence and mortality of CRC, therefore it is important to establish and verify beneficial agents and potential barriers to receiving CRC-related services. In SC, the clusters of centers performing colonoscopy, particularly in urban

areas, may create pockets of poor accessibility to colonoscopy services where people must travel a great distance to be screened for CRC. Therefore, it is of great interest to visualize and understand the catchment areas of these centers, and the corresponding population that they reach and attract. This analysis (for Aim 1) has not been done for colonoscopy centers in SC and has the potential to inform the colonoscopy centers of the range of their service.

It is widely known that living in a healthier environment, or an environment with health-promoting opportunities, is associated with better health outcomes. However, the relationship between the obesogenic environment and CRC has not been well established. Aim 2 seeks to determine if areas with less healthy options influence colorectal outcomes outside of the known pathway through obesity. A significant finding would draw attention to neighborhoods that appear "unhealthy" to determine a true cause of the outcome.

Finally, adherence to surveillance after a CRC diagnosis is not as well studied as CRC screening. Aim 3 will establish the prevalence of surveillance uptake in SC over time and across racial/ethnic and age groups, which currently does not exist. This is an important step in recognizing how disparities change over time and potential intervention targets for CRC survivors at the highest risk of surveillance non-adherence.

CHAPTER 2

LITERATURE REVIEW

2.1 Anatomy[4,46]

The colon, or the large intestine, removes water, breaks down and extracts remaining nutrients in the digestive process. Using the muscles that line the colon wall, the residual contents, called stool, are pushed to the rectum, then finally out of the body through the anus. The colon is comprised of four sections: the ascending, transverse, descending, and sigmoid colon. The ascending colon begins at the cecum, which connects the colon to the small intestine, and runs up the right side of the abdomen. The transverse colon runs above the abdomen and is the connection between the ascending and descending colon. The descending colon runs down the left side of the abdomen, connects to the sigmoid colon, which is joined to the rectum. The ascending and transverse colon are also referred to as the proximal colon, and the descending and sigmoid are referred to as the distal colon. Together, the colon and rectum are approximately six feet long.

The colon is a tubular organ with multiple layers. The innermost layer of the colon and rectum is the mucosa. The mucosa is comprised of the epithelium, connective tissue or the lumen, and thin strips of muscle. The submucosa is a layer of connective tissue containing mucous glands, blood vessels, lymphatic vessels, and nerves immediately beneath the mucosa. The muscularis propia is a thick layer of muscle that

lies just below the submucosa. Finally, the serosa is the outermost layer and the only layer not found on the rectum.

2.1.1 Polyps

In certain situations, the mucosal layer can become hyperproliferative and form a benign growth called a polyp. Polyps can be complex, vary in size, and location of the colon and rectum. Inflammatory, hyperplastic and adenomas (i.e. adenomatous polyps) are the most common. Inflammatory polyps are typically found in the colon of those with inflammatory disease like Crohn's disease or ulcerative colitis.[47] Inflammatory and hyperplastic polyps typically will not develop into cancer, and they both can be removed during a colonoscopy.[47,48]

2.1.2 Adenomas

Adenomas arise from the glandular cells found on the mucosal surface; the purpose of these cells is to produce the mucous that lubricates the colon and rectum. CRC develops through one of three pathways: 1) the adenoma-carcinoma pathway (most common for sporadic CRC), 2) the CpG island methylator phenotype (CIMP), high microsatellite instability, and 3) the microsatellite instability through mismatch repair pathway.[49,50] Adenomatous polyps are precursors to CRC and account for 96% of all CRCs.[7] These polyps arise through the first pathway and can be classified into tubular, villous, tubulovillous (a mix), or serrated. Tubular adenomas are protruding, spherical, and pedunculated (i.e. elongated) and account for about 80% of adenomas found in the colon and have a less than a 5% chance of progressing to cancer.[51] Tubulovillous

adenomas account for 10 – 15% of adenomas and have an elevated risk of malignancy of 20 – 25%.[51] Villous adenomas are typically sessile with a hairy-like surface, account about 5 – 10% of adenomas, and have between 30 – 45% chance of progressing to cancer.[51] Serrated adenomas have a sawtooth appearance and are responsible for approximately 30% of colorectal cancers.[52]

Serrated adenomas/polyps arise from the CIMP pathway and can be classified as hyperplastic, sessile, and traditional. This pathway is particularly important because individuals with serrated polyps have a higher risk of CRC compared to individuals with other advanced adenomas.[53] Traditional serrated adenomas are smaller in size and rare, and sessile serrated polyps are typically located in the proximal colon and tend to be missed during endoscopic procedures, which leads to interval cancer.[52,54] Because of the malignancy of serrated polyps, surveillance after a polypectomy are more frequent than the standard 10 year interval, ranging from 3 – 5 years.[50,55]

The Microsatellite instability (MSI) pathway is caused by mutations in the mismatch repair (MMR) gene. Microsatellites are short repeats of DNA sequences. Instability occurs when the number of repeats is different from the number of inherited DNA repeats.[56] Previous research has estimated that MSI accounted for 13% of sporadic CRC.[57] MSI tumors are mostly found on the right side and individuals diagnosed with a MSI-positive tumor have better prognosis and overall survival compared to other right-sided tumors.[58,59]

2.2 Biological Causes of Colorectal Cancer

CRC is a consequence of genetic and epigenetic mutations that transform normal tissue into adenocarcinoma.[60] Like most cancers, CRC is a multifactorial disease, and results from the inability to control cell replication and differentiation.[61] For example, inactivation of tumor suppressor genes due to DNA mutation can trigger tumorigenesis. Tumorigenesis, or the initiation of CRC, develops overtime from precancerous polyps. In the most common pathway, these polyps advance in size from small to larger adenoma(s), then finally to cancer.[62] While large adenomas are associated with higher malignancy, most adenomas found in the colon or rectum are small, having a diameter less than one cm.[63,64]

Genetics play a role, with increased predisposition to CRC related to familial diseases, like Lynch Syndrome or Familial Adenomatous Polyposis. Of note, these high risk individuals only account for 5 – 10% of all diagnosed cases.[65] Another known pathway to CRC is through aberrant DNA methylation. DNA methylation is the process of activating or silencing cell activity. Previous research has shown that aberrant hypermethylation in specific regions has the potential to silence tumor suppressor genes; the downstream effect is the same as mutation-induced inactivation of tumor suppressor genes as previously discussed.[60] Increasing evidence shows a connection between lifestyle factors and epigenetic modification. Raskov et al. noted that mucosal cells quickly adapt to carcinogens and diet changes which result in epigenetic changes, and can result in tumor formation; these changes can be amplified if genetic predispositions already exist.[66]

Many of the molecular-focused studies consistently found smoking to increase the risk of CRC through the serrated pathway, with the highest risk (Hazard Ratio ≈ 2) associated with MSI.[62] Smoking cessation was found to have a protective effect on the DNA methylation pathway where at least 10 years of cessation was associated with a 50% lower risk of CIMP-high CRC.[67] The effect of dietary patterns also differed by microsatellite stable (MSS) tumors where an increased consumption of red meat, total and saturated fats, and cholesterol were associated with increased odds of CRC.[68] Some epidemiologic studies have also found obesity to be positively associated with CRC for MSS tumors.[69,70]

2.3 Disease Progression

The progression from onset to colorectal cancer symptoms can take up to 20 years for the average risk population, or as little as three years in patients with familial predisposition for familial diseases.[2,60] CRC typically begins as a small adenomatous polyp and the probability of cancer increases as the adenoma grows.[4] Approximately 30 – 50% of individuals will develop at least one adenoma, but less than 10% progress to cancer.[71] Adenocarcinoma, developed from abnormal proliferation of the glandular cells, is the most common form of CRC (96% of cases).[7] The stage of CRC indicates the severity, or spread of cancer. CRC begins on the inner lining of the colon or rectum (in situ), expands to the colon or rectum wall (local), into the lymph and blood vessels (regional), then into other organs (distant).[4] Approximately 38% and 43% of patients are diagnosed with colon and rectum cancer at the localized stage, respectively, where the survival rate is highest.[7]

There are usually no signs or symptoms at the onset and early stages of CRC. As the cancer develops, individuals may experience bloody stool, bleeding from the rectum, a change in the color or shape of stool, discomfort in the abdomen area, unintentional weight loss, vomiting, constipation or diarrhea, or a decreased appetite.[72] Although there are a lack of symptoms in the progression of CRC, it can be caught early or prevented with various screening methods.

2.4 Observational & Randomized Control Trial findings

CRC is a multifactorial disease that is influenced by both modifiable and non-modifiable risk factors. There are two hereditary patterns related to CRC, those that are associated with colon polyps (polyposis) and those that are not (non-polyposis). Individuals with a family history have the greatest lifetime risk of developing CRC. Those with one first-degree relative diagnosed CRC have two times the risk, and those with more than one relative have four times the risk of developing CRC.[73] Epidemiologic studies also show an association between incidence of sporadic CRC and lifestyle behaviors like heavy red meat consumption, smoking, large body weight, and lack of physical activity.[7,74,75]

2.4.1 Genetics

Familial Adenomatous Polyposis (FAP) is a genetic disorder that has both autosomal dominant and autosomal recessive forms, and has an incidence of 1 per 8,000 – 10,000, which only accounts for <1% of all CRC cases.[1,76] An individual with FAP can develop hundreds to thousands of colonic polyps that increase in frequency with age;

these polyps can progress to cancer if not removed. In the milder (recessive) form of FAP, an individual can develop less than 100 polyps over a lifetime. Individuals with FAP or attenuated FAP have almost a 100% lifetime risk of developing CRC, which is significantly greater than the sporadic forms. The average age of CRC onset is 39 for FAP and 55 for attenuated (delayed) FAP, compared to 69 for the average risk population. The cause of FAP and its attenuated form is a mutation of the adenomatous polyposis coli (APC) gene, a tumor suppressor gene that control normal cell growth and function.[77] The cause of autosomal recessive FAP is a mutation in the MUTYH gene, which controls DNA correction during the replication process before cell division.

Lynch syndrome (LS), or hereditary nonpolyposis colorectal cancer, is an autosomal dominant that accounts for 3% of the new cases of CRC.[78] LS manifests through the MSI pathway by variations in the MMR genes: MLH1, MLH2, MLH6, PMS2, and EPCAM.[57,79] Similar to FAP, these genes are involved in repairing errors during DNA replication. The continuation of more cells dividing and replicating with errors leads to uncontrolled cell growth, and possibly malignant tumors. LS does not only lead to CRC, it can lead to cancer of related and distant organs like the digestive organs, the upper urinary tract, brain, and skin.[78]

2.4.2 Polyp Location

The location of a colon polyp or adenomatous tissue has implications for the severity and survival of CRC. Individuals with right-sided cancer are more likely to experience interval cancer (i.e. cancer between screenings),[80] and have a higher risk of mortality.[58,81] The increase in mortality is related to right-sided cancers being diagnosed

at later stages and in older adults, which leads to poorer survival compared to left-sided cancers.[81,82] Although colonoscopy is effective in reducing the incidence and mortality of CRC, the reductions are lower for the proximal (right side) compared to distal cancers.[54] It is hypothesized that these differences are attributable to some polyps, like serrated, in the proximal (right) region being harder to detect. Adenomas and serrated polyps, specifically sessile serrated, are more likely to be in the proximal colon than distal.[83] Large serrated polyps were found to be a strong risk factor for CRC, particularly for proximal cancers.[84] Further, Qumseya et al. found that a right-sided polyp is three times more likely to have dysplasia (i.e. abnormal cell growth) compared to a left-sided polyp.[85]

2.4.3 Age

Advanced age is also a known risk for various chronic diseases like colorectal cancer. Approximately 90% of diagnosed CRC cases occur in adults 50 years and older, and over 70% in adults between the ages of 50 and 80 years.[86] The number of colorectal polyps, low and high risk, also increase with age.[2,87,88] Therefore, CRC screening exists primarily in this age range. Although the average age of diagnosis is 69, the CRC incidence and mortality rate is growing in the younger population, individuals younger than 50 years old.[7] Even though younger patients are more likely to have hereditary diseases, most of the cases are sporadic with no family history.[89,90] Because screening is not recommended or covered by insurance for average-risk, young adults, this population tends to be diagnosed after symptoms manifest and in advanced stages.[89,91,92] However,

even when diagnosed in later stages, younger patients have survival at least as good as older CRC patients.[91]

2.4.4 Sex

Males have consistently had a higher CRC incidence and mortality rate than females, even as the overall rates continue to decrease. This is consistent across race, age, and colorectal sites.[93] The median age of diagnosis is 68 for men and 72 for women[7], and a similar mortality age gap is seen across multiple developed nations.[94] While men and women have similar stage at diagnosis, women have a higher 5-year survival, particularly for individuals under 65 years.[95,96] Men also have a higher prevalence of adenomas.[83,88] In SC screening cohorts with similar socioeconomic status and health care access, more adenomas and cancers were detected in men compared to women.[97,98]

The differences in CRC outcomes can be attributable to differences in biology, and lifestyle factors. Microsatellite instable tumors have better prognosis than non-MSI tumors, and are more prevalent in women than men.[99] The difference in penetrance of LS (i.e. women have lower lifetime risk of CRC) was attributable to lifestyle factors like diet, smoking habits, and estrogen exposure.[100] Epidemiologic studies have estimated a 20% reduction in colon and rectal cancer diagnosis and increased CRC survival for postmenopausal women who ever used hormone replacement therapy.[100] Women overall have a more consistent relationship with a physician, tend to be more knowledgeable about health literacy, and more willing to participate in CRC screening.[101,102] Further, single men (including those divorced, separated, or widowed) have a lower screening prevalence than those that are married or in a committed relationship.[103]

2.4.5 Race/Ethnicity

Ethnic minorities, particularly African Americans, have a higher incidence and mortality of CRC compared to White Americans.[3] While the burden of disease has decreased over time, this disparity has remained constant.[3,20,26,104] The incidence of CRC per 100,000 persons was 49.2 for African Americans, 45.7 for American Indian/Alaska Natives, 40.2 for White, 35.5 for Hispanic, and 32.2 for Asian Americans.[7] The disparity is consistent for CRC mortality as well; per 100,000, there were is 20.5 deaths for African Americans, 16.4 for American Indian/Alaska Native, 14.6 for White, 11.7 for Hispanic, and 10.3 for Asian Americans. African American and American Indian/Alaska Natives are also more likely to be diagnosed at later (distant) stages and have slightly lower 5-year survival rates.[7]

Research has consistently reported the differences in polyp distribution between African Americans and Whites. African Americans have a higher prevalence of proximal or right-sided polyps compared to Whites.[105–107] These findings are consistent with later stage diagnosis, and higher incidence and mortality for African Americans. These factors can be mitigated through regular screening. Screening is known to reduce the incidence and mortality of CRC[108–111], and accounts for approximately 40% of the racial disparities in these CRC outcomes.[86] Screening has increased for all US adults, but the racial disparities, like incidence and mortality, have remained persistent over time. The 2015 National Health Interview Survey (NHIS) estimates that 61.8% of African American, 54.3% of American Indian/Alaska Native, 65.4% of White, 49.9% of Hispanic, and 54.3% of Asian Americans were up-to-date on CRC screening of any kind.[86]

While race is genetically assigned and not modifiable, Simon et al suggested that disparities in CRC are not racially-related, but rather sociodemographic.[112] This is supported by the fact that, globally, African nations have significantly lower incidence and mortality rates compared to African Americans.[113] In South Carolina CRC screening programs for low-income and uninsured adults, there was no racial difference in the prevalence of polyps and adenomas.[97,98] Likewise, in the national Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial, a similar proportion of African American and White participants had abnormal flexible sigmoidoscopy reports, however African Americans were significantly less likely to receive a follow-up colonoscopy compared to Whites.[31] And among those that received the diagnostic colonoscopy, there were no significant differences in the presence or severity of adenomas. In addition, a national study on cancer survivorship found that the odds of cost-related medication non-adherence in older African American and Hispanic survivors were over two times the odds of White survivors.[16]

2.5 Lifestyle

Maintaining a healthy diet and physical activity (PA) is not only important for aiding in healthy body weight, but a healthy colon as well. Exhibiting a healthy lifestyle is the first line of defense in preventing chronic disease. The American Cancer Society (ACS) recommends that individuals should tailor their diets to maintain a healthy body weight, limit red and processed meat consumption, eat 2-3 cups of fruits and vegetables daily, and choose whole grains.[114] Research has consistently shown that the regular consumption of foods high in fiber lowers the risk of CRC.[66,115–117] The function of the

colon is to extract energy through fermentation of undigested food remnants.[66] Insoluble fibers, found in wheat bran foods, balance and control intestinal pH, and increase and move fecal bulk through the intestines, which reduce mucosal exposure to potential carcingens.[115]

Regular PA reduces the risk of chronic disease through the obesity pathway.[114] Globally, obese men and women have a higher risk of CRC than non-obese adults.[118] PA is also thought to have a direct impact on CRC as well, like decreasing gastrointestinal transit time, thus reducing exposure time to carcinogens and lowering insulin levels.[119] A recent meta-analysis estimates an 23% overall risk reduction in CRC for physically active adults, and an even lower reduction (44%) for adults with no family history.[120] Likewise, a 25% reduction in CRC-specific and all-cause mortality was estimated for pre-cancerous adults that participated in any PA with an increased protective dose-response effect for higher levels of PA.[121] Similar reductions in CRC incidence and mortality were observed for adults with higher BMI and smokers.[122–124]

Cigarette smoking and alcohol consumption are the top modifiable risk factors attributable to CRC incidence behind physical inactivity, accounting for 11.7% and 12.8% of cancer cases, respectively.[75] Longer duration and higher intensity of smoking were both found to be associated with an increased risk of CRC.[125] Along with current smokers carrying a higher risk than former smokers,[126] they also have worse overall and CRC-specific survival.[127] In addition, heavy drinkers, or those that consume a high volume of alcohol were consistently found to have an increased risk of CRC compared to non or light drinkers.[128–130] More specifically, a national study found that unhealthy lifestyle factors contribute significantly to the SES disparities seen in CRC risk.[131]

2.6 Screening

Screening is considered secondary prevention and is most effective if performed before disease symptoms arise. In 2010, approximately 63% of CRC deaths were attributable to lack of screening.[132] Average-risk adults are advised to undergo CRC screening between the ages of 50 and 75. Because sporadic CRC occurs at younger ages for African Americans, screening begins at age 45 for this population.[133] However, because of the increasing incidence in younger adults, the ACS updated the guidelines and recommends screening to begin at age 45 for all adults.[134] High-risk adults, or those with a family history, are screened more frequently and begin at earlier ages. There are various screening modalities that are currently in use by individuals and medical professionals. These methods can be broken up into three classes, from easy (cost and administering) to difficult: stool, imaging, and optical tests.

2.6.1 Stool Tests

Stool tests are relatively simple and can be completed without a physician. Stool tests detect blood in the stool, even if not visually noticeable, because CRC lesions (benign and cancerous) are more likely to bleed.[135] The Fecal Occult Blood Test (FOBT), Fecal Immunochemical Based Stool Test (FIT), and DNA Stool tests are among the most popular. FOBT works by using a chemical to detect a component of hemoglobin protein. Because this component, heme, is contained in some foods, dietary restrictions are necessary.[136] FIT is an improvement to the FOBT because it uses antibodies to detect the specific hemoglobin protein in humans and requires no dietary restrictions.[136] The DNA stool test use DNA mutations from the cells of the colonic mucosa (lining) as biomarkers

for CRC. For the most accurate results, individuals should collect samples from consecutive bowel movements.[135]

Although they are less invasive and easy to administer on a large scale, stool tests have a higher false-positive rate, and they can only detect blood or DNA changes in the stool, which may be indicative of cancer.[137] The U.S. Multi-Society Task Force (USMSTF) recommends a FIT every year as first-tier option, followed by a DNA stool test every three years as second-tier for average-risk populations.[138] If a stool test returns positive, it will need to be followed up with a colonoscopy. A randomized control trial (RCT) comparing FIT, FOBT, and FS found participation rates to be higher for FIT, and FS detected cancer at a higher rate followed by FIT.[139] Similarly, another RCT found a higher participation rate for FIT compared to colonoscopy, a comparable cancer detection, but a lower ability to detect adenomas.[140] However, the adenoma detection potential increases for positive-FIT followed by colonoscopy procedures.[141,142]

2.6.2 Imaging Tests

These tests allow the physician to visualize the colon without having to enter the colon. In a double-contrast barium enema (DCBE), the patient is given an enema with barium solution. Then, multiple x-ray images of the entire colon and rectum. A virtual colonoscopy, or computed tomographic (CT) colonography, uses a CT scanner to take multiple pictures of the colon and rectum that can show polyps or other abnormalities. Imaging tests can be more expensive than stool tests, requires no sedation, but still require a colonoscopy if the tests have abnormal findings. The USMSTF recommends a

CT colonography every 5 years as a second-tier option for average risk populations.[138] The 2018 ACS guidelines does not recommend DCBE as a screening modality.[134]

2.6.3 Optical Test

Optical tests involve the insertion of a scope through the anus, which requires stricter bowel preparation. The scope pumps air so the doctor can have a better visual of the colon. A flexible sigmoidoscopy (FS) uses a sigmoidoscope, a tube with a lens, to exam the rectum and distal colon. The physician can remove abnormal lesions that were located for a biopsy. Sedation is not usually required for this test. A colonoscopy examines the entire colon and rectum and can remove abnormal growths. Because of this, it is considered the gold-standard of all screening tests.

The USMSTF recommends a colonoscopy every 10 years as the first-tier option, followed by a FS every 5 years.[138] These recommendations are made from consistent evidence of a beneficial effect. Epidemiologic studies show a 77% and 65% reduction in CRC incidence and mortality due to colonoscopy, respectively when compared to no screening.[109,143,144] A meta-analysis on endoscopic screening revealed a 31% and 26% reduction in distal CRC incidence and mortality for FS in randomized control trials (RCT), respectively, which also included a one-time FS.[145] Further, RCT evidence shows a slightly lowered risk of all-cause mortality after FS screening.[146,147]

2.7 Surveillance after a CRC diagnosis

The number of cancer survivors continues to increase over time. In 2016, there were approximately 1.5 million CRC survivors (9% of all cancer survivors), and the

proportion is projected to be approximately the same by 2026 representing 1.8 million survivors.[148] After a cancer diagnosis, patients undergo a myriad of events to progress to survivorship: surgery and treatment regimens, adjustment of lifestyle behaviors, and coping with the reality of cancer.[149] One major adjustment is incorporating surveillance visits to prevent CRC recurrence. After curative resection of the colon or rectum, the USMSTF recommends the first surveillance colonoscopy one year after surgery, followed by a 3-year then 5-year colonoscopy.[15] In addition to the this regimen, patients diagnosed with localized rectal cancer should also receive surveillance through FS every three to six months for 2-3 years following surgery. One study estimated that only 18-61% of CRC survivors received a colonoscopy visit within 12-18 months of surgery.[44] The large variability in surveillance rates could be due to the cost. In addition, modifiable pre-diagnosis lifestyle factors like a healthy diet, PA, and not smoking have shown evidence in reducing the risk of CRC recurrence and prolonging survival.[11,13,121,150]

2.8 Endoscopist

Receiving timely CRC screening is imperative in reducing CRC risk, but the physician that administers these recommended endoscopic procedures also play a role. Gastroenterologists (GE) are internal medicine physicians that complete additional, on-going trainings to specialize in endoscopic procedures related to digestive health. Colorectal surgeons (CRS) are general surgeons that complete additional trainings for procedures of the colon and rectum. While GEs and CRSs perform a higher volume of colonoscopies, other physicians in general surgery and primary care (i.e. general internal medicine and family medicine) also perform colonoscopy.[151]

Differences in colonoscopy quality and later colorectal outcomes have been noted and vary by physician specialty.[152–155] While colonoscopy reduces CRC mortality overall, a national case-control study found that colonoscopies performed by GEs had the lowest odds of CRC mortality compared to other specialties.[156] A population-based Ontario study found that colonoscopies performed in hospitals by GEs reduced the risk of incident CRC compared to general surgeons.[157] In the Medicare population, patients that received a colonoscopy from general surgeons or other physicians had 1.3 and 3.0 times the risk of interval cancer, respectively compared to GEs.[158] In addition, CRSs were found to have better emergency surgery postoperative outcomes[159] and lower mortality rates after rectal surgery[160] compared to general surgeons.

Quality measures of colonoscopy like the cecal intubation rate (CIR), adenoma detection rate (ADR), withdrawal time, and polypectomy rate are associated with decreased postcolonoscopy CRC (PCCRC),[152,161–165] and also vary by endoscopist specialty. A Canadian study found that surgeons were half as likely to remove polyps that GEs.[153] Likewise, a U.S. study of average risk adults undergoing colonoscopy screening found that GEs had a higher proximal sessile serrated adenomas detention rate compared to surgeons.[166] In SC, the primary care physicians (PCPs) from the SC Medical Endoscopy Center receive training from GEs, CRSs, or a board-certified internist, and assistance from a gastrointestinal technician during the procedure. As a result, the quality metrics of CIR, polyp detection rate (PDR), ADR, withdrawal time, and minimal adverse events were comparable to the quality of GEs.[167]

Endoscopist volume is also related to the quality of the procedure, where quality metrics improve with the number of colonscopies,[168,169] but differ greatly by endoscopist

specialty.[170] Higher endoscopist and hospital volume were both found to be associated with a lower risk of mortality after colon cancer resection,[171,172] and 5-year survival.[155] In the Medicare population, surgeons that performed a very high volume of colon cancer resections had lower odds of postoperative complications.[173] However, in a group of general surgeons, higher volume was not associated with the ADR.[169]

2.9 Environmental Influences

2.9.1 Socioeconomic status

It has been said that socioeconomic status (SES) and zip code predicts our later health outcomes more than our genetic code. Epidemiologic studies have consistently shown that people with lower income have lower overall health, more hospitalizations, lower screening rates, and an overall lower life expectancy.[174–177] Numerous factors like lower health literacy and limited access to healthy food outlets contribute to these disparities.[178] For example, a systematic review found low health literacy to be associated with less preventative visits, higher emergency room utilization, and a contributor to racial health disparities.[179] The screening rate for CRC increases for every level of higher education as well as insurance status.[86] When considering CRC incidence by poverty level, the decreasing trend applied to mainly moderate to high income areas.[180]

2.9.2 Geographic location

Public health literature consistently recognizes geographic location as determinant of health. The built environment influences and affects the decisions that people make about their health. In particular, geographic distance can be a barrier to accessing health-

promoting opportunities and receiving health care.[181] Individuals that live further from health facilities have lower screening rates[182–184] and experience delayed or no care[185,186]. In addition, individuals that have less access or greater travel distance to care are often diagnosed with cancer at later stages[187–189] and have a higher mortality rate[190–192]. Some studies have also found geographic distance to PA opportunities and healthy food outlets create negative outcomes and inequities in health. In particular, residents with more access to supermarkets and limited access to convenient stores and fast food restaurants tend to have healthier diets and lower prevalence of obesity.[35] When multiple social determinants like race, SES, and geographic distance are interacting, CRC outcomes can be compounded.[23,193]

Rural families tend to be at the disadvantage as it relates to geographic distance and health. Compared to rural residents, urban residents have more flexibility in choosing a health facility, more access to specialists, and shorter travel distances.[194] For example, having more GEs reduced the delay in diagnosis in rural areas, but had no effect in urban areas.[195] There are larger clusters of health services and specialty doctors in urban areas compared to rural.[196] National studies reveal that as the level of rurality increase, the density of physicians decrease, with the most drastic declines in the proportion of available specialists.[197,198] Particularly in SC, many of the endoscopists performing colonoscopy primarily practice in urban areas, which include 87% of GEs and 100% of CRSs.[151] Thus, rural residents travel farther for overall care and CRC-related services.[184,199,200] As a result of these differences in access to care, rural residents have lower screening rates.[22,197,201]

2.9.3 Obesogenic Environment

An obesogenic environment is defined as the sum of influences that the surroundings, opportunities, or conditions of life have on promoting obesity in individuals or populations.[202] Chaput et al. noted that many of our modern comforts like readily available, high calorie food are counter to our natural biology.[203] Obesity is a natural response to obesogenic environments.[204] For example, a national study found the number of fitness centers and natural amenities to be negatively associated with obesity, while a higher number of fast food restaurants positively associated.[205] Lower income areas suffer the most harm from obesogenic environments. In particular, lower income neighborhoods were found to have a higher density of fast food outlets compared to higher income neighborhoods.[206]

There have been mixed findings about the relationship between the obesogenic environment and cancer. Canchola et al. found that traffic density was inversely associated with CRC risk in African American and Latino residents, but positively associated with White Americans.[40] Conroy et al. found that mixed-land development was positively associated with breast cancer risk in Latino women, but negatively associated with White women.[207] However, these studies did not find a significant association between the food and recreational environment with cancer, even with a large sample size. Therefore, it is possible that the obesogenic environment does not have a direct impact on cancer risk but operates through other pathways.

CHAPTER 3

METHODS

3.1 Data Sources

3.1.1 SC Ambulatory Surgery Discharge Database

The SC Ambulatory Surgery Discharge Database is an all-payer, population-based ambulatory outpatient database for endoscopic procedure claims in South Carolina between 2000 and 2014. The procedures (colonoscopy or sigmoidoscopy) were identified by the ICD-9 and/or HCPCS procedure code (see Appendix A). The de-identified database was constructed by the Revenue & Fiscal Affairs Office in Columbia, SC in 2017. Each claim (row) contains information about the patient, facility of procedure, and the physician(s) performing the procedure. The patient-level data include: a unique identifier, the month and year of the admission, diagnostic code(s), procedure code(s), payor, age group, race, sex, state, county and Zip code. The facility-level data include: name, address, county, and type. The physician-level data include: SC license number(s), physician National Provider Identification (NPI) number, and medical specialty. The 2009 and 2013 SC Medical Board licensing directory and the 2017 NPI registry were used to supplement physician specialty information.

3.1.2 Colorectal Cancer Prevention Network (CCPN)

In 2008, the Center for Colon Cancer Research at the University of South Carolina established the CCPN, a statewide screening program that promotes education

and awareness of CRC. The CCPN is a collaborative effort of patient navigators, board-certified gastroenterologists, licensed pathologists, and cancer treatment specialists. Eligibility for the program include: uninsured adults aged 50 – 64 (45 for African Americans) that lived at or below 150% of the federal poverty line and receive care from safety-net practices (like FQHCs and FMCs). Exclusion criteria include: having a colonoscopy within the last 10 years, symptoms of CRC, personal history of cancer, and other gastrointestinal-specific criteria. Colonoscopies were performed by board certified gastroenterologists, and diagnoses were confirmed by contracted pathologists. Data collection in this screening cohort includes over 1,000 variables about patient demographics, personal/family history, health behaviors, and clinical outcomes. The clinical outcomes include the colonoscopy results, quality metrics, and may include a pathology report about the findings of any cancer or lesions. More information about the CCPN can be found elsewhere.[97]

3.1.3 South Carolina Central Cancer Registry (SCCCR)

The SCCCR contains records for individuals diagnosed with cancer and living in SC from 2000 to 2014. For these aims, only a colorectal (colon or rectum) cancer diagnosis is relevant. This database contains demographic and clinical for data for each patient. The demographic information includes: sex, race, age, county, rurality, 2000 and 2010 patient ZCTA, census tract poverty indicator, and unique identifier. The clinical information include month and year of diagnosis, cancer sequence number, primary site, behavior, histology, stage, grade, laterality, cause of death, death status, survival time.

3.2 Paper 1

3.2.1 Study Population

The SC Ambulatory Surgery Discharge Database will be used to identify unique patients that visited a center for a screening colonoscopy between 2010 – 2014. To isolate screening procedures, patients will be excluded if younger than 50 and older than 75 years, had a previous CRC cancer diagnosis, a documented personal history of CRC, more than one colonoscopy within a 3-year period, or received an emergency colonoscopy. Personal history will be assessed based on procedure codes from the discharge database, and we will determine a previous cancer diagnosis by cross-referencing patient identifiers in the SCCCR.

3.2.2 Analysis

We will create facility catchment areas (CAs) for each colonoscopy facility in SC based on the location (i.e., ZIP code centroid) of patients seeking screening colonoscopies from each respective facility. For each facility, we will create a dataset with patient demographic data, which includes sex, race, age group, insurance, and ZIP code. To estimate the proportion of patients (from each ZIP code) that chose to visit a given facility (n = 98), we will utilize hierarchical Bayesian logistic regression as laid out by Wang and Wheeler.[208] The patient ZIP code will capture the residual effect after adjusting for demographic variables. The overall logistic model is:

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \beta_0 + \beta_1 Male_{ij} + \beta_2 Black_{ij} + \beta_3 Other_{ij} + \beta_4 Age60_{ij} + \beta_5 Age70_{ij} + \beta_6 Public\ Insurance_{ij} + \beta_7 Other\ Insurance_{ij} + v_i$$

where p_{ij} is the probability of person j from ZIP code i receiving a screening colonoscopy, and v_i is the ZIP code-specific random effect. The random effect is expected to capture the remaining heterogeneity of each ZIP code, like the rurality, local policies and norms, and socioeconomic features. The reference group is female sex, white for race, the 50 – 59 group for age, and commercial/HMO for insurance.

To fit the hierarchical Bayesian logistic model, we will use R2jags in R version 3.5.2. The exceedance probability for assigning a ZIP code to a CA will be $q = 0.95$. The exceedance probability is estimated by calculating the number of ZIP code odds ratios (ORs) from the posterior samples that exceed one. We will map the CAs to illustrate the regions that do not fall in any catchment area (Figure 1). We will also create tables with descriptive statistics to compare the demographics of patients inside and outside the CAs (Table 2) and the effect of the variables on the CAs (Table 3) of select facilities.

3.3 Paper 2

3.3.1 Study Population

This aim will utilize the CCPN data and the cohort that was screened between January 1, 2014 and August 31, 2018.

3.3.2 Obesogenic Environment Score

The obesogenic environment score is the exposure of interest and will be constructed using county and census tract data such as the median household income, food environment (retail, food deserts), neighborhood safety, and park availability. This score is currently in development by Principal Investigators Kaczynski and Eberth as part

of a cooperative agreement with the Health Resources and Services Administration (HRSA). The obesogenic environment score will be calculated at the county and census tract level using data from 2012 – 2014. The CCPN database will be merged to the obesogenic environmental score by the patient's county of residence at time of enrollment in the CCPN Program.

3.3.3 Outcomes

The outcomes of interest are 1) presence of any histologically-confirmed polyp or adenoma and 2) presence of any histologically-confirmed high-risk polyp or adenoma. High risk polyps are defined as any polyp 1 cm or greater, including hyperplastic, any traditional serrated or sessile serrated adenoma/ polyp, any polyp w/villous components, and/or high-grade dysplasia.[97] Low risk is considered to be all other polyps. Covariates of interest are age, sex, race, education, family history of CRC, obesity status (body mass index or waist-to-hip ratio), smoking history, alcohol consumption, comorbidities, urban/rural status, and area-level income.

3.3.4 Analysis

For this aim, we will estimate the effect of the obesogenic environment on the presence of polyps (overall and high-risk) through mediation analysis, where the mediator is obesity. We will use the mediation approach built from the counterfactual theory that incorporates exposure induced confounders (See Figure 3.1).[209] In addition, we will perform a sensitivity analysis to estimate the unmeasured effect of diet since this is an important confounders were either unmeasured or unreliable.

We will construct a table of demographics of the CCPN cohort of all participants, those with polyps, and those with high-risk polyps (Table 1). An additional table with the mediated effects, the controlled, direct, direct, and the total effect (Table 2). This table will house results for both outcomes (all polyps and high-risk polyps).

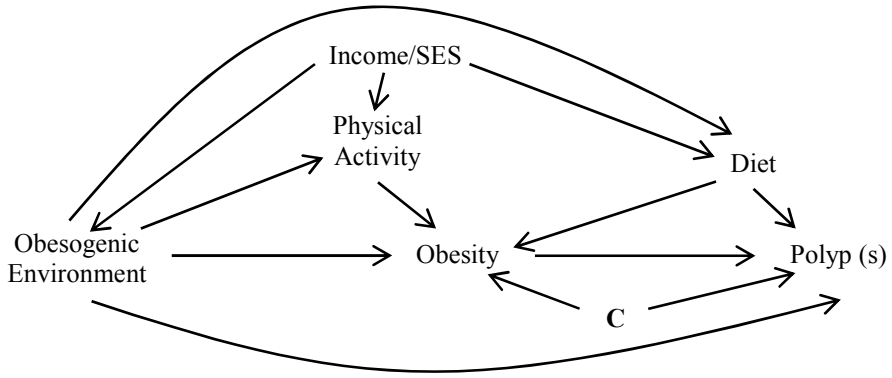

Figure 3.1. Directed acyclic graph illustrating the relationship between the obesogenic environment and polyps through obesity.

3.4 Paper 3

3.4.1 Study Population

The SC Ambulatory Surgery Discharge Database and the SCCCR will be merged to only include patients between the ages of 18 and 75 diagnosed with colorectal cancer between January 2001 and June 2013. Persons diagnosed in distant stage cancer, <65 years with Medicare, with an inflammatory condition, and death before the surveillance window will be excluded.

3.4.2 Outcome

Colonoscopy records between 2001 and 2014 for those diagnosed with cancer will be linked to the patient records to create the main outcome variable: adherence to the

1-year surveillance colonoscopy. It will be a binary variable (yes or no). The 1-year window is measured as 9 – 18 months after date of CRC diagnosis.

3.4.3 Analysis

We will use multivariate log binomial regression to model the prevalence ratio of adherence to surveillance colonoscopy within one year. An interaction term between age and race will also be tested to directly address this aim. Covariates include sex, primary insurance, stage at diagnosis (local or regional), tumor site (colon or rectum) and residential location (urban vs. rural). Descriptive statistics will be calculated and compared by adherence status (Table 1). In bivariate analyses, we will use the Chi-square test for categorical covariates and t-tests for continuous covariates. A model results table, stratified by age group, will present the effect of the variables on the surveillance (Table 2). Finally, we will calculate the age-adjusted prevalence of surveillance adherence over the study period and construct a figure to illustrate the trend overall and by race and sex (Figure 1).

CHAPTER 4

CATCHMENT AREA ANALYSIS FOR COLONOSCOPY CENTERS IN SOUTH CAROLINA[1]

[1] Josey MJ, McLain A, Merchant AT, Eberth JM to be submitted to *Health & Place*

4.1 Abstract

Colorectal cancer (CRC) is the third most common cancer in adults but is mostly preventable through a healthy lifestyle and screening procedures like colonoscopy. While colonoscopy can be a life-saving procedure, obstacles like lack of awareness and distance to care, particularly for rural residents, continues to be a barrier. The purpose of this study was to explore the geographic distribution of colonoscopy services by creating catchment areas (CAs) around each colonoscopy facility in South Carolina (SC).

We used the SC Outpatient Ambulatory Surgery Database to identify adults who received a screening colonoscopy between 2010-2014. Adults were included if they were between the ages of 50-74 and living in SC and excluded if they had a personal or suspected history of CRC or CRC-related diseases. We performed catchment area (CA) analysis using 2-stage Bayesian hierarchical logistic regression, with a ZIP code random effect. We repeated this model for all colonoscopy facilities in SC.

Of the 98 colonoscopy facilities, 96 had at least one ZIP code within its CA and covered 88% of ZIP codes in SC. Many ZIP codes, particularly those in metropolitan areas, were included in 2-3 CAs. Only 2% of patients resided in a ZIP code that fell outside of a CA, which were mostly along the state border.

The colonoscopy facilities reached a large portion of SC. While this study was on the actual utilization of patients that chose to be screened, the distance and other non-spatial barriers may still be present in the unscreened population.

4.2 Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women, and was estimated to be the 2nd leading cause of cancer death in South Carolina for 2018.[210] However, CRC is mostly preventable through regular screenings and a healthy lifestyle, which could advert 58% and 50% of incident CRC cases in men and women, respectively.[75] The U.S. Multi-Society Task Force (USMSTF) on CRC recommends colonoscopy as the primary tier procedure for CRC prevention because it can remove lesions from the colon, thus reducing or eliminating the potential for cancer.[138] Research has shown that colonoscopy prevents an estimated 77% of CRC-related deaths.[109,143,144]

Although colonoscopy can be a life-saving procedure, only 68% of age-eligible adults have received any CRC screening, with state-level rates as low as 50 - 60%, with adults aged 50 – 64 having the lowest rates.[7] The USMSTF recommends that adults participate in screening from age 50 through 75.[138] Barriers to screening, particularly for colonoscopy, include lack of awareness, cost, distance to care, and negative views about the procedure.[8–10] While there have been improvements in public awareness and cost, distance continues to be a barrier, particularly for rural residents. People that live in rural areas travel a longer distance to colorectal screening and care, and have almost twice the travel time compared to urban residents.[184,199] Amongst other factors, this obstacle manifests in higher incidence and mortality for rural residents.[33,211]

With largely preventable diseases like CRC, national committees set goals to increase screening utilization and reduce mortality rates. For example, HealthyPeople 2020 published a goal for 70.5% of recommended eligible adults to be up-to-date with

CRC screening guidelines by 2020.[212] More recently, the National Colorectal Cancer Roundtable set a goal for 80% of eligible adults to be up-to-date with screening by 2018 and encouraged local agencies and health facilities to partner with the mission by taking a pledge to action.[213] While these initiatives spark enthusiasm, they also draw attention to the issue of CRC screening capacity and handling an influx of new customers. In a simulation study, Joseph et al. found that in the first year, a colonoscopy-only screening program would require 16.2 million colonoscopies across the United States, with the maximum capacity (current and unrealized) being enough to handle the demand.[214] While capacity may be adequate nationally, some counties and states have found mixed results in their ability to handle the growing demand.[215,216] A study in Arizona found that urban and rural counties could increase their capacity by 36% and 53%, respectively, but only the urban counties needed more manpower to realize the maximum. In South Carolina (SC), the number of centers performing colonoscopy and the annual physicians volume of colonoscopies has noticeably increased in urban areas, but remained constant or declined over time in rural areas.[151] Therefore, it is necessary for researchers and health care providers to know the geographic distribution of services as well as target areas for potential growth, where services are most underutilized and where resources can be shared or expanded. One way to make inferences on the capacity of health care services is to investigate the spatial distribution of available resources and the potential consumer demand. In the healthcare field, a catchment area (CA) is a geographic region that contains a population of people that are more likely to utilize services at a specific health facility. A simple CA may include the population of people that live within a 30-minute or 30-mile buffer of the facility. However, this method assumes that people that do not

live in close proximity will not use the services. CA analyses continue to grow in complexity by taking into account commuting and public transportation,[217,218] urban versus rural driving normalcy,[219,220] and competing businesses[221].

We implemented a Bayesian Hierarchical method proposed by Wang and Wheeler that does not limit a CA to a specific distance or time boundary.[208] This is particularly important because these factors may not be as important when seeking elected, specialty services like colonoscopy, particularly in regions outside of major cities where driving is the most feasible mode of transportation. Therefore, individuals that are willing to travel farther have a chance to be included in the CA. In addition, many CA methods estimate the potential accessibility, however this method allows for retrospective, patient-level data to estimate the realized accessibility. Another aspect of this CA analysis is that it can quantify and illustrate where individuals choose to get a colonoscopy, and how their demographic characteristics affect the formation of each CA.

Currently, the literature is limited for CA analysis of healthcare facilities, particularly colonoscopy centers. Much of the current literature in the United States revolves around primary care facilities as opposed to specialty services. The purpose of this project is to illustrate and describe the catchment areas (i.e. service areas) of facilities in SC providing screening colonoscopies from 2010 – 2014, and the travel patterns of their patients. Using data from the population-based SC Outpatient Ambulatory Surgery Database, we examined travel patterns of age-eligible adults seeking a colonoscopy in SC. Specifically, our study aimed to identify areas within the state that underutilize colonoscopy screening and describe the characteristics of patients within (or outside) existing CRC screening facility CAs.

4.3 Methods

4.3.1 Data source

We used the all-payer, population-based SC Outpatient Ambulatory Surgery Database (ASD) for the years 2010 – 2014. This individual-level database houses demographic, insurance, zip code, and county data for colonoscopy patients, the SC license information and specialty code for physicians, and the name and address of the facility where the procedure was performed. The type of endoscopic procedure was classified using ICD-9, CPT, and HCPCS codes (see Appendix A). Only colonoscopy procedures were retained for this study.

4.3.2 Study population

The target population was adults living in SC that were eligible for a screening colonoscopy. The patients in this study were between the ages of 50 and 74, which is the recommended age range for colonoscopy screening. To isolate the screening-eligible population, patients were excluded if they were diagnosed with cancer prior to the colonoscopy or had more than one colonoscopy within a 3-year window because these patients are more likely to be on a more intense, surveillance regime. Patients were also excluded if they received a colonoscopy in the emergency room, which indicates a diagnostic or non-elected procedure.

4.3.3 Colonoscopy facility

Any SC facility performing at least one colonoscopy procedure for the screening-eligible population between 2010 and 2014 was eligible for inclusion in this study.

4.3.4 Statistical Analysis

We utilized the method presented by Wang and Wheeler, specifically a 2-stage Bayesian hierarchical logistic regression.[208] Our model estimates the probability, p_{ij} that a patient received a colonoscopy at a particular facility (yes or no). The model included a ZIP code random effect so we could estimate the residual variation in the odds of being screened at a facility after adjusting for demographic variables. For a ZIP code to be considered for inclusion in a CA, at least one patient from that ZIP code had to visit a colonoscopy facility. Therefore, if no one received a colonoscopy, all patients from that ZIP code was dropped from the analysis. The logistic regression model was:

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \beta_0 + \beta_1 Male_{ij} + \beta_2 Black_{ij} + \beta_3 Other_{ij} + \beta_4 Age60_{ij} + \beta_5 Age70_{ij} + \beta_6 Public\ Insurance_{ij} + \beta_7 Other\ Insurance_{ij} + \alpha_j$$

where α_j is the random effect of ZIP code j for patient i. The priors for the β coefficients were chosen to be non-informative from the Normal distribution with mean zero and precision of 0.00001 (which is equivalent to standard deviation of 1×10^5). The prior on the random effect was Normal with mean zero and precision τ, where the prior on τ was also chosen to be non-informative from the Gamma distribution with parameters $a = 0$ and $b = 0.0005$. We used two chains with 15,000 iterations each, a burn-in period of 10,000 samples per chain, and a thinning rate of 2, resulting in a total of 5,000 posterior samples. The starting values for the first chain was zero for each α and β coefficient, and 1 for τ. The starting values for the second chain was -1 for each α and β coefficient, and 10 for τ. We repeated this process for each colonoscopy facility in SC.

To determine if a ZIP code was included in a CA, we used a threshold exceedance probability, q_j. The exceedance probability is the number of times the odds ratio (OR) for

ZIP code *j* from the Monte Carlo Markov Chain (MCMC) posterior samples (after burn-in) exceeded one. We chose $q_j \geq 0.95$, which means: at least 95% of the ORs from the MCMC samples were greater than one, which indicates that the association between ZIP code *j* and the facility is larger than average after adjusting for the covariates (these are similar to hypothesis tests that the random effects are greater than zero). Our choice of q_j was more stringent than the conventional threshold chosen by Wang and Wheeler to try to capture ZIP codes that are truly included in a CA.[208] We also performed a sensitivity analysis using a range of thresholds (0.85, 0.90, 0.95).

The demographic variables included in the model were binary indicators for age group, sex, race, and insurance type. The reference level for each variable was 50 – 59 age group, female, white, and commercial/HMO insurance. To reduce the collinearity between age and insurance, a public insurance category was created that included Medicare and Medicaid. We also compared the patients and results by rurality status. Rurality was categorized using the 2010 Rural-Urban Commuting Area (RUCA) Codes by the United States Department of Agriculture. RUCA codes categorize areas based upon their population density and commuting patterns.[222] Patients were classified as either urban (codes 1.0, 1.1, 2.0, 2.1, 3.0, 4.1, 5.1, 7.1, 8.1, 10.1) or rural (4.0, 5.0, 6.0, 7.0, 7.2, 8.0, 8.2, 9.0, 10.0, 10.2, 10.3). The univariate associations with the covariates and being included in a CA were compared using the Chi-Square test and the Wilcoxon Sum-Rank (because of skewness) test for continuous covariates. The Bayesian hierarchical logistic models were fit and the maps created using the R2jags package and ggplot2 package, respectively in R version 3.5.2. The complete address for each facility

(street, city, zip) was geocoded in ArcGIS Pro with a match rate of at least 98.6%, and the ZIP code shapefile was publicly available and provided by ESRI.[223]

4.4 Results

There were 394,816 adults included in our study. Most of the colonoscopy patients were aged 60 – 69 (68%), female (56%), White (65%), used commercial/HMO insurance (53%), and resided in an urban ZIP code (93%); see Table 4.1. Only 9120 (2%) of patients resided in a ZIP code that was not included in a CA. The distance of the chosen colonoscopy facility was approximately two times the distance of the closest facility (5.71 vs. 11.86 miles), with rural patients traveling a greater distance, particularly for rural patients not within a CA. The age and sex demographic distribution of patients outside of a CA was similar to those within a CA. However, there was a larger proportion of White patients not included in CA (77% vs. 65%) and distribution of rural patients not included in a CA was significantly smaller (0.4% vs. 7%).

Between 2010 and 2014, there were 98 facilities that performed an average of 813 (SD = 802) screening colonoscopies per year. The CAs included 476 different ZIP codes, covering 88% of ZIP codes in SC. The average number of ZIP codes within a CA was 16 and ranged from zero to 63. Having zero ZIP codes in a CA means that a facility has no CA or had a very low chance of patients within those ZIP codes being screened there. On average, the longest distance patients within a CA traveled to the utilized facility was 8.7 miles. The mean CA size increased slightly between the current cutoff value $q_j = 0.95$ and 0.85 to 18 ZIP codes, and the maximum distance traveled stayed consistent at 8.9 miles in the sensitivity analysis. Facilities located in urban counties collectively reached 87% of

ZIP codes compared to 75% for rural facilities. Of the 62 ZIP codes not included in a CA, 15% were rural and clustered in the Midlands and Lowcountry counties bordering Georgia, which was similar to the overall distribution of rural ZIP codes in SC (13%).

Figure 4.1 shows the distribution of catchment areas of facilities performing screening colonoscopies in SC, where darker colors indicate more overlap of the CAs. Many of the colonoscopy facilities were clustered in urban areas with the darker shading, particularly the Charleston, Greenville, and Columbia metropolitan areas. Approximately 53% of the ZIP codes fell within 2-3 CAs, and ZIP codes with the most overlap (i.e. 12 CAs) were surrounding or within the most populated areas of SC like Richland and Charleston counties.

Table 4.2 shows a summary of the odds ratios of the variables included in the model for a sample facility in SC with a particularly large CA. Black patients and patients classified as Other race were significantly less likely to come to this facility (Black: OR = 0.42, 95% Confidence Interval (CI): 0.40, 0.44; Other race: OR = 0.04, 95% CI: 0.03, 0.04) compared to White patients. Those with public insurance were 29% less likely to come to this facility (OR = 0.71, 95% CI: 0.68, 0.75) and those with other insurance had 25% lower odds of coming to this facility (OR = 0.75, 95% CI: 0.70, 0.79) compared to those with commercial/HMO insurance. This facility provided one of the highest annual volumes, and provided colonoscopy services to patients from across SC.

4.5 Discussion

This study quantified and illustrated the CAs of centers providing screening colonoscopies in South Carolina using hierarchical Bayesian logistic regression. The CAs

of the colonoscopy facilities covered most ZIP codes in SC, overall and for urban and rural facilities separately. ZIP codes located in or near larger cities within the state had the most overlap and fell within multiple CAs. The CA sizes varied with most facilities having a large reach and span of customers across their county.

Like many specialty services, colonoscopy providers were clustered in urban areas. Although the facilities may compete for consumers, the CAs of these facilities overlap the surrounding population without a clear distinction. Wan et. al used a three-step catchment area method to address overestimation of clustered facilities and identify shortage areas.[221] Using the actual utilization of colonoscopy patients, our study was able to handle clustered facilities and identified shortage areas, which were mainly located along the edges of the state (i.e. edge-effect). This may not indicate underuse of colonoscopy screening because some of these patients may choose to go to an out-of-state facility in neighboring counties, which may be closer in distance and possibly covered by their employer and associated insurance plan. This is supported by our data; a larger proportion of patients in our study with commercial insurance were located outside of a CA than within compared to those with public insurance. In addition to the ZIP codes along the edges, ZIP codes that were comprised mainly of businesses (e.g. hospital and universities) were not estimated to be a part of any CAs, even if it was near a colonoscopy facility.

Previous literature has shown that rural areas have more barriers to receiving care than urban residents.[196,224] While rural patients in our study must travel farther for a colonoscopy, most patients from rural ZIP codes that chose to be screened were within at least one CA. McGrail and Humphreys used multiple distance buffers to account for rural

travelers.[219] Without presetting distance thresholds, our study identified multiple CAs that rural ZIP codes fell within, with a wide range of travel distances. While the patients in SC seeking a colonoscopy had the ability to bypass their closest facility, the CAs for the facilities generally represented the ZIP codes in closest proximity.

The implications of this study lay the groundwork for understanding the screening capacity and accessibility of physicians performing colonoscopy in SC. A physician being physically available does not imply access. For the same population, a study estimated the density of colonoscopy providers by adjusting for annual volume and down-weighting physicians that performed few procedures per year.[225] There were two facilities that did not have a CA, although they were identified as a colonoscopy facility. Thus, a simple count of physicians or facilities would overestimate the supply of physicians and facilities performing colonoscopy. In addition, a deeper investigation of the association of patient demographics on visiting a facility would further elucidate non-spatial barriers. Although most ZIP codes were included in at least one CA, inclusion does not indicate barriers or burden of travel. The patients in this study are those that chose to be screened and do not account for the 31% of eligible residents in SC that were not up-to-date with any CRC screening.[86] Future studies should consider the age-eligible population and their demographics to account for the unrealized potential.

There are a few limitations to consider. The purpose of this data was billing of administrative claims, and the accuracy was dependent on those coding the data. However, this dataset was extremely large, and thus more robust to non-systematic errors in original data. We were also unable to include out-of-state patients in our analysis because we did not have complete information about colonoscopy utilization of

neighboring states, although they were present in the original data. Thus, measuring capacity for screening colonoscopy should consider cross-state health seeking activity. By linking databases across state lines, future studies can quantify the additional demand of out-of-state patients. Also, the CA formation was dependent on a subjective cutoff value. We chose to use a more conservative value than the conventional value,[208] yet the results were similar and have a higher sensitivity, which was desired. Despite these limitations, using the population-based, all-payer ASD, this is the first study to quantify CAs for colonoscopy facilities for an entire state. Future studies should consider how CAs change as the health insurance landscape continues to evolve, specifically for screening or preventative procedures.

4.6 Conclusion

The reach of current facilities performing screening colonoscopies span the state of SC, leaving only a small proportion of residents outside of a CA. Urban facilities provided colonoscopy services for most SC patients. Yet, the presence of rural facilities remains important to serving current demands of rural residents, as well as the growing future capacity.

Table 4.1. Characteristics of patients seeking a screening colonoscopy in South Carolina, 2010 – 2014

Characteristic	All patients	In CA	Outside CA	*p*-value
***n* (%)**	394816 (100)	385696 (98)	9120 (2)	
Age				
50 – 59	99825 (25)	97288 (25)	2537 (28)	<0.001
60 – 69	268696 (68)	262695 (68)	6001 (66)	
70 – 74	26295 (7)	25713 (7)	582 (6)	

Sex				
Male	174839 (44)	170553 (44)	4286 (47)	<0.001
Race				
Black	73591 (19)	71825 (19)	1766 (19)	<0.001
White	256759 (65)	249724 (65)	7035 (77)	
Other	64466 (16)	64147 (17)	319 (3)	
Insurance				
Commercial/HMO	211756 (54)	206250 (53)	5506 (60)	<0.001
Public	152729 (39)	149500 (39)	3229 (35)	
Medicare	142300 (36)	139305 (36)	2995 (33)	
Medicaid	10429 (3)	10195 (3)	234 (3)	
Other	30331 (8)	29946 (8)	385 (4)	
Rurality				
Rural	26336 (7)	26296 (7)	40 (0)	<0.001
Distance (miles)	**Mean (SD)**			
Nearest facility	5.71 (5.07)	5.69 (5.09)	6.61 (4.03)	<0.001
Urban	5.53 (4.92)	5.50 (4.94)	6.60 (4.03)	<0.001
Rural	8.26 (6.24)	8.26 (6.25)	8.86 (3.50)	0.129
Chosen facility	11.86 (12.23)	11.92 (12.26)	9.16 (10.5)	<0.001
Urban	11.32 (11.72)	11.37 (11.75)	9.03 (10.2)	<0.001
Rural	19.39 (12.14)	19.36 (16.11)	43.71 (22.15)	<0.001
Footnotes: Distance was calculated as the straight-line distance from the ZIP code centroid to the colonoscopy facility. CA – Catchment Area				

Table 4.2. Odds ratios of patient demographics for a sample facility in South Carolina.

Coefficient	Odds Ratio	95% CI
Male	0.91	(0.87, 0.95)
Black	0.42	(0.40, 0.44)
Other race	0.04	(0.03, 0.04)
Age 60 – 69	1.05	(1.00, 1.10)
Age 70 – 74	1.25	(1.14, 1.38)
Public Insurance	0.71	(0.68, 0.75)
Other Insurance	0.75	(0.70, 0.79)

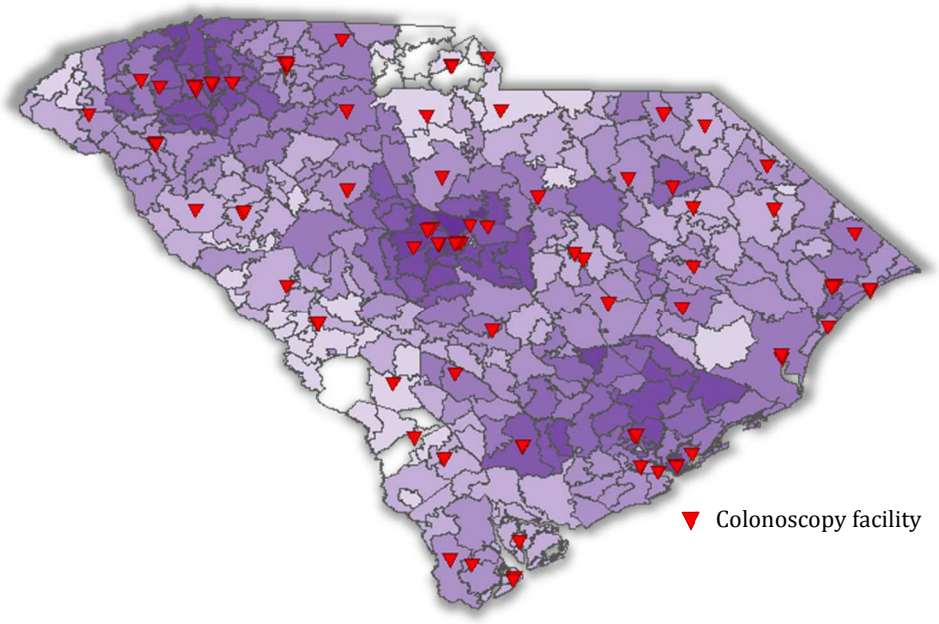

Figure 4.1. Map of the 98 colonoscopy facilities and their catchment areas in South Carolina, 2010 – 2014.

CHAPTER 5

THE OBESOGENIC ENVIRONEMNT AND COLORECTAL POLYPS: A MEDIATION ANALYSIS APPROACH[2]

[2] Josey MJ, Merchant AT, LaFrance D, Eberth JM, Caldwell R, Thibault A to be submitted to *BMC Public Health*

5.1 Abstract

Adenomatous polyps, or abnormal growths in the colon or rectum lining, account for 96% of all CRCs. While individual behaviors like smoking and poor diet play a role in the development of colorectal polyps, the environment also contributes to cancer outcomes. The obesogenic environment is a neighborhood-level measure of obesity-promoting attributes, and the relationship with CRC has mixed findings in the literature. The purpose of this study was to explore the pathways between the obesogenic environment and colorectal polyps.

The participants from this study were screened by colonoscopy through the Colorectal Cancer Prevention Network, a program for low-income, uninsured adults living in SC. Adults were included if they were 50-64 (or 45-64 for African Americans). We used mediation analysis to decompose the natural direct effect (NDE) and natural indirect effect (NIE) of the obesogenic environment on colorectal polyps through obesity. We considered both general and high-risk polyps as outcomes. We also ran a sensitivity analysis to adjust for unmeasured confounding.

Of the 959 participants included in the study, 63% and 15% had at least one polyp or high-risk polyp, respectively. The NDE for having a high-risk polyp was 0.74 (0.44, 0.99) for full-service restaurants. Obesity did not mediate the relationship between the obesogenic environment and colorectal polyps. The sensitivity analysis revealed that the food environment becomes more protective as unmeasured confounding increases.

Most of the obesogenic environment did not reduce the risk of having colorectal polyps. While people may not be able to move to a better environment, creating a healthy lifestyle within any community can offset the neighborhood-level influences.

5.2 Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death in the United States (U.S.).[210] In 2013, an estimated 800,000 person-years of life lost was due to CRC.[226] However, a healthy lifestyle and regular screening CRC can reduce occurrence of new cases and CRC-related deaths.[1,6,7] Approximately 90% of new CRC cases and deaths occur in adults aged 50 and older, respectively.[86] Thus, the Multi-Society Task Force on CRC recommends screening for the average-risk population aged 50 – 75 years. Nationally, the CRC screening prevalence has increased for this group, from 52% in 2008 to 67% in 2014.[227,228] However, an estimated 63% of CRC deaths in 2010 were attributable to non-screening.[132]

Research shows a 77% and 65% reduction in CRC incidence and mortality, respectively due to receipt of at least one colonoscopy.[143,144] Colonoscopy is the primary (first tier), recommended modality for cancer prevention due to its ability to remove potentially cancerous legions or polyps.[134,138] Polyps are precursors to CRC and vary in size and location, where each contributes to the severity and development of CRC. Hyperplastic polyps are very common, but rarely develop into cancer,[49] while adenomatous polyps account for 96% of all CRCs.[7] Some lifestyle behaviors are associated with the development of polyps. For example, smoking was shown to increase the risk of serrated polyps, a highly malignant adenoma that accounts for 30% of CRCs.[52] In addition, poor diet, particularly those lacking fiber, and a lack of physical activity are hypothesized to increase the risk of CRC.[66,116,117] Higher fiber diets and physical activity decrease the transit time of fecal bulk in the intestines, which reduces the exposure time of potential carcinogens on the colon lining.[115,119]

While individual behaviors play a role in the development of CRC, the environment has also been shown to contribute to various cancer outcomes. Pesticides, radiation, fibers and dust, metals, and second-hand smoke have been found to be associated with an increased risk of multiple cancers, particularly organs in the respiratory system.[229] Beyond influences of the physical environment, the "built environment" has more recently been investigated for its role in the development of cancer. People are nested within their communities, and while they are mobile, the ability to participate in health-promoting opportunities is often dependent on their immediate environment. For example living in a more walkable neighborhood was associated with higher physical activity levels.[230] Better access to healthy food (e.g. from grocery stores or supermarkets) and limited access to convenience stores has been associated with healthier diets and healthier weight.[35] Disparities arise because healthy food tends to be more expensive and lower income and rural residents live further from healthy food and closer to fast food.[231]

The obesogenic environment is a measure of neighborhood-level obesity-promoting attributes, such as high density of fast food restaurants and fewer grocery stores and physical activity locations. Obesity is strongly correlated with CRC,[2,232] with obese adults having a 20% higher risk of developing CRC than non-obese adults.[232] Obesity was also estimated to be attributable to 5.2% of CRC cases.[75] Figure 1 shows our hypothesized, literature-supported relationship between the obesogenic environment, obesity, having at least one polyp identified during a screening colonoscopy.

There is a gap in the literature about the relationship between the obesogenic environment, individual level obesity, and CRC. A national study found traffic, vehicle

transit, and more restaurants to be associated with an increased risk of CRC in some ethnic subgroups.[40] Further, the association between the obesogenic environment and precursors to CRC (i.e. polyps) has yet to be quantified. This study proposes to consider the bigger picture of the relationship between the obesogenic environment and polyp risk. Research consistently supports the path from the obesogenic environment to obesity,[207] as well as the path from obesity to the presence of colorectal polyps.[120,233] However, the path through obesity has yet to be quantified (see indirect pathway in Figure 3.1). While people that live in an obesogenic environment may develop CRC through obesity, this study seeks to determine if there is a direct effect of the environment on CRC independent of individual-level obesity. Using a standardized population that controls for many SES factors like income and insurance access, we will address the following aims:

1. Examine the pathways between the obesogenic environment and the presence of CRC polyps.
2. To explore whether the association of the obesogenic environment on the presence CRC polyp(s) differs by polyp type (any and high-risk).

Hypotheses:

1. The pathway between the obesogenic environment and having a polyp is mostly mediated through obesity.
2. The direct pathway (not through individual-level obesity) has a stronger effect on high-risk polyps than the general class of polyps.

5.3 Methods

5.3.1 Study Population

The participants from this study were screened through the Colorectal Cancer Prevention Network (CCPN), a program established by the Center for Colon Cancer Research at the University of South Carolina as a strategic method to reduce CRC morbidity and mortality disparities in SC. The CCPN is a navigation program that provides free colonoscopy screenings to low-income, uninsured adults by partnering with Free Medical Clinics and Federally Qualified Health Clinics throughout the state. The program utilizes the services of board-certified gastroenterologists, pathologists, and cancer treatment specialists. Additional information about the CCPN is available elsewhere.[97]

To be eligible for inclusion in the CCPN, potential participants had to be aged 50 – 64 or 45 – 64 for African Americans, live at or below 150% of the federal poverty line, and uninsured. This analysis included CCPN participants who had a colonoscopy between January 2014 and August 2018. Individuals were excluded if they had a colonoscopy within the past 10 years, a personal history CRC, recently experienced CRC-related symptoms, a known history of inflammatory bowel disease, or a personal history of cancer other than skin cancer. CCPN gastroenterologists can also exclude individuals from screening based on other personalized factors such as morbid obesity. The program guidelines are in alignment with the U.S. Multi-Society Task Force recommendations for CRC screening of the average-risk population.[138]

5.3.2 Mediation

Valeri and Vansteelandt (2009) introduced a causal mediation analysis method using the counterfactual approach to decompose and estimate the controlled direct, natural direct, and indirect effects of an exposure on an outcome.[234] In this study, the controlled direct and natural direct effects are equivalent because we do not believe that there is an interaction between the obesogenic environment and obesity. The controlled direct effect (CDE) is the average difference of having a polyp had all the participants lived in a highly obesogenic environment versus if all participants lived in a lower obesogenic environment across all obesity levels. Similarly, the natural direct effect (NDE) is the average difference of having a polyp had all the participants lived in a highly obesogenic environment versus if all participants lived in a lower obesogenic environment, and all participants were not obese. The natural indirect effect (NIE) is the average difference of having a polyp had all the participants lived in a highly obesogenic environment then became obese versus living in a highly obesogenic environment and not becoming obese. The same interpretations hold for high-risk polyps.

The assumptions for this causal mediation analysis are: no unmeasured confounding between the exposure and outcome, exposure and mediator, mediator and outcome, and none of the mediator-outcome confounders are induced (or caused) by the exposure. However, because diet is unmeasured, sensitivity analyses are necessary to estimate the possible effect on the results (Figure 3.1). The remaining variables in the minimally-sufficient set to control for confounding are income/SES, and the variables included in C. Because our population is restricted to low-income, uninsured adults in SC, this is a feasible model to estimate.

5.3.3 Exposure

The main exposure for this study is the obesogenic environment. The obesogenic environment index (OEI) was created by a team of researchers at the University of South Carolina in a project funded by the Federal Office of Rural Health Policy on childhood obesity. The process of constructing the index began with compiling area-level variables from a comprehensive literature review, then verifying them in an expert review. Ten final variables that were potentially associated with childhood obesity were included in the index, nine at the county level and one at the state level. The publicly available variables were the availability of: grocery stores and superstores, farmers markets, fast food restaurants, full service restaurants, convenience stores, exercise opportunities, school proximity, walkability, violent crime, and births at baby-friendly facilities (state-level). Grocery stores/superstores, farmers markets, births at baby-friendly hospitals, exercise opportunities, school proximity, and walkability were hypothesized or previously shown to be inversely related to obesity and were reversed coded so that lower OEI meant a healthier environment. The variables were then ranked and allocated a percentile, where 0 = least obesogenic/healthy and 100 – most obesogenic/unhealthy. The final county-level OEI was the average percentile across all non-missing variables. Only 6% of U.S. counties had missing data (1, 2, or 3 variables), with zero missing data for SC counties. We assumed that the patients lived in the same or a county with similar exposure levels during the polyp development period.

5.3.4 Mediator

The mediator was whether the participant was obese. Obesity status was determined by the standard definition of having a body mass index (BMI) greater than 30 kg/m^2. Measurement of height and weight were self-reported and compared to measures from recent office visits within 7 – 30 days of the colonoscopy.

5.3.5 Outcome

The primary outcomes were 1) the presence of any histologically-confirmed colorectal polyp or adenoma (yes/no) and 2) the presence of any histologically confirmed high-risk polyp or adenoma. High risk polyps are defined as any polyp one cm or greater, including hyperplastic, any traditional serrated or sessile serrated adenoma/ polyp, any polyp w/villous components, and/or high-grade dysplasia.[97] If participants did not have a subpathology report, they were removed from the high-risk polyp analysis (n = 237).

5.3.6 Confounders

The variables considered for entry in the model were age at program inclusion, sex, race/ethnicity, highest attained education, family history of CRC, smoking history, alcohol consumption, non-steroidal anti-inflammatory drugs (NSAIDs) usage, physical activity, income level, and urban/rural designation. Age was categorized as 45-49, 50-54, 55-59, and 60-64. Race/ethnicity was classified as Non-Hispanic Black, Non-Hispanic White, or other. Education was categorized as: less than high school (HS), GED or HS diploma, some college or Associate's degree, or Bachelor's degree or higher. Family history of CRC was determined if the participant reported having a mother, father, or

sibling ever diagnosed with CRC. NSAID utilization was indicated by NSAID or aspirin usage and categorized as daily, 4 – 6 days, 1 – 3 days, or zero days per week. Physical activity (PA) was measured as the number of days during the last week spent doing no, moderate, or vigorous physical activity. We categorized PA to be in close alignment with the standards for PA; whether a participant was moderately or vigorously active for zero days, 1-3 days, 4-6 days, and 7 days per week.

Smoking status was categorized using the CDC definition for never, former, and current smoker.[235] Alcohol consumption was also determined by the CDC.[236] Heavy consumption was defined as having greater than 14 and 7 drinks per week for men and women, respectively. Moderate consumption was having no more than two drinks and one drink per day (which we expanded to ≤14 and ≤7 per week) for men and women, respectively. And no consumption was zero drinks per week. ZIP code level median household income was obtained from the 2007-2011 American Community Survey, an ongoing survey performed by the U.S. Census Bureau that provides area-level sociodemographic information and categorized into tertiles.[237] Urban/rural status was determined using the ZIP code approximated 2010 Rural-Urban Commuting Area (RUCA) Codes by the United States Department of Agriculture. RUCA codes categorize areas based upon their population density and commuting patterns.[222] A participant was considered an urban resident if their ZIP code RUCA was metropolitan (RUCA = 1.0, 1.1, 2.0, 2.1, 3.0, 4.1, 5.1, 7.1, 8.1, 10.1) and rural otherwise. Participants were excluded if they were missing any covariate (n = 30).

5.3.7 Statistical Analysis

We used the chi-square test for categorical variables in the univariate analysis. The mediation analysis utilized the product method described by Valeri and VanderWeele to estimate the decomposition of effects (direct and indirect) of the exposure on the outcome.[238] The confidence intervals were estimated using 1000 bootstrap samples. We used logistic regression to estimate the effect of the exposure on the mediator (obese vs. not obese) and loglinear regression to estimate the effect of the exposure and mediator on the outcome (polyp vs. no polyp). The parameter estimates from the two models were used to estimate the natural direct effect (NDE) and the natural indirect effect (NIE), which were interpreted as relative risks (RR). A sensitivity analysis for unmeasured confounding of a mediator-outcome confounder was conducted using a method proposed by Vanderweele and Chiba.[239] The sensitivity analysis explores how the estimates would change over values of the expected relationship between the exposure, mediator, and all measured and unmeasured confounders on the outcome. We categorized the composite OEI and individual variables by classifying each as 'high' if greater than or equal to the 75th percentile and low otherwise. All variables in the OEI were in the analysis except availability of baby-friendly hospitals because it was a state-level variable and does not vary among participants in SC. Data management was carried out in R version 3.5.2 and analysis was carried out using the mediation macro in SAS by Valeri and VanderWeele.[238]

5.4 Results

The final sample included 959 adults that had a colonoscopy within the study period. Table 1 shows that most the study population was aged 50-54 (44%), non-Hispanic Black (53%), obtained a high school diploma (42%), lived in an urban ZIP code (84%), had no family history of CRC (94%), and lived in a low-level obesogenic environment (73%). Many of the participants were also current (39%) or never smokers (40%), consumed moderate levels or no alcohol (47% each), were obese (51%), and either never took NSAIDs (32%) or took at least one NSAID daily (31%). The overall polyp detection was 63% and was higher in males (68% vs. 60%; $p < 0.01$), urban residents (65% vs. 54%; $p = 0.02$), current smokers ($p < 0.001$), and heavy drinkers ($p = 0.044$). The high-risk polyp detection was 15% and did not vary by any demographic or lifestyle variables.

The mediation analysis revealed that features of the obesogenic environment were not associated with having any colorectal polyp. For high-risk polyps, the NDE was 0.74 (95% CI: 0.44, 0.99) for full-service restaurants and non-significant for the remaining index and composite variables. Obesity did not mediate the association between the obesogenic environment and having a polyp or high-risk polyp.

The sensitivity analysis revealed that as the (realistic) differences in the outcome of having a polyp increased between the exposed and unexposed populations, the direct effect became stronger and more protective across the food environment, specifically grocery store and convenience store availability. The difference in the proportion of having a polyp across the exposure levels amongst obesity groups had to be at least 10% for the residual confounding to reduce the risk of polyps. Farmers markets and restaurant

access required stronger differences. The direct effect remained null across the physical activity environment and the overall composite score. For the high-risk polyps, the difference in the outcome by exposure and mediator required for the residual confounding to affect the risk of polyp was complex for many of the obesogenic variables. The food environment had similar findings as general polyps, however, fast food restaurant access only required a 1% difference. Access to PA locations and the composite OEI reduced the risk of high-risk polyps when differences were at least a 5%. As the difference in the outcome increased across the exposure populations (1%), the indirect effect of the exposure on the outcome through the obesity increased for all polyp types, increasing the risk of having a polyp.

5.5 Discussion

Full-service restaurants had an unexpected direct and preventative effect on having a high-risk polyp. Obesity did not mediate the relationship between the individual variables or composite OEI on the risk of having a polyp. However, the sensitivity analysis showed how accounting for unmeasured confounding increased the strengths of the associations. Therefore, our hypotheses were somewhat confirmed in this study. Rather, elements of the obesogenic environment seem to have an independent effect on risk of polyps in this low-income, uninsured population.

Grocery/superstore availability has been hypothesized to be associated with positive health outcomes, although there have been mixed findings in the literature.[35,240] Cummins et al. found that after the establishment of a new grocery store, dietary habits of residents remained unchanged.[241] Likewise, a longitudinal study found that grocery store

availability was unrelated to changes in fruit and vegetable consumption.[242] Restaurants tend to be clustered in urban areas,[231] so it is possible that these associations are indicative of the type of neighborhood and its associated assets that might contribute to more positive health outcomes (e.g., density of primary care physicians). Our study included area-level income and rurality; future studies could explore how the obesogenic environment affects the risk of polyps when considering the individual distance to food and the PA environments.

There have been various findings about the relationship between physical activity and CRC.[124,244] Epidemiologic studies suggest that physical activity could prevent CRC by reducing or maintaining a healthy body weight, or improving circulation and metabolism.[75,114,119] Boehmer et al. found that the being located farther from physical activity locations and feeling unsafe due to crime to be associated with obesity.[245] Another study found that non-socially isolated adults that lived in areas with more access to physical activity locations were less likely to be physically inactive.[246] Through the sensitivity analysis, we found that having a higher availability of physical activity locations could potentially reduce the risk of high-risk polyps. Future studies on the obesogenic environment and cancer should also consider the social networks of individuals because the social environment can be more influential than the geography of the built environment.[247]

In this population, the polyp detection rate (PDR) for overall and high-risk for obese participants was slightly lower compared to the normal weight participants. This may be unique to the low-income, uninsured population, as overweight and obese adults overall tend to have more polyps than normal weight adults.[248–250] This dynamic directly

affected the overall results of the study. Previous research have reported mixed findings about the availability of food outlets and body weight, noting that residential access to various types of food outlets does not encompass the total utilized food resources (e.g. while at work or in transit).[243] Similarly, Fuzhong et al. found that positive OEI features, like walkability, was associated with a decrease in body weight, while negative features like fast food restaurants, was associated with an increase in body weight, among those that utilized these outlets.[242] In our sensitivity analysis, we found that when accounting for unmeasured confounding, particularly individual diet, obesity mediated the relationship of the exposure on the outcome by increasing the risk of having a polyp, as the difference in the outcome across the exposure levels increased. In addition, we found that aspects of the food environment were possibly protective of colorectal polyps.

There are a few limitations to consider. Our data did not include information on individual diet patterns. However, we were able to include a sensitivity analysis that accounted for unmeasured confounding to find that the food environment may have a stronger effect on the risk of having a polyp. We also used county-level data to measure the area-level obesogenic environment. While counties are macro-level in nature, we were able to find a significant effect on the outcome. Future studies could utilize smaller areas to measure the neighborhood obesogenic environment, or a GIS approach to capture individual proximity. Despite these limitations, the CCPN cohort is ideal for making causal inferences on colorectal outcomes because it was a controlled population where many barriers to accessing colonoscopy were removed. The CCPN cohort also represents a hard-to-reach population, and more likely to contribute to those with higher incidence and mortality in SC, thus these estimates are extremely meaningful.

5.6 Conclusion

Although the obesogenic environment is thought to be obesity-promoting, obesity did not mediate the effect of the environment on the odds of having polyp in a controlled population. There were direct effects of the environment on colorectal polyp risk. While people may not be able to move to a better environment, creating a healthy lifestyle within any community can offset neighborhood-level influences. Obesity is not the sole measure for health status, so future studies should examine the additional ways that the obesogenic environment affects CRC outside of the commonly studied pathways.

Table 5.1. Characteristics of participants and polyp detection in the CCPN Program, January 2014 – August 2018.

			Polyp Detection	
Characteristic	**Overall Population**		**Any polyp**	**High-risk polyps** [a]
No. of participants (%)	959		606 (63.2)	114 (15.8)
Demographics				
Age			$p = 0.2642$	$p = 0.3149$
45 – 49	46 (4.0)		31 (67.4)	3 (8.1)
50 – 54	422 (44.0)		252 (59.7)	45 (14.2)
55 – 59	300 (31.3)		198 (66.0)	40 (17.7)
60 – 64	191 (19.9)		125 (65.5)	26 (18.3)
Sex			$\mathbf{p = 0.0058}$	$p = 0.2404$
Male	378 (39.4)		259 (68.5)	54 (17.6)
Female	581 (60.6)		347 (59.7)	60 (14.4)
Race			$p = 0.4499$	$p = 0.3899$
Non-Hispanic Black	507 (52.9)		311 (61.3)	53 (14.1)
Non-Hispanic White	399 (41.6)		260 (65.2)	53 (17.3)
Other	53 (5.5)		35 (66.0)	8 (20.0)
Education			$p = 0.1815$	$p = 0.1576$
Less than High School	250 (26.1)		167 (66.8)	38 (20)
High School Diploma	405 (42.3)		254 (62.7)	39 (12.6)
Some college/Associate's degree	243 (25.4)		154 (63.4)	29 (16.0)
Bachelor's degree or higher	60 (6.3)		31 (51.7)	8 (20.5)
ZIP code-level income ($)			$\mathbf{p = 0.0467}$	$p = 0.1832$
≤ 35,297	338 (35.3)		197 (58.3)	45 (18)
≤ 43,133	305 (31.8)		206 (67.5)	39 (16)

≤ 77,901	316 (33.0)		203 (64.2)	30 (12)
Rurality			***p* = 0.0205**	*p* = 0.1340
Urban	801 (83.5)		519 (64.8)	91 (14.9)
Rural	158 (16.5)		87 (55.1)	23 (20.5)
Family History of CRC			*p* = 0.1090	*p* = 0.3213
No	903 (94.2)		565 (62.6)	104 (15.4)
Yes	56 (5.8)		41 (73.2)	10 (20.8)
Obesogenic Environment			*p* = 0.5219	*p* = 0.2033
Low	703 (73.3)		440 (62.6)	88 (16.9)
High	256 (26.7)		166 (64.8)	26 (13.0)
Lifestyle				
Smoking status			***p* < 0.001**	*p* = 0.2568
Never	386 (40.3)		215 (55.7)	35 (13.1)
Former	196 (20.4)		122 (62.2)	24 (16.0)
Current	377 (39.3)		269 (71.4)	55 (18.1)
Alcohol Consumption			***p* = 0.0436**	*p* = 0.8478
None/Low	454 (47.3)		277 (61.0)	51 (15.3)
Moderate	450 (46.9)		286 (63.4)	55 (15.9)
Heavy	55 (5.7)		43 (78.2)	8 (18.6)
Obesity			*p* = 0.5334	*p* = 0.3345
Underweight	11 (1.2)		9 (81.8)	0
Normal weight	172 (17.9)		111 (64.5)	26 (19.6)
Overweight	288 (30.0)		184 (63.9)	32 (14.5)
Obese	488 (50.9)		302 (61.9)	56 (15.6)
NSAID Use			*p* = 0.0978	*p* = 0.7740
None	303 (31.6)		202 (66.7)	38 (16.0)
Occasionally	184 (19.2)		117 (63.6)	21 (15.8)
1 – 3 days/week	129 (13.5)		86 (66.7)	19 (19.8)
4 – 6 days/week	48 (5.0)		33 (68.8)	6 (15.8)
Daily	295 (30.8)		168 (57.0)	30 (13.8)
Procedure Quality				
Bowel Preparation			*p* = 0.4914	*p* = 0.7936
Excellent/Good	868 (92.1)		551 (63.5)	101 (15.3)
Fair/Poor	74 (7.9)		44 (59.5)	8 (16.7)
Footnotes: [a] This number is based on the 722 participants that had a subpathology report.				

Table 5.2. Decomposition of effects of the obesogenic environment on having a polyp

		Decomposition of Effects (RR)		
Obesogenic Environment Index		**NDE**	**NIE**	**Total Effect**
Any Polyp				
Food Environment				
Grocery Stores	↓	0.92 (0.81, 1.00)	1.00 (0.99, 1.00)	0.92 (0.81, 1.00)
Farmers Markets	↓	0.97 (0.87, 1.08)	1.00 (0.99, 1.00)	0.97 (0.87, 1.08)
Convenience Stores	↑	0.94 (0.74, 1.02)	1.00 (0.99, 1.01)	0.94 (0.74, 1.02)
Full-Service Restaurants	↑	1.01 (0.93, 1.09)	1.00 (0.99, 1.01)	1.01 (0.93, 1.09)
Fast Food Restaurants	↑	1.00 (0.92, 1.07)	1.00 (0.99, 1.00)	1.00 (0.92, 1.07)
Physical Activity Environment				
School Access	↓	1.04 (0.97, 1.14)	1.00 (0.99, 1.01)	1.04 (0.97, 1.14)
PA Access	↓	0.99 (0.90, 1.08)	1.00 (0.98, 1.00)	0.98 (0.90, 1.08)
Walkability	↓	1.05 (0.97, 1.15)	1.00 (0.99, 1.01)	1.05 (0.97, 1.15)
Violent Crime	↑	1.02 (0.93, 1.10)	1.00 (0.99, 1.01)	1.02 (0.93, 1.10)
Composite Score	↑	1.01 (0.93, 1.09)	1.00 (0.99, 1.00)	1.01 (0.93, 1.09)
High-Risk Polyp				
Food Environment				
Grocery Stores	↓	0.91 (0.60, 1.27)	1.00 (0.98, 1.02)	1.26 (0.77, 1.96)
Farmers Markets	↓	0.91 (0.54, 1.35)	1.00 (0.98, 1.02)	0.91 (0.54, 1.35)
Convenience Stores	↑	0.86 (0.53, 1.17)	1.00 (0.98, 1.03)	0.86 (0.53, 1.17)
Full-Service Restaurants	↑	**0.74 (0.44, 0.99)**	1.00 (0.96, 1.03)	**0.74 (0.44, 0.99)**
Fast Food Restaurants	↑	0.78 (0.49, 1.03)	1.00 (0.98, 1.02)	0.78 (0.49, 1.02)
Physical Activity Environment				
School Access	↓	1.04 (0.68, 1.51)	1.00 (0.96, 1.03)	1.04 (0.68, 1.51)
PA Access	↓	0.86 (0.53, 1.21)	1.00 (0.97, 1.02)	0.86 (0.53, 1.20)
Walkability	↓	1.05 (0.70, 1.51)	1.00 (0.96, 1.03)	1.04 (0.70, 1.48)
Violent Crime	↑	0.99 (0.67, 1.39)	1.00 (0.99, 1.02)	0.99 (0.67, 1.39)
Composite Score	↑	0.84 (0.53, 1.14)	1.00 (0.99, 1.01)	0.84 (0.53, 1.14)

Footnotes: * $p < 0.05$, ** $p < 0.001$

The logistic and loglinear models used to calculate the natural direct effect (NDE), natural indirect effect (NIE), and the total effect (TE) adjusted for sex, smoking status, weekly alcohol consumption, NSAID use, ZIP code-level income and rurality. The controlled direct effect (CDE) = NDE since both the exposure and mediator are binary. The decomposed effects are interpreted as risk ratio (RR). The high-risk mediation analysis was based on the 722 participants that had a subpathology report. The arrows represent the expected direction of the association on having a polyp.

CHAPTER 6

INCREASED INSURANCE ACCESS AND SURVEILLANCE OF COLORECTAL CANCER[3]

[3] Josey MJ, McLain A, Merchant AT, Eberth JM, Schootman M. Submitted to *Cancer Causes & Control*, 7/18/19

6.1 Abstract

Surveillance colonoscopy is recommended one year after a colorectal cancer (CRC) diagnosis and treatment to prevent cancer recurrence, but uptake is suboptimal and understudied among minority populations. We examined whether racial disparities in adherence to surveillance are less pronounced over time in older (age 65+) versus younger CRC survivors (age <65) due to improved access to health insurance.

We linked colonoscopy records from the population-based, all-payer SC Outpatient Ambulatory Surgery Database from 2001-2014 to the SCCCR to identify those diagnosed with a primary CRC from 2001-2013. We calculated the age-adjusted prevalence of one-year surveillance and used multivariable loglinear regression to model the prevalence ratio of adherence to colonoscopy within one year (9-18 months) after CRC diagnosis. Covariates included race, sex, primary insurance, stage at diagnosis and urban/rural status. The final model was stratified by year of diagnosis (2001-2007 and 2008-2013) to determine if disparities persist over time.

Among the 9016 survivors included in the study, 5041 (56%) received a colonoscopy within 1-year of diagnosis. The difference in adherence between White and Black survivors fell from 9.2% to 3.7% for men and 8.9% to -1.0% for women from 2002 to 2013. Among younger male survivors, the prevalence of adherence was 14% lower in Black versus White survivors over time. However, the disparity was no longer present in the older survivors in the later years.

The disparity in receiving a 1-year surveillance colonoscopy diminished over time between Black and White survivors, but younger Black male survivors remained at increased risk of recurrence due to lower surveillance colonoscopy adherence.

6.2 Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States (U.S.) and the third leading cause of cancer death in both men and women in 2018.[1] The recent decline in CRC incidence and mortality has been attributed to increased screening and improved treatment.[2] The 5-year survival rate has also increased over time, ranging from 14% for distant stages to 90% for localized stages.[3] Although there are overall improvements in morbidity, mortality, and late staging of CRC, racial and socioeconomic disparities in CRC outcomes persist.[4,5]

The burden of a cancer diagnosis does not necessarily end with treatment. Cancer survivorship begins when a person is diagnosed and continues until death. In 2016, there were approximately 1.5 million CRC survivors in the U.S.,[6] a 25% increase from 2012.[7] In addition to coping with a life-altering disease, life after a cancer diagnosis includes a plethora of changes including treatment, interacting with new doctors, adjusting to a wellness plan, and handling financial stresses.[8] The Institute of Medicine and the National Research Council name prevention, surveillance, intervention, and coordination as essential components of survivorship care in the health care delivery system.[9] For CRC survivors in the U.S., having health insurance is imperative to begin to navigate this system and help alleviate the added financial stress. For example, in the U.S., the average out-of-pocket cost of a colonoscopy is $3000,[10] a cost that is typically absorbed under the Affordable Care Act when it is considered a preventive, screening procedure. However, for diagnostic or surveillance procedures including post-CRC colonoscopy, individuals may face high deductibles and cost-sharing with their insurance. Research has shown that

ethnic minorities are less likely to receive cancer follow-up care,[11] and face more financial hardship during survivorship[12].

The U.S. Multi-Society Task Force on CRC recommends a surveillance colonoscopy one year after curative resection (treatment) of the colon or rectum, followed by a three-year and five-year colonoscopy.[13] Observational studies and randomized controlled trials found surveillance colonoscopies to be associated with reduced CRC recurrence and improved overall survival.[13] A systematic review in 2013 found that 18 – 61% of survivors received a post-treatment colonoscopy within 12 – 18 months.[14] Adherence to surveillance colonoscopy among specific subgroups is not as well-studied as screening adherence,[15,16] therefore disparities have also yet to be quantified. While there have been improvements in CRC screening uptake over time, these results cannot simply be extrapolated to CRC surveillance. While many states have established CRC screening programs and insurance coverage is more comprehensive for screening, few have done so focusing on surveillance following cancer diagnosis.

The purpose of this study was to determine adherence to guideline-concordant surveillance colonoscopy, overall and by racial subgroup, over time in South Carolina. We hypothesize that the disparity between older (65+ years) Black and White CRC survivors will be significantly reduced compared to younger CRC survivors (<65 years) due to increased access to health insurance coverage (i.e. Medicare benefits).

6.3 Methods

6.3.1 Data Sources

The South Carolina Ambulatory Surgery Database (ASD) is a retrospective, longitudinal population-based data set of outpatient procedures performed in SC. Using ICD-9 and HCPCS codes (in Appendix A.1), we identified records indicating colonoscopy between 2001 and 2014. This database provides patient demographic and procedure information like age, race, sex, insurance, county, zip code, and colonoscopy date. The South Carolina Central Cancer Registry (SCCCR), one of the National Program of Cancer Registries, contains records on all individuals diagnosed with cancer in SC. In addition to demographic characteristics, the registry has clinical data like age at diagnosis, stage, location, grade, laterality, cause of death, and survival time.

The ASD was merged with the SCCCR by a unique, de-identified patient identifier to determine if a cancer patient received a colonoscopy after CRC diagnosis. The ASD database was constructed and merged with the SCCCR by the South Carolina Revenue & Fiscal Affairs (RFA) Office in 2017.

6.3.2 Study Population

The target population for this study was adults living in SC that were diagnosed with a primary CRC between January 2001 and June 2013. Survivors were included if they were adults between the ages of 18 and 75. This upper age limit coincides with the current CRC screening guidelines; there is no standard for surveillance colonoscopy in elderly patients; it is based on the individual life expectancy.[17] Individuals were excluded if they were diagnosed with in-situ or distant stage CRC according to SEER stage, as the

surveillance recommendations were based on patients in stages I – III.[13] Individuals were also excluded if they were younger than 65 years and their primary payer was Medicare because these patients tend to be less healthy prior to a diagnosis due to co-occurring disease such as end-stage renal disease (ESRD). We also excluded individuals that died before the end of the surveillance window. Finally, individuals were excluded if diagnosed with an inflammatory condition (e.g. Crohn's disease, ulcerative colitis, irritable bowel syndrome) to reduce the likelihood of accounting for patients that had a total colectomy.

6.3.3 Outcome

The outcome of interest was whether an individual received a colonoscopy 1 year after a CRC diagnosis (yes/no). The 1-year window was measured as 9 – 18 months after CRC diagnosis to allow for scheduling difficulties and post-diagnosis clearing procedures.

6.3.4 Statistical Analysis

We used multivariable log binomial regression to model the prevalence ratio (PR) of adherence to the 1-year surveillance colonoscopy. An interaction term between age (at diagnosis) and race was included to assess if there are differences in the adherence prevalence. We divided the study window into two (semi-equal) time periods to determine if racial disparities were consistent over time: diagnosis year between 2001-2007 or 2008-2013. Demographic covariates included were sex, primary insurance (Commercial/HMO, Medicare, Medicaid, Other), and rurality (urban vs. rural). Race was

categorized into Black, White, or Other. The final model considered all race by sex subgroups, as heterogeneity exists within these groups,[3,18] however model results for 'Other' race will not be reported due to the small sample size. Rurality was defined using the 2003 Rural-Urban Continuum Code (RUCC) Codes by the United States Department of Agriculture. A survivor was considered an urban resident if their county RUCC was considered metropolitan or urban (RUCC = 1,2,3) and rural otherwise (RUCC=4-9). Clinical covariates were stage at diagnosis (local or regional), and primary cancer site (colon or rectum).

Because both the ASD and SCCCR are population-based databases, including a near census of colonoscopies provided and cancers diagnosed in SC, we calculated the age-adjusted prevalence of surveillance adherence for each year using the Surveillance, Epidemiology, and End Results Program (SEER) guide for calculating age-adjusted rates.[19] The adherence prevalence was measured for the year following the diagnosis. We calculated the prevalence for the overall population and by race and sex subgroups from 2002 – 2013. Differences in demographics variables were calculated using the Chi-square test, and the significance level was 0.05.

6.4 Results

There were 8,869 patients included in the final sample (Figure 1). The age-adjusted prevalence of adherence to the 1-year surveillance colonoscopy post-diagnosis was 55.7% for CRC survivors in SC across the entire study period and remained stable over time; 57.0% in 2002 to 54.0% in 2013 (p_{trend} = 0.17*)*. White survivors had a significantly higher prevalence of adherence compared to Black survivors across the

study period (58.2% vs. 50.0%, $p < 0.001$). Over time, the racial difference in colonoscopy adherence by sex diminished. Figure 2 shows that adherence difference between White and Black men fell from 9.0% in 2002 to 3.0% in 2013 ($p_{trend} = 0.10$). For women, the difference between White and Black survivors fell from 9.4% in 2002 to -0.7% in 2013 ($p_{trend} = 0.002$; see Appendix B.1).

Table 1 shows that survivors residing in urban areas had a higher adherence prevalence compared to rural survivors (57.6% vs. 51.4%, $p < 0.001$), and those with Other insurance or that self-paid for the procedure had a lower prevalence compared to commercial/HMO and Medicare ($p < 0.001$). Those diagnosed with colon cancer were more likely to adhere compared to rectal cancer survivors ($p < 0.001$), and a higher proportion of survivors that received the 1-year colonoscopy were alive at the end of the study ($p < 0.001$).

The interaction between race and age was significant in the log binomial model ($p < 0.001$). Table 2 shows that Black male survivors were approximately 13% less likely to adhere to the 1-year surveillance colonoscopy compared to White males for the younger age group across both time periods. Older Black males were less likely to adhere compared to White males in the early study period [PR = 0.73, 95% Confidence Interval (CI): (0.62, 0.87)] but were no different in the later years [PR = 1.01 (0.86, 1.18)]. Younger Black females were less likely to adhere to the surveillance colonoscopy in the early years compared to White men [PR = 0.82 (0.73, 0.92)], but were no different in the later years [PR = 0.98 (0.88, 1.10)]. There were no significant differences between older Black women or White women overall compared to White men.

Younger survivors that self-paid were less likely to adhere compared to those with commercial/HMO insurance for the early years [PR = 0.72 (0.61, 0.85)] and the later years [PR = 0.85 (0.74, 0.98)]. For the older age group, there were significantly fewer survivors that self-paid and no difference was detected compared to commercial/HMO insurance.

6.5 Discussion

This study quantified the prevalence of adherence to surveillance colonoscopy after CRC diagnosis over time and determined if increased access to health insurance reduced racial disparities in colonoscopy adherence. Over half (56.0%) of CRC survivors received their first surveillance colonoscopy within the recommended timeframe. This study showed that young White survivors had a higher prevalence of adherence and were more likely to receive a colonoscopy compared to young Black (male) survivors, regardless of the time period. However, this disparity was eliminated for the older age group (65+ years) in the later end of the study period, supporting our hypothesis of diminished racial disparities in the older population.

In comparison to our estimated SC statewide adherence rate (56%), a study using electronic medical records of health systems across various states also found that 55% of CRC survivors received a colonoscopy within 18 months of curative surgery.[20] Overall, it is difficult to compare studies because of different study settings and analytic designs. For example, a cancer institute in Alberta, Canada observed an adherence rate of 67% where their study participants were enrolled in a surveillance program.[21] Older national studies report large racial disparities in receiving a surveillance colonoscopy for both the

Medicare-eligible and younger populations.[22,23] Our study shows the reduction in these disparities over time and also reflects how surveillance uptake has increased over time, particularly for older Black survivors, but not yet for younger Black survivors.

Our results show the powerful role that insurance can play in the health care delivery system. Survivors younger than 65 years that self-paid were less likely to adhere compared to all other insurance types. While disparities diminish when opportunities are available, access to health insurance is not always enough to completely remove the financial burden that comes with being a cancer survivor. For example, Lee and Salloum found that Black and Hispanic survivors were two times more likely to experience cost-related medical non-adherence compared to White cancer survivors.[12] Under the Affordable Care Act, colonoscopies for high-risk individuals, particularly those with a personal history (i.e. survivors), will more than likely have to share the cost of the procedure.[24]

There are limitations of this study to consider. There was no available individual-level socioeconomic (SES) variable in the cancer registry or ambulatory surgery discharge database. When using surrogate SES variables at the aggregate level, like the census tract poverty index, the values were similar across adherence groups and were not significant in a univariate model. However, primary insurance is highly correlated with household income,[25] and was included in the models. It is possible that an accurate measure of individual SES is a true confounder and explains the remaining difference in prevalence by race. A Veteran's Affairs study found that White veterans were 32% less likely than Black veterans to receive a surveillance colonoscopy within 7 – 18 months.[26] In addition, we were unable to disentangle whether patients had a total colectomy and

needed a surveillance colonoscopy. However, survivors included in the study were diagnosed in local and regional stages and no record of an inflammatory disease. Total colectomy is mainly an option for adults with inflammatory diseases or genetic conditions, which represents a very small proportion of CRC cases.[27] We were unable to include CRC survivors in the model if they had no colonoscopy record in the ambulatory surgery discharge database, which houses their insurance information. This could include CRC survivors receiving their surveillance colonoscopies out-of-state or within the Veteran's Affairs healthcare system. However, this only accounted for 7% of the total cancer registry records within the study period and this is unlikely to explain our findings.

6.6 Conclusion

This study highlights reductions in racial disparities in surveillance colonoscopy following CRC diagnosis. Closing the surveillance adherence gap is instrumental in reducing the overall burden of CRC. Access to health insurance coverage seems to play a role in these improvements. Future studies should monitor surveillance adherence following CRC as the landscape of insurance availability and cost continues to evolve in the U.S. It is possible that future changes could help improve utilization in younger Black men.

Table 6.1. Baseline characteristics of adults diagnosed with CRC from 2001 – 2013.

Characteristic	Adherence Prevalence (95% CI)		Adhered *n* (%)	Did not adhere *n* (%)	*p*-value
	56.0 (54.9, 57.0)		4964 (56.0)	3905 (44.0)	
Demographic					
Sex					0.041
Male	54.9 (53.0, 56.9)		2561 (51.6)	2101 (53.8)	
Female	57.1 (55.1, 59.1)		2403 (48.4)	1804 (46.2)	
Age					0.017
18 – 64	57.1 (55.3, 58.9)		2913 (58.7)	2192 (56.1)	
65 – 75	54.5 (52.3, 56.7)		2051 (41.3)	1713 (43.9)	
Race					<0.001
White	58.2 (56.6, 59.7)		3766 (75.9)	2710 (69.4)	
Black	50.1 (47.2, 53.0)		1143 (22.8)	1131 (29.0)	
Other	50.0 (37.8, 62.2)		64 (1.3)	64 (1.6)	
Primary Insurance					<0.001
Commercial/HMO	58.5 (56.5, 60.4)		2495 (50.3)	1773 (45.4)	
Medicare	56.1 (53.8, 58.4)		1770 (35.7)	1385 (35.5)	
Medicaid	52.3 (45.8, 58.9)		223 (4.5)	203 (5.2)	
Self-Pay	45.4 (38.3, 52.4)		192 (3.9)	231 (5.9)	
Other	47.6 (41.8, 53.4)		284 (5.7)	313 (8.0)	
Rurality					<0.001
Urban	57.6 (56.0, 59.2)		3762 (75.8)	2770 (70.9)	
Rural	51.4 (48.6, 54.3)		1202 (24.2)	1135 (29.1)	
Census Tract Poverty					<0.001
<5%	60.9 (56.6, 65.2)		508 (10.1)	330 (8.3)	
5 – <10%	58.6 (55.7, 61.5)		1144 (22.7)	813 (20.4)	
10 – <20%	55.3 (53.1, 57.8)		2003 (39.6)	1615 (40.7)	
20 – 100%	53.4 (50.8, 56.1)		1379 (27.5)	1207 (30.6)	
Clinical					
Stage					<0.001
Local	53.2 (51.3, 55.2)		2529 (50.9)	2221 (56.9)	
Regional	59.1 (57.2, 61.1)		2435 (49.1)	1684 (43.1)	
Primary Site					<0.001
Large Intestine	58.6 (57.0, 60.1)		3930 (79.2)	2780 (71.2)	
Rectum	47.9 (44.8, 50.9)		1034 (20.8)	1125 (28.8)	
Alive at study end	58.4 (56.8, 60.0)		3734 (75.2)	2661 (68.1)	<0.001

Footnotes: The unadjusted prevalence of the 1-year surveillance colonoscopy (95% CI) and the proportion of those that did and did not adhere to across the study period.

Table 6.2. Adjusted prevalence ratios (95% CI) stratified by diagnosis year and age group for adherence to the one-year surveillance colonoscopy.

		2001 – 2007	2008 – 2013
< 65 Population			
Race by sex	White male	1.00	1.00
	White female	1.04 (0.98, 1.12)	1.06 (0.98, 1.15)
	Black male	0.87 (0.78, 0.97) *	0.86 (0.76, 0.98) *
	Black female	0.82 (0.73, 0.92) ***	0.98 (0.88, 1.10)
Rurality	Urban	1.00	1.00
	Rural	0.87 (0.80, 0.94) ***	0.91 (0.84, 0.99) *
Insurance	Commercial/HMO	1.00	1.00
	Medicaid	0.86 (0.74, 1.00)	0.98 (0.87, 1.10)
	Self-Pay	0.71 (0.60, 0.85) ***	0.85 (0.74, 0.98) *
	Other	0.82 (0.72, 0.93) **	0.87 (0.77, 0.98) *
Stage	Local	1.00	1.00
	Regional	1.15 (1.08, 1.22) ***	1.10 (1.03, 1.18) **
Primary Site	Large Intestine	1.00	1.00
	Rectum	0.83 (0.77, 0.90) ***	0.78 (0.71, 0.85) ***
Race by sex	White male	1.00	1.00
	White female	0.97 (0.90, 1.05)	1.01 (0.91, 1.13)
	Black male	0.73 (0.62, 0.87) ***	1.01 (0.86, 1.18)
	Black female	0.91 (0.81, 1.04)	1.02 (0.88, 1.19)
Rurality	Urban	1.00	1.00
	Rural	0.89 (0.82, 0.97) **	0.93 (0.83, 1.04)
Insurance	Commercial/HMO	1.00	1.00
	Medicare	1.10 (0.97, 1.26)	1.15 (1.00, 1.32) *
	Medicaid	0.41 (0.12, 1.42)	0.96 (0.61, 1.51)
	Self-Pay	0.91 (0.51, 1.62)	0.65 (0.28, 1.49)
	Other	0.63 (0.35, 1.13)	0.49 (0.24, 1.01)
Stage	Local	1.00	1.00
	Regional	1.08 (1.00, 1.16) *	1.03 (0.94, 1.13)
Primary Site	Large Intestine	1.00	1.00
	Rectum	0.88 (0.79, 0.97) *	0.83 (0.72, 0.95) **
Footnotes: * $p < 0.05$, ** $p < 0.01$, § $p < 0.001$			

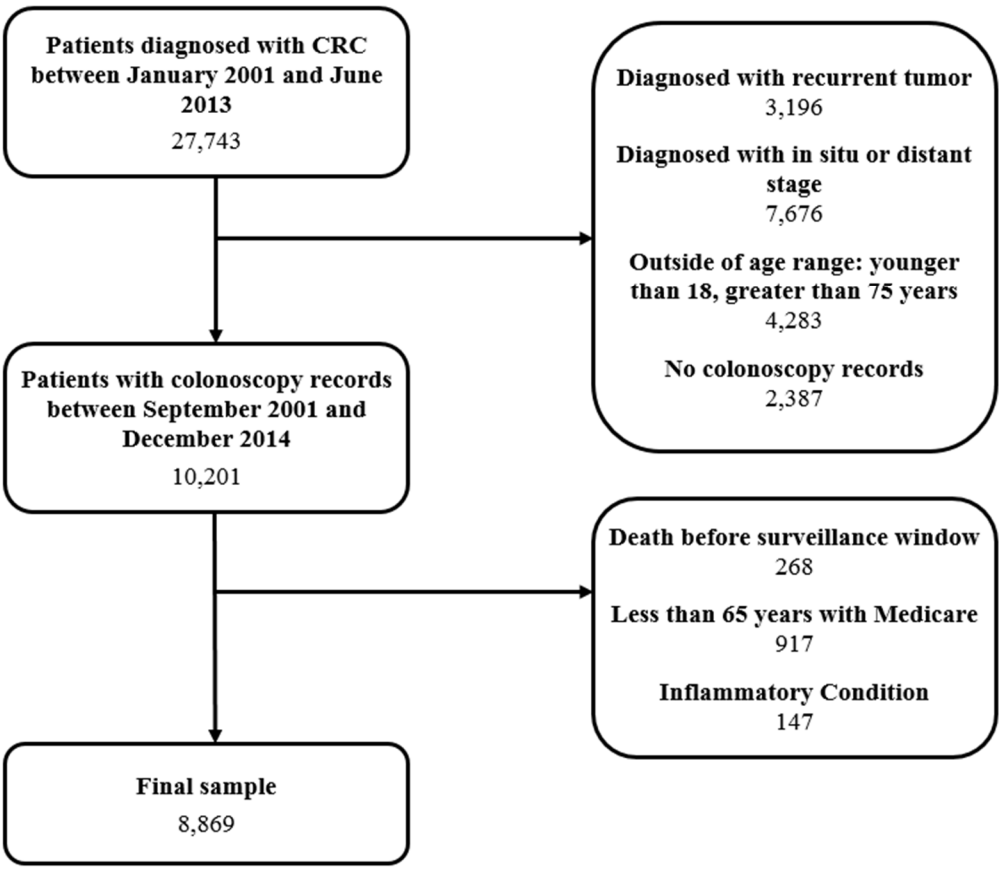

Figure 6.1. Formation of the study population of adults diagnosed with CRC.

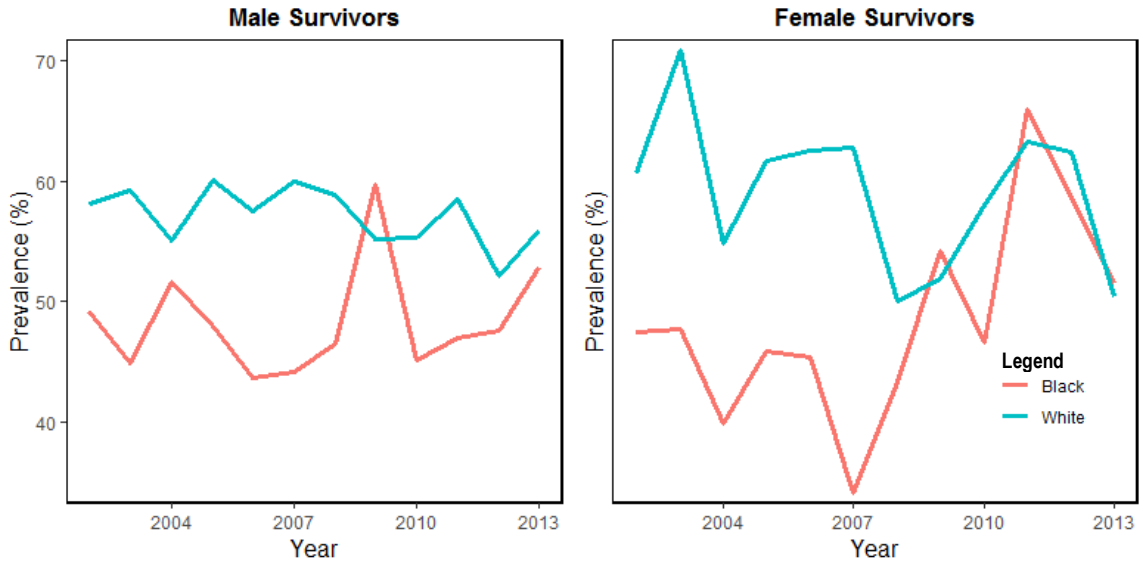

Figure 6.2. Age-adjusted prevalence of one-year surveillance colonoscopy in South Carolina for male and female CRC survivors from 2002 – 2013.

CHAPTER 7

SUMMARY

This dissertation provides a wide view of CRC, from screening access to surveillance uptake. This is the first study to examine the CAs colonoscopy facilities for an entire state, specifically using a method that modeled the realized demand. We also used a unique approach to learn how the obesogenic environment affects colorectal polyps, through different pathways. Finally, we provided the one-year surveillance colonoscopy prevalence over time for the population of CRC survivors in SC and identified racial disparities.

Chapter 4 illustrated how the colonoscopy centers in SC provided services for patients across the entire state. Overall, the CA method was able to examine the realized accessibility or utilization of patients receiving a screening colonoscopy in SC. The catchment areas of these facilities span 88% of the ZIP codes in SC, leaving only a small fraction outside of CAs, which were mainly along the state borders. Fifty-three percent of the ZIP codes fell into 2-3 different CAs, which were typically located near the most populated areas in SC. Diving further into each CA could elucidate accessibility to facilities beyond geography. While most of the ZIP codes were included in at least one CA, the patients in this study only represented individuals seeking a screening colonoscopy and do not account for diagnostic or surveillance colonoscopies. Future methods should account for the unscreened population as well as other colonoscopy

procedures in order to expand these results to estimating the true available screening capacity of colonoscopy providers.

The obesogenic environment measures the obesity-promoting aspects of a neighborhood or community. While there have been mixed findings between the obesogenic environment and CRC, work needs to be done to understand the relationship with the precursor to CRC, or polyps. Polyps that continue to grow without being removed can progress to cancer. In Chapter 5, we found that full-service restaurants had a direct effect on having high-risk polyps. Our sensitivity analysis showed that when accounting for unmeasured confounding, the positive aspects of the food environment had the potential to reduce the risk of having a polyp. Research has shown that living in an unhealthy environment does not always imply that one would have an equivalent lifestyle. Even if one lives in an unhealthy environment, making good health decisions within those communities can offset the overall effect of the environment. Our sensitivity analysis also showed that obesity does mediate the effect of the obesogenic environment on having a polyp and increased the risk of colorectal polyps. Future studies should investigate what aspect of the obesogenic environment not through obesity has an effect on colorectal polyps (e.g. water and air quality).

In Chapter 6, we explored whether increased access to health reduced racial disparities in surveillance colonoscopy over time. Surveillance colonoscopies are beneficial to survivors to prevent recurrence of CRC and prolong survival. The prevalence of receiving a surveillance colonoscopy in SC decreased slightly over time from 57% to 54% overall, from 58% to 56% for White men, 49% to 53% for Black men, 60% to 53% for White women, and 51% to 53% for Black women from 2002 to 2013.

For adults younger than 65 years, there was a disparity in receiving a surveillance colonoscopy where Black survivors were 14% less likely to receive the colonoscopy compared to White survivors during both time periods. For Medicare-eligible adults at least 65 years in age, the disparity was eliminated in the later study period. Having more access to health insurance played a role in reducing the disparity in receiving timely care to prevent cancer recurrence. Future studies could investigate how the disparities change as the health care market continues to evolve, particularly for those that were formerly uninsured.

Colorectal cancer is primarily preventable through a healthy lifestyle, which includes regular screening colonoscopies and surveillance colonoscopies for recurrence prevention. For SC, most of the age-eligible adults for CRC screening have access to available resources. In addition to having available colonoscopy facilities, having access to healthy outlets is beneficial to adults in reducing the risk of colorectal polyps. Taking these steps have shown to prevent CRC. However, once CRC is discovered, early if screened regularly, survivors can prolong their survival by receiving regular surveillance colonoscopies. Future qualitative studies can explore what empowers individuals to engage in healthy decision-making (like health screenings) in order to help tailor community messages that would be effective in preventing chronic diseases like CRC.

REFERENCES

1. Haggar F, Boushey R. Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. *Clin Colon Rectal Surg*. 2009;22(04):191-197. doi:10.1055/s-0029-1242458
2. Øines M, Helsingen LM, Bretthauer M, Emilsson L. Epidemiology and risk factors of colorectal polyps. *Best Pract Res Clin Gastroenterol*. 2017;31(4):419-424. doi:10.1016/j.bpg.2017.06.004
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30. doi:10.3322/caac.21387
4. American Cancer Society. *Colorectal Cancer Facts & Figures, 2014-2016*.; 2014. https://old.cancer.org/acs/groups/content/documents/document/acspc-042280.pdf.
5. Lai SM, Zhang KB, Uhler RJ, Harrison JN, Clutter GG, Williams MA. Geographic variation in the incidence of colorectal cancer in the United States, 1998-2001. *Cancer*. 2006;107(5 Suppl):1172-1180. doi:10.1002/cncr.22014
6. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet*. 2005;366(9499):1784-1793. doi:10.1016/S0140-6736(05)67725-2
7. American Cancer Society. *Colorectal Cancer Facts & Figures 2017 - 2019*.; 2017. doi:http://dx.doi.org/10.1016/S0140-6736(13)61649-9
8. Beyer KMM, Malecki KM, Hoormann KA, Szabo A, Nattinger AB. Perceived Neighborhood Quality and Cancer Screening Behavior: Evidence from the Survey of the Health of Wisconsin. *J Community Health*. 2016;41(1):134-137. doi:10.1007/s10900-015-0078-1
9. Lasser KE, Ayanian JZ, Fletcher RH, Good M-JD. Barriers to colorectal cancer screening in community health centers: A qualitative study. *BMC Fam Pract*. 2008;9(1):15. doi:10.1186/1471-2296-9-15
10. Honein-AbouHaidar GN, Kastner M, Vuong V, et al. Systematic Review and Meta-study Synthesis of Qualitative Studies Evaluating Facilitators and Barriers to Participation in Colorectal Cancer Screening. *Cancer Epidemiol Biomarkers Prev*. 2016;25(6):907-917. doi:10.1158/1055-9965.EPI-15-0990
11. van Zutphen M, Kampman E, Giovannucci EL, van Duijnhoven FJB. Lifestyle after Colorectal Cancer Diagnosis in Relation to Survival and Recurrence: A Review of the Literature. *Curr Colorectal Cancer Rep*. 2017;13(5):370-401. doi:10.1007/s11888-017-0386-1
12. Tuan J, Chen Y-X. Dietary and Lifestyle Factors Associated with Colorectal Cancer Risk and Interactions with Microbiota: Fiber, Red or Processed Meat and Alcoholic Drinks. *Gastrointest Tumors*. 2016;3(1):17-24. doi:10.1159/000442831
13. Van Blarigan EL, Meyerhardt JA. Role of Physical Activity and Diet After Colorectal Cancer Diagnosis. *J Clin Oncol*. 2015;33(16):1825-1834. doi:10.1200/JCO.2014.59.7799

14. Baron TH, Smyrk TC, Rex DK. Recommended intervals between screening and surveillance colonoscopies. *Mayo Clin Proc*. 2013;88(8):854-858. doi:10.1016/j.mayocp.2013.04.023
15. Kahi CJ, Boland CR, Dominitz JA, et al. Colonoscopy Surveillance after Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2016;150(3):758-768e11. doi:10.1053/j.gastro.2016.01.001
16. Lee M, Salloum RG. Racial and ethnic disparities in cost-related medication non-adherence among cancer survivors. *J Cancer Surviv*. 2016;10(3):534-544. doi:10.1007/s11764-015-0499-y
17. McDougall JA, Banegas MP, Wiggins C, et al. Disparities in treatment-related financial burden and recurrence in a diverse sample of colorectal cancer survivors. *J Clin Oncol*. 2017;35(15_suppl):e18067-e18067. doi:10.1200/JCO.2017.35.15_suppl.e18067
18. Gonzalez-Saenz de Tejada M, Bilbao A, Bare M, et al. Association of social support, functional status, and psychological variables with changes in health-related quality of life outcomes in patients with colorectal cancer. *Psychooncology*. 2016;25(8):891-897. doi:10.1002/pon.4022
19. Haviland J, Sodergren S, Calman L, et al. Social support following diagnosis and treatment for colorectal cancer and associations with health-related quality of life: Results from the UK ColoREctal Wellbeing (CREW) cohort study. *Psychooncology*. 2017;26(12):2276-2284. doi:10.1002/pon.4556
20. Siegel R, Desantis C, Jemal A. Colorectal Cancer Statistics, 2014. *CA Cancer J Clin*. 2014;64(1):104-117. doi:10.3322/caac.21220.
21. Wallace K, Brandt HM, Bearden JD, et al. Race and Prevalence of Large Bowel Polyps Among the Low-Income and Uninsured in South Carolina. *Dig Dis Sci*. 2016;61(1):265-272. doi:10.1007/s10620-015-3862-y
22. Cole AM, Jackson JE, Doescher M. Urban-rural disparities in colorectal cancer screening: cross-sectional analysis of 1998-2005 data from the Centers for Disease Control's Behavioral Risk Factor Surveillance Study. *Cancer Med*. 2012;1(3):350-356. doi:10.1002/cam4.40
23. Cole AM, Jackson JE, Doescher M. Colorectal Cancer Screening Disparities for Rural Minorities in the United States. *J Prim Care Community Health*. 2013;4(2):106-111. doi:10.1177/2150131912463244
24. Jackson CS, Oman M, Patel AM, Vega KJ. Health disparities in colorectal cancer among racial and ethnic minorities in the United States. *J Gastrointest Oncol*. 2016. doi:10.3978/j.issn.2078-6891.2015.039
25. Dimou A, Syrigos KN, Saif MW. Disparities in colorectal cancer in African-Americans vs Whites: Before and after diagnosis. *World J Gastroenterol*. 2009;15(30):3734-3743. doi:10.3748/wjg.15.3734
26. Alexander DD, Waterbor J, Hughes T, Funkhouser E, Grizzle W, Manne U. African-American and Caucasian disparities in colorectal cancer mortality and survival by data source: an epidemiologic review. *Cancer Biomark*. 2007;3(6):301-313. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2667694&tool=pmcentrez&rendertype=abstract.

27. Fenton JJ, Tancredi DJ, Green P, Franks P, Baldwin LM. Persistent racial and ethnic disparities in up-to-date colorectal cancer testing in medicare enrollees. *J Am Geriatr Soc*. 2009;57(3):412-418. doi:10.1111/j.1532-5415.2008.02143.x
28. Lian M, Schootman M, Doubeni CA, et al. Geographic variation in colorectal cancer survival and the role of small-area socioeconomic deprivation: A multilevel survival analysis of the NIH-AARP diet and health study cohort. *Am J Epidemiol*. 2011;174(7):828-838. doi:10.1093/aje/kwr162
29. White A, Vernon SW, Franzini L, Du XL. Racial and ethnic disparities in colorectal cancer screening persisted despite expansion of medicare's screening reimbursement. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):811-817. doi:10.1158/1055-9965.EPI-09-0963
30. Allyson G. Hall, Christy Harris Lemak, Heather Steingraber, Stephen Schaffer. Expanding the Definition of Access: It Isn't Just About Health Insurance. *J Health Care Poor Underserved*. 2008;19(2):625-638. doi:10.1353/hpu.0.0011
31. Laiyemo AO, Doubeni C, Pinsky PF, et al. Race and colorectal cancer disparities: Health-care utilization vs different cancer susceptibilities. *J Natl Cancer Inst*. 2010;102(8):538-546. doi:10.1093/jnci/djq068
32. Zahnd WE, Fogleman AJ, Jenkins WD. Rural–Urban Disparities in Stage of Diagnosis Among Cancers With Preventive Opportunities. *Am J Prev Med*. 2018;54(5):688-698. doi:10.1016/j.amepre.2018.01.021
33. Zahnd WE, James AS, Jenkins WD, et al. Rural–Urban Differences in Cancer Incidence and Trends in the United States. *Cancer Epidemiol Biomarkers Prev*. 2018;27(11):1265-1274. doi:10.1158/1055-9965.EPI-17-0430
34. Housing Assistance Council. Race & Ethnicity in Rural America Minorities in Rural & Small Town Areas. *HAC Rural Res Br*. 2012;(April):1-11. www.ruralhome.org.
35. Larson NI, Story MT, Nelson MC. Neighborhood Environments. Disparities in Access to Healthy Foods in the U.S. *Am J Prev Med*. 2009;36(1):74-81.e10. doi:10.1016/j.amepre.2008.09.025
36. Engler-Stringer R, Shah T, Bell S, Muhajarine N. Geographic access to healthy and unhealthy food sources for children in neighbourhoods and from elementary schools in a mid-sized Canadian city. *Spat Spatiotemporal Epidemiol*. 2014;11:23-32. doi:10.1016/j.sste.2014.07.001
37. Walker RE, Keane CR, Burke JG. Disparities and access to healthy food in the United States: A review of food deserts literature. *Heal Place*. 2010;16(5):876-884. doi:10.1016/j.healthplace.2010.04.013
38. Sallis JF, Floyd MF, Rodriguez DA, Saelens BE. Role of Built Environments in Physical Activity, Obesity, and Cardiovascular Disease. *Circulation*. 2012;125(5):729-737. doi:10.1161/CIRCULATIONAHA.110.969022
39. Moore L V., Diez Roux A V., Evenson KR, McGinn AP, Brines SJ. Availability of Recreational Resources in Minority and Low Socioeconomic Status Areas. *Am J Prev Med*. 2008;34(1):16-22. doi:10.1016/j.amepre.2007.09.021
40. Canchola AJ, Shariff-Marco S, Yang J, et al. Association between the neighborhood obesogenic environment and colorectal cancer risk in the Multiethnic Cohort. *Cancer Epidemiol*. 2017;50(March):99-106. doi:10.1016/j.canep.2017.08.009

41. Leader AE, Michael YL. Social Capital and Cancer Screening. *Am J Heal Behav*. 2013;37(5):683-692.
42. Beyer KMM, Malecki KM, Hoormann KA, Szabo A, Nattinger AB. Behavior: Evidence from the Survey of the Health of Wisconsin. *J Community Health*. 2016;41(1):134-137. doi:10.1007/s10900-015-0078-1
43. Steele SR, Chang GJ, Hendren S, et al. Practice Guideline for the Surveillance of Patients After Curative Treatment of Colon and Rectal Cancer. *Dis Colon Rectum*. 2015;58(8):713-725. doi:10.1097/DCR.0000000000000410
44. Carpentier MY, Vernon SW, Bartholomew LK, Murphy CC, Bluethmann SM. Receipt of recommended surveillance among colorectal cancer survivors: A systematic review. *J Cancer Surviv*. 2013;7(3):464-483. doi:10.1007/s11764-013-0290-x
45. National Cancer Institute. State Cancer Profiles. https://statecancerprofiles.cancer.gov/index.html. Accessed March 15, 2017.
46. Canadian Cancer Society. The colon and rectum. http://www.cancer.ca/en/cancer-information/cancer-type/colorectal/colorectal-cancer/the-colon-and-rectum/?region=bc. Published 2018. Accessed March 22, 2018.
47. Morson BC. Precancerous Lesions of the Colon and Rectum. *JAMA - J Am Med Assoc*. 1962;179(5):316. doi:10.1001/jama.1962.03050050006002
48. Turner JR. The Gastrointestinal Tract. In: *Robbins and Cotran Pathologic Basis of Disease*. 9th ed. Philadelphia: Elsevier; 2015:749-816.
49. Michalopoulos G, Tzathas C. Serrated polyps of right colon: Guilty or innocent? *Ann Gastroenterol*. 2013;26(3):212-219.
50. Kalady MF. Sessile Serrated Polyps: An Important Route to Colorectal Cancer. *J Natl Compr Cancer Netw*. 2013;11(12):1585-1594. doi:10.6004/jnccn.2013.0182
51. Amersi F, Agustin M, Ko CY. Colorectal cancer: Epidemiology, risk factors, and health services. *Clin Colon Rectal Surg*. 2005;18(3):133-140. doi:10.1055/s-2005-916274
52. Rex DK, Ahnen DJ, Baron JA, et al. Serrated Lesions of the Colorectum: Review and Recommendations From an Expert Panel. *Am J Gastroenterol*. 2012;107(9):1315-1329. doi:10.1038/ajg.2012.161
53. Holme Ø, Bretthauer M, Eide TJ, et al. Long-term risk of colorectal cancer in individuals with serrated polyps. *Gut*. 2015;64(6):929-936. doi:10.1136/gutjnl-2014-307793
54. Makkar R, Pai RK, Burke CA. Sessile serrated polyps: Cancer risk and appropriate surveillance. *Cleve Clin J Med*. 2012;79(12):865-871. doi:10.3949/ccjm.79a.12034
55. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for Colonoscopy Surveillance After Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology*. 2012;143(3):844-857. doi:10.1053/j.gastro.2006.03.012
56. National Cancer Institute N. NCI Dictionary of Cancer Terms. NCI Dictionaries. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/microsatellite-instability. Accessed July 24, 2018.
57. Boland CR, Goel A. Microsatellite Instability in Colorectal Cancer. *Gastroenterology*. 2010;138(6):2073-2087.e3. doi:10.1053/j.gastro.2009.12.064

58. Weiss JM, Pfau PR, Connor ESO, et al. Mortality by Stage for Right- Versus Left-Sided Colon Cancer: Analysis of Surveillance, Epidemiology, and End Results – Medicare Data. *J Clin Oncol*. 2011;29(33):4401-4409. doi:10.1200/JCO.2011.36.4414
59. Moritani K, Hasegawa H, Okabayashi K, Ishii Y, Endo T, Kitagawa Y. Difference in the recurrence rate between right- and left-sided colon cancer: A 17-year experience at a single institution. *Surg Today*. 2014;44(9):1685-1691. doi:10.1007/s00595-013-0748-5
60. Grady WM, Carethers JM. Genomic and Epigenetic Instability in Colorectal Cancer Pathogenesis. *Gastroenterology*. 2008;135(4):1079-1099. doi:10.1053/j.gastro.2008.07.076
61. Kumar V, Abbas AK, Aster JC. Neoplasia. In: *Robbins and Cotran Pathologic Basis of Disease*. Nineth. Philadelphia: Elsevier; 2015:265-340.
62. Hughes LAE, Simons CCJM, van den Brandt PA, van Engeland M, Weijenberg MP. Lifestyle, Diet, and Colorectal Cancer Risk According to (Epi)genetic Instability: Current Evidence and Future Directions of Molecular Pathological Epidemiology. *Curr Colorectal Cancer Rep*. 2017;13(6):455-469. doi:10.1007/s11888-017-0395-0
63. Tsai FC, Strum WB. Prevalence of advanced adenomas in small and diminutive colon polyps using direct measurement of size. *Dig Dis Sci*. 2011;56(8):2384-2388. doi:10.1007/s10620-011-1598-x
64. Butterly LF, Chase MP, Pohl H, Fiarman GS. Prevalence of clinically important histology in small adenomas. *Clin Gastroenterol Hepatol*. 2006;4(3):343-348. doi:10.1016/j.cgh.2005.12.021
65. Ponz de Leon M, Percesepe A. Pathogenesis of colorectal cancer. *Dig Liver Dis*. 2000;32(9):807-821. doi:10.1016/S1590-8658(00)80361-8
66. Raskov H, Pommergaard HC, Burcharth J, Rosenberg J. Colorectal carcinogenesis-update and perspectives. *World J Gastroenterol*. 2014;20(48):18151-18164. doi:10.3748/wjg.v20.i48.18151
67. Nishihara R, Morikawa T, Kuchiba A, et al. A prospective study of duration of smoking cessation and colorectal cancer risk by epigenetics-related tumor classification. *Am J Epidemiol*. 2013;178(1):84-100. doi:10.1093/aje/kws431
68. Mrkonjic M, Chappell E, Pethe V V., et al. Association of apolipoprotein e polymorphisms and dietary factors in colorectal cancer. *Br J Cancer*. 2009;100(12):1966-1974. doi:10.1038/sj.bjc.6605097
69. Hoffmeister M, Blaker H, Kloor M, et al. Body Mass Index and Microsatellite Instability in Colorectal Cancer: A Population-based Study. *Cancer Epidemiol Biomarkers Prev*. 2013;22(12):2303-2311. doi:10.1158/1055-9965.EPI-13-0239
70. Carr PR, Alwers E, Bienert S, et al. Lifestyle factors and risk of sporadic colorectal cancer by microsatellite instability status: a systematic review and meta-analyses. *Ann Oncol*. 2018;29(4):825-834. doi:10.1093/annonc/mdy059
71. Risio M. The natural history of adenomas. *Best Pract Res Clin Gastroenterol*. 2010;24(3):271-280. doi:10.1016/j.bpg.2010.04.005
72. Del Giudice ME, Vella ET, Hey A, Simunovic M, Harris W, Levitt C. Guideline for referral of patients with suspected colorectal cancer by family physicians and other primary care providers. *Can Fam physician Médecin Fam Can*.

2014;60(8):717-723, e383-90. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4131960&tool=pmcentrez&rendertype=abstract.
73. Butterworth AS, Higgins JPT, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: A meta-analysis. *Eur J Cancer*. 2006;42(2):216-227. doi:10.1016/j.ejca.2005.09.023
74. American Cancer Society. Cancer Facts and Figures 2017. *Am Cancer Soc*. 2017;21(20):2525-2538. doi:10.1101/gad.1593107
75. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2017;68(1):31-54. doi:10.3322/caac.21440
76. Aretz S, Vasen HF, Olschwang S. Clinical Utility Gene Card for: Familial adenomatous polyposis (FAP) and attenuated FAP (AFAP). *Eur J Hum Genet*. 2015;23(6):e1-e4. doi:10.1038/ejhg.2014.193
77. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis*. 2009;4(1):1-23. doi:10.1186/1750-1172-4-22
78. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: History, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. *Clin Genet*. 2009;76(1):1-18. doi:10.1111/j.1399-0004.2009.01230.x
79. NIH. Lynch syndrome. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/lynch-syndrome#. Published 2018.
80. Richter JM, Campbell EJ, Chung DC. Interval colorectal cancer after colonoscopy. *Clin Colorectal Cancer*. 2015;14(1):46-51. doi:http://dx.doi.org/10.1016/j.dcc.2014.11.001
81. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer a systematic review and meta-analysis. *JAMA Oncol*. 2017;3(2):211-219. doi:10.1001/jamaoncol.2016.4227
82. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107(3). doi:10.1093/jnci/dju427
83. Sanaka MR, Gohel T, Podugu A, et al. Adenoma and Sessile Serrated Polyp Detection Rates. *Dis Colon Rectum*. 2014;57(9):1113-1119. doi:10.1097/DCR.0000000000000183
84. Hiraoka S, Kato J, Fujiki S, et al. The presence of large serrated polyps increases risk for colorectal cancer. *Gastroenterology*. 2010;139(5):1503-1510. doi:10.1053/j.gastro.2010.07.011
85. Qumseya BJ, Coe S, Wallace MB. The effect of polyp location and patient gender on the presence of dysplasia in colonic polyps. *Clin Transl Gastroenterol*. 2012;3(7):e20-5. doi:10.1038/ctg.2012.14
86. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal Cancer Statistics, 2017. *CA Cancer J Clin*. 2017;67(3):177-193. doi:10.3322/caac.21395
87. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: Estimates based on 840 149 screening colonoscopies. *Gut*. 2007;56(11):1585-1589. doi:10.1136/gut.2007.122739

88. Corley DA, Jensen CD, Marks AR, et al. Variation of Adenoma Prevalence by Age, Sex, Race, and Colon Location in a Large Population: Implications for Screening and Quality Programs. *Clin Gastroenterol Hepatol*. 2013;11(2):172-180. doi:10.1016/j.cgh.2012.09.010
89. Myers EA, Feingold DL, Forde KA, Arnell T, Jang JH, Whelan RL. Colorectal cancer in patients under 50 years of age: A retrospective analysis of two institutions' experience. *World J Gastroenterol*. 2013;19(34):5651-5657. doi:10.3748/wjg.v19.i34.5651
90. Kushnir VM, ILKe Nalbantoglu, Watson R, et al. Advanced Colorectal Adenomas in Patients Under 45 Years of Age Are Mostly Sporadic. *Dig Dis Sci*. 2014;59(11):2757-2764. doi:10.1007/s10620-014-3245-9
91. Mitchell EP. Colorectal cancer in the young. *Color Cancer*. 2012;1(5):355-358.
92. Weinberg BA, Marshall JL, Salem ME. The Growing Challenge of Young Adults With Colorectal Cancer. *Oncology*. 2017;31(5):381-389. http://www.ncbi.nlm.nih.gov/pubmed/28516436.
93. Murphy G, Devesa SS, Cross AJ, Inskip PD, McGlynn KA, Cook MB. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. *Int J Cancer*. 2011;128(7):1668-1675. doi:10.1002/ijc.25481
94. Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: Implications for age at initiation of screening. *Br J Cancer*. 2007;96(5):828-831. doi:10.1038/sj.bjc.6603628
95. Brenner B. Cancer of the colon and rectum: Potential effects of sex-age interactions on incidence and outcome. *Med Sci Monit*. 2013;19:203-209. doi:10.12659/MSM.883842
96. Majek O, Gondos A, Jansen L, et al. Sex Differences in Colorectal Cancer Survival: Population-Based Analysis of 164,996 Colorectal Cancer Patients in Germany. *PLoS One*. 2013;8(7):1-7. doi:10.1371/journal.pone.0068077
97. Eberth JM, Thibault A, Caldwell R, et al. A statewide program providing colorectal cancer screening to the uninsured of South Carolina. *Cancer*. 2018;124(9):1912-1920. doi:10.1002/cncr.31250
98. Xirasagar S, Li Y-J, Burch JB, Daguisé VG, Hurley TG, Hébert JR. Reducing Colorectal Cancer Incidence and Disparities: Performance and Outcomes of a Screening Colonoscopy Program in South Carolina. *Adv Public Heal*. 2014;2014(9):1-8. doi:10.1155/2014/787282
99. Slattery ML, Potter JD, Curtin K, et al. Estrogens reduce and withdrawal of estrogens increase risk of microsatellite instability-positive colon cancer. *Cancer Res*. 2001;61(1):126-130.
100. Koo JH, Leong RW. Sex differences in epidemiological, clinical and pathological characteristics of colorectal cancer. *J Gastroenterol Hepatol*. 2010;25(1):33-42. doi:10.1111/j.1440-1746.2009.05992.x
101. Davis JL, Buchanan KL, Katz R V., Green BL. Gender Differences in Cancer Screening Beliefs, Behaviors, and Willingness to Participate: Implications for Health Promotion. *Am J Mens Health*. 2012;6(3):211-217. doi:10.1177/1557988311425853
102. Ritvo P, Myers RE, Paszat L, Serenity M, Perez DF, Rabeneck L. Gender differences in attitudes impeding colorectal cancer screening. *BMC Public Health*.

2013;13(1):1. doi:10.1186/1471-2458-13-500
103. El-Haddad B, Dong F, Kallail KJ, Hines RB, Ablah E. Association of marital status and colorectal cancer screening participation in the USA. *Color Dis*. 2015;17(5):O108-O114. doi:10.1111/codi.12926
104. Williams R, White P, Nieto J, Vieira D, Francois F, Hamilton F. Colorectal Cancer in African Americans: An Update. *Clin Transl Gastroenterol*. 2016;7(7):e185. doi:10.1038/ctg.2016.36
105. Jackson CS, Vega KJ. Higher prevalence of proximal colon polyps and villous histology in African-Americans undergoing colonoscopy at a single equal access center. *J Gastrointest Oncol*. 2015;6(6):638-643. doi:10.3978/j.issn.2078-6891.2015.096
106. Thomas CRJ, Jarosz R, Evans N. Racial differences in the anatomical distribution of colon cancer. *Arch Surg*. 1992;127(10):1241-1245. doi:10.1001/archsurg.1992.01420100107018
107. Offerhaus GJ, Giardiello FM, Tersmette KW, et al. Ethnic differences in the anatomical location of colorectal adenomatous polyps. *Int J cancer*. 1991;49(5):641-644.
108. Aran V, Victorino AP, Thuler LC, Ferreira CG. Colorectal Cancer: Epidemiology, Disease Mechanisms and Interventions to Reduce Onset and Mortality. *Clin Colorectal Cancer*. 2016;15(3):195-203. doi:10.1016/j.clcc.2016.02.008
109. Dinh T, Ladabaum U, Alperin P, Caldwell C, Smith R, Levin TR. Health Benefits and Cost-effectiveness of a Hybrid Screening Strategy for Colorectal Cancer. *Clin Gastroenterol Hepatol*. 2013;11(9):1158-1166. doi:10.1016/j.cgh.2013.03.013
110. Meester RGS, Doubeni CA, Zauber AG, et al. Public health impact of achieving 80% colorectal cancer screening rates in the United States by 2018. *Cancer*. 2015;121(13):2281-2285. doi:10.1002/cncr.29336
111. Grubbs SS, Polite BN, Carney J, et al. Eliminating racial disparities in colorectal cancer in the real world: It took a village. *J Clin Oncol*. 2013;31(16):1928-1930. doi:10.1200/JCO.2012.47.8412
112. Simon MS, Thomson CA, Pettijohn E, et al. Racial differences in colorectal cancer incidence and mortality in the Women's Health Initiative. *Cancer Epidemiol Biomarkers Prev*. 2011;20(7):1368-1378. doi:10.1158/1055-9965.EPI-11-0027
113. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683-691. doi:10.1136/gutjnl-2015-310912
114. American Cancer Society. *Cancer Facts & Figures 2016*.; 2016. doi:10.1097/01.NNR.0000289503.22414.79
115. Ahmed FE. Effect of Diet, Life Style, and Other Environmental/Chemopreventive Factors on Colorectal Cancer Development, and Assessment of the Risks. *J Environ Sci Heal Part C*. 2004;22(2):91-148. doi:10.1081/LESC-200038263
116. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. *Gastroenterology*. 2010;138(6):2029-2043. doi:10.1053/j.gastro.2010.01.057.Primary
117. Teixeira MC, Braghiroli MI, Sabbaga J, Hoff PM. Primary prevention of colorectal cancer: Myth or reality? *World J Gastroenterol*. 2014;20(41):15060-15069. doi:10.3748/wjg.v20.i41.15060

118. Whitlock K, Gill RS, Birch DW, Karmali S. The association between obesity and colorectal cancer. *Gastroenterol Res Pract*. 2012;2012. doi:10.1155/2012/768247
119. Friedenreich CM, Orenstein MR. Physical Activity and Cancer Prevention: Etiologic Evidence and Biological Mechanisms. *J Nutr*. 2002;132(11):3456S-3464S. doi:https://doi.org/10.1093/jn/132.11.3456S
120. Shaw E, Farris MS, Stone CR, et al. Effects of physical activity on colorectal cancer risk among family history and body mass index subgroups: a systematic review and meta-analysis. *BMC Cancer*. 2018;18(1):71. doi:10.1186/s12885-017-3970-5
121. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: A meta-Analysis of prospective cohort studies. *Int J Cancer*. 2013;133(8):1905-1913. doi:10.1002/ijc.28208
122. Colbert LH, Hartman TJ, Malila N, et al. Physical Activity in Relation to Cancer of the Colon and Rectum in a Cohort of Male Smokers. *Cancer Epidemiol Biomarkers Prev*. 2001;10(3):265-268. http://cebp.aacrjournals.org/content/10/3/265.
123. Moore SC, Lee IM, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med*. 2016;176(6):816-825. doi:10.1001/jamainternmed.2016.1548
124. Shaw E, Farris MS, Stone CR, et al. Effects of physical activity on colorectal cancer risk among family history and body mass index subgroups: a systematic review and meta-analysis. *BMC Cancer*. 2018;18(1):71. doi:10.1186/s12885-017-3970-5
125. Liang PS, Chen T-Y, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: Systematic review and meta-analysis. *Int J Cancer*. 2009;124(10):2406-2415. doi:10.1002/ijc.24191
126. Tsoi KKF, Pau CYY, Wu WKK, Chan FKL, Griffiths S, Sung JJY. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol*. 2009;7(6):682-685. doi:10.1016/j.cgh.2009.02.016
127. Ordóñez-Mena JM, Walter V, Schöttker B, et al. Impact of prediagnostic smoking and smoking cessation on colorectal cancer prognosis: A meta-analysis of individual patient data from cohorts within the CHANCES consortium. *Ann Oncol*. 2018;29(2):472-483. doi:10.1093/annonc/mdx761
128. Klarich DS, Brasser SM, Hong MY. Moderate Alcohol Consumption and Colorectal Cancer Risk. *Alcohol Clin Exp Res*. 2015;39(8):1280-1291. doi:10.1111/acer.12778
129. Bongaerts BWC, Van Den Brandt PA, Goldbohm RA, De Goeij AFPM, Weijenberg MP. Alcohol consumption, type of alcoholic beverage and risk of colorectal cancer at specific subsites. *Int J Cancer*. 2008;123(10):2411-2417. doi:10.1002/ijc.23774
130. Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: An overall and dose-Response meta-analysis of published studies. *Ann Oncol*. 2011;22(9):1958-1972. doi:10.1093/annonc/mdq653
131. Doubeni CA, Major JM, Laiyemo AO, et al. Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence. *J*

Natl Cancer Inst. 2012;104(18):1353-1362. doi:10.1093/jnci/djs346
132. Meester RGS, Doubeni CA, Lansdorp-Vogelaar I, et al. Colorectal Cancer Deaths Attributable to Nonuse of Screening in the United States. *Ann Epidemiol*. 2015;25(3):208-213. doi:10.1016/j.annepidem.2014.11.011
133. Carethers JM. Should African Americans be screened for colorectal cancer at an earlier age? *Nat Clin Pract Gastroenterol Hepatol*. 2005;2(8):352-353. doi:10.1038/ncpgasthep0241
134. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2018;00(00):1-32. doi:10.3322/CAAC.21457
135. Geiger TM, Ricciardi R. Screening options and recommendations for colorectal cancer. *Clin Colon Rectal Surg*. 2009;22(4):209-217. doi:10.1055/s-0029-1242460
136. National Cancer Institute N. Tests to Detect Colorectal Cancer and Polyps. https://www.cancer.gov/types/colorectal/screening-fact-sheet. Published 2016. Accessed March 14, 2018.
137. Levin B, Lieberman DA, McFarland B, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin*. 2008;58(3):130-160. doi:10.3322/CA.2007.0018
138. Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol*. 2017;112(7):1016-1030. doi:10.1038/ajg.2017.174
139. Hol L, Van Leerdam ME, Van Ballegooijen M, et al. Screening for colorectal cancer: Randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut*. 2010;59(1):62-68. doi:10.1136/gut.2009.177089
140. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening. *N Engl J Med*. 2012;366(8):697-706. doi:10.1056/NEJMoa1108895
141. Kligman E, Li W, Eckert GJ, Kahi C. Adenoma Detection Rate in Asymptomatic Patients with Positive Fecal Immunochemical Tests. *Dig Dis Sci*. 2018;63(5):1167-1172. doi:10.1007/s10620-018-4984-9
142. van Doorn SC, van der Vlugt M, Depla A, et al. Adenoma detection with Endocuff colonoscopy versus conventional colonoscopy: a multicentre randomised controlled trial. *Gut*. 2017;66(3):438-445. doi:10.1136/gutjnl-2015-310097
143. Doubeni CA, Corley DA, Quinn VP, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. *Gut*. 2018;67(2):291-298. doi:10.1136/gutjnl-2016-312712
144. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection From Colorectal Cancer After Colonoscopy A Population-Based, Case-Control Study. *Ann Intern Med*. 2011;154(1):22-30.
145. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies.

BMJ. 2014;348(apr09 1):g2467-g2467. doi:10.1136/bmj.g2467
146. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010;375(9726):1624-1633. doi:10.1016/S0140-6736(10)60551-X
147. Swartz AW, Eberth JM, Josey MJ, Strayer SM. Reanalysis of All-Cause Mortality in the U.S. Preventive Services Task Force 2016 Evidence Report on Colorectal Cancer Screening. *Ann Intern Med*. 2017;167(8):602. doi:10.7326/M17-0859
148. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66(4):271-289. doi:10.3322/caac.21349
149. Hewitt M, Greenfield S, Stovall E. *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, D.C.: National Academies Press; 2005. doi:10.17226/11468
150. Wu W, Guo F, Ye J, et al. Pre- and post-diagnosis physical activity is associated with survival benefits of colorectal cancer patients: a systematic review and meta-analysis. *Oncotarget*. 2016;7(32):52095-52103. doi:10.18632/oncotarget.10603
151. Eberth JM, Josey MJ, Mobley LR, et al. Who Performs Colonoscopy? Workforce Trends Over Space and Time. *J Rural Heal*. 2017;34:138-147. doi:10.1111/jrh.12286
152. Baxter NN, Sutradhar R, Forbes SS, Paszat LF, Saskin R, Rabeneck L. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. *Gastroenterology*. 2011;140(1):65-72. doi:10.1053/j.gastro.2010.09.006
153. Jiang M, Sewitch MJ, Barkun AN, Joseph L, Hilsden RJ. Endoscopist specialty is associated with colonoscopy quality. *BMC Gastroenterol*. 2013;13:78. doi:10.1186/1471-230X-13-78
154. Chen SC, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. *Am J Gastroenterol*. 2007;102(4):856-861. doi:10.1111/j.1572-0241.2006.01054.x
155. Archampong D, Borowski D, Lh I, et al. Workload and surgeon's specialty for outcome after colorectal cancer surgery (Review). *Cochrane Database Syst Rev*. 2012;(3):1-134. doi:10.1002/14651858.CD005391.pub3.Copyright
156. Baxter NN, Warren JL, Barrett MJ, Stukel TA, Doria-Rose VP. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol*. 2012;30(21):2664-2669. doi:10.1200/JCO.2011.40.4772
157. Rabeneck L, Paszat LF, Saskin R. Endoscopist Specialty Is Associated With Incident Colorectal Cancer After a Negative Colonoscopy. *Clin Gastroenterol Hepatol*. 2010;8(3):275-279. doi:10.1016/j.cgh.2009.10.022
158. Fedewa SA, Flanders WD, Ward KC, et al. Racial and ethnic disparities in interval colorectal cancer incidence a population-based cohort study. *Ann Intern Med*. 2017;166(12):857-866. doi:10.7326/M16-1154
159. Biondo S, Kreisler E, Millan M, et al. Impact of surgical specialization on emergency colorectal surgery outcomes. *Arch Surg*. 2010;145(1):79-86. doi:10.1001/archsurg.2009.208
160. Etzioni DA, Young-Fadok TM, Cima RR, et al. Patient survival after surgical treatment of rectal cancer: Impact of surgeon and hospital characteristics. *Cancer*.

2014;120(16):2472-2481. doi:10.1002/cncr.28746
161. Williams JE, Holub JL, Faigel DO. Polypectomy rate is a valid quality measure for colonoscopy: Results from a national endoscopy database. *Gastrointest Endosc*. 2012;75(3):576-582. doi:10.1016/j.gie.2011.12.012
162. Calderwood AH, Jaconson BC. Colonoscopy Quality: Metrics and Implementation. *Gastrointest Endosc Clin N Am*. 2013;42(3):599-618. doi:10.1016/j.gtc.2013.05.005.
163. Anderson JC, Butterly LF. Colonoscopy: Quality Indicators. *Clin Transl Gastroenterol*. 2015;6(2):e77-83. doi:10.1038/ctg.2015.5
164. Lieberman D, Mascarenhas R. Adenoma detection rate: in search of quality improvement, not just measurement. *Gastrointest Endosc*. 2015;82(4):683-685. doi:10.1016/j.gie.2015.02.020
165. Rees CJ, Bevan R, Zimmermann-Fraedrich K, et al. Expert opinions and scientific evidence for colonoscopy key performance indicators. *Gut*. 2016;65(12):2045-2060. doi:10.1136/gutjnl-2016-312043
166. Parikh MP, Muthukuru S, Jobanputra Y, et al. Sessile Serrated Adenomas Are More Prevalent in Caucasians , and Gastroenterologists Are Better Than Nongastroenterologists at Their Detection. *Gastroenterol Res Pract*. 2017;2017(1). doi:10.1155/2017/6710931
167. Xirasagar S, Hurley TG, Sros L, et al. Quality and Safety of Screening Colonoscopies Performed by Primary Care Physicians With Standby Specialist Support. *Med Care*. 2010;48(8):703-709. www.jstor.org/stable/25701524.
168. Pace D, Borgaonkar M, Lougheed M, et al. Effect of Colonoscopy Volume on Quality Indicators. *Can J Gastroenterol Hepatol*. 2016;2016. doi:10.1155/2016/2580894
169. Pace D, Borgaonkar M, Evans B, et al. Annual colonoscopy volume and maintenance of competency for surgeons. *Surg Endosc*. 2017;31(6):2630-2635. doi:10.1007/s00464-016-5275-1
170. Brown ML, Klabunde CN, Mysliwiec P. Current capacity for endoscopic colorectal cancer screening in the United States: data from the National Cancer Institute Survey of Colorectal Cancer Screening Practices. *Am J Med*. 2003;115(2):129-133. doi:10.1016/S0002-9343(03)00297-3
171. Ko CY, Chang JT, Chaudhry S, Kominski G. Are high-volume surgeons and hospitals the most important predictors of inhospital outcome for colon cancer resection? *Surgery*. 2002;132(2):268-273. doi:10.1067/msy.2002.125721
172. Schrag D, Panageas KS, Riedel E, et al. Surgeon volume compared to hospital volume as a predictor of outcome following primary colon cancer resection. *J Surg Oncol*. 2003;83(2):68-78. doi:10.1002/jso.10244
173. Billingsley KG. Surgeon and Hospital Characteristics as Predictors of Major Adverse Outcomes Following Colon Cancer Surgery. *Arch Surg*. 2007;142(1):23. doi:10.1001/archsurg.142.1.23
174. Chen BK, Cheng X, Bennett K, Hibbert J. Travel distances, socioeconomic characteristics, and health disparities in nonurgent and frequent use of Hospital Emergency Departments in South Carolina: a population-based observational study. *BMC Health Serv Res*. 2015;15:203. doi:10.1186/s12913-015-0864-6
175. Eapen ZJ, McCoy LA, Fonarow GC, et al. Utility of Socioeconomic Status in

Predicting 30-Day Outcomes after Heart Failure Hospitalization. *Circ Hear Fail*. 2015;8(3):473-480. doi:10.1161/CIRCHEARTFAILURE.114.001879
176. Saydah SH, Imperatore G, Beckles GL. Socioeconomic status and mortality: Contribution of health care access and psychological distress among U.S. adults with diagnosed diabetes. *Diabetes Care*. 2013;36(1):49-55. doi:10.2337/dc11-1864
177. Gershon AS, Hwee J, Victor JC, Wilton AS, To T. Trends in Socioeconomic Status–related Differences in Mortality among People with Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. 2014;11(8):1195-1202. doi:10.1513/AnnalsATS.201403-094OC
178. Institute of Medicine (US) Roundtable on Health Literacy. *Innovations in Health Literacy : Workshop Summary*. Washington, D.C.: National Academies Press; 2011.
179. Berkman, Nancy, PhD; Stacey L. Sheridan, MD, MPH; Katrina E. Donahue, MD, MPH; David J. Halpern, MD M and KC. Annals of Internal Medicine Review Low Health Literacy and Health Outcomes : An Updated. 2014;155(2). doi:10.7326/0003-4819-155-2-201107190-00005
180. Siegel RL, Jemal A, Thun MJ, Hao Y, Ward EM. Trends in the incidence of colorectal cancer in relation to county-level poverty among blacks and whites. *J Natl Med Assoc*. 2008;100(12):1441-1444. doi:10.1016/S0027-9684(15)31544-3
181. Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? A systematic review. *BMJ Open*. 2016;6(11):e013059. doi:10.1136/bmjopen-2016-013059
182. Wheeler SB, Kuo TM, Goyal RK, et al. Regional variation in colorectal cancer testing and geographic availability of care in a publicly insured population. *Heal Place*. 2014;29:114-123. doi:10.1016/j.healthplace.2014.07.001
183. Khan-Gates JA, Ersek JL, Eberth JM, Adams SA, Pruitt SL. Geographic Access to Mammography and Its Relationship to Breast Cancer Screening and Stage at Diagnosis: A Systematic Review. *Women's Heal Issues*. 2015;25(5):482-493. doi:10.1016/j.whi.2015.05.010
184. Anderson AE, Henry KA, Samadder NJ, Merrill RM, Kinney AY. Rural vs Urban Residence Affects Risk-Appropriate Colorectal Cancer Screening. *Clin Gastroenterol Hepatol*. 2013;11(5):526-533. doi:10.1016/j.cgh.2012.11.025
185. Lin CC, Bruinooge SS, Kirkwood MK, et al. Association Between Geographic Access to Cancer Care and Receipt of Radiation Therapy for Rectal Cancer. *Int J Radiat Oncol*. 2016;94(4):719-728. doi:10.1016/j.ijrobp.2015.12.012
186. Wheeler SB, Kuo T-M, Durham D, Frizzelle B, Reeder-Hayes K, Meyer A-M. Effects of distance to care and rural or urban residence on receipt of radiation therapy among North Carolina Medicare enrollees with breast cancer. *N C Med J*. 2014;75(4):239-246.
187. Ananthakrishnan AN, Hoffmann RG, Saeian K. Higher Physician Density is Associated with Lower Incidence of Late-stage Colorectal Cancer. *J Gen Intern Med*. 2010;25(11):1164-1171. doi:10.1007/s11606-010-1457-z
188. Tatalovich Z, Zhu L, Rolin A, Lewis DR, Harlan LC, Winn DM. Geographic disparities in late stage breast cancer incidence: Results from eight states in the United States. *Int J Health Geogr*. 2015;14(1):1-12. doi:10.1186/s12942-015-

0025-5
189. Mobley LR, Kuo TMM, Watson L, Gordon Brown G. Geographic disparities in late-stage cancer diagnosis: Multilevel factors and spatial interactions. *Heal Place*. 2012;18(5):978-990. doi:10.1016/j.healthplace.2012.06.009
190. Yao N, Foltz SM, Odisho AY, Wheeler DC. Geographic Analysis of Urologist Density and Prostate Cancer Mortality in the United States. Hernandez-Boussard T, ed. *PLoS One*. 2015;10(6):e0131578. doi:10.1371/journal.pone.0131578
191. Stewart SL, Cooney D, Hirsch S, et al. Effect of gynecologic oncologist availability on ovarian cancer mortality. *World J Obstet Gynecol*. 2014;3(2):71. doi:10.5317/wjog.v3.i2.71
192. Sadowski DJ, Geiger SW, Mueller GS, Zahnd WE, Alanee SR, McVary KT. Kidney Cancer in Rural Illinois: Lower Incidence Yet Higher Mortality Rates. *Urology*. 2016;94:90-95. doi:10.1016/j.urology.2016.05.022
193. Towne SD, Smith ML, Ory MG. Geographic variations in access and utilization of cancer screening services: Examining disparities among American Indian and Alaska Native Elders. *Int J Health Geogr*. 2014;13:1-11. doi:10.1186/1476-072X-13-18
194. Alford-Teaster J, Lange JM, Hubbard RA, et al. Is the closest facility the one actually used? An assessment of travel time estimation based on mammography facilities. *Int J Health Geogr*. 2016;15(1):8. doi:10.1186/s12942-016-0039-7
195. Blankart CR. Does healthcare infrastructure have an impact on delay in diagnosis and survival? *Health Policy (New York)*. 2012;105(2-3):128-137. doi:10.1016/j.healthpol.2012.01.006
196. Aboagye JK, Kaiser HE, Hayanga AJ. Rural-Urban Differences in Access to Specialist Providers of Colorectal Cancer Care in the United States. *JAMA Surg*. 2014;149(6):537. doi:10.1001/jamasurg.2013.5062
197. Bennett KJ, Probst JC, Bellinger JD. Receipt of Cancer Screening Services: Surprising Results for Some Rural Minorities. *J Rural Heal*. 2012;28(1):63-72. doi:10.1111/j.1748-0361.2011.00365.x
198. Croft JB, Lu H, Zhang X, Holt JB. Geographic Accessibility of Pulmonologists for Adults With COPD. *Chest*. 2016;150(3):544-553. doi:10.1016/j.chest.2016.05.014
199. Murage P, Bachmann M, Jones A, Murchie P, Crawford M. Impact of travel time and rurality on presentation and outcomes of symptomatic colorectal cancer: A cross-sectional cohort study in primary care. *Br J Gen Pract*. 2017;67(660):e460-e466. doi:10.3399/bjgp17X691349
200. Charlton ME, Matthews KA, Gaglioti A, et al. Is Travel Time to Colonoscopy Associated With Late-Stage Colorectal Cancer Among Medicare Beneficiaries in Iowa? *J Rural Health*. 2016;32(4):363-373. doi:10.1111/jrh.12159
201. Sanders SR, Erickson LD, Call VRA, Mcknight ML, Hedges DW. Rural health care bypass behavior: How community and spatial characteristics affect primary health care selection. *J Rural Heal*. 2015;31(2):146-156. doi:10.1111/jrh.12093
202. Lake A, Townshend T. Obesogenic environments: exploring the built and food environments. *J R Soc Promot Health*. 2006;126(6):262-267. doi:10.1177/1466424006070487
203. Chaput JP, Klingenberg L, Astrup A, Sjödin AM. Modern sedentary activities promote overconsumption of food in our current obesogenic environment. *Obes*

Rev. 2011;12(501):12-20. doi:10.1111/j.1467-789X.2010.00772.x
204. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: Shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804-814. doi:10.1016/S0140-6736(11)60813-1
205. Slack T, Myers CA, Martin CK, Heymsfield SB. The Geographic Concentration of US Adult Obesity Prevalence and Associated Social, Economic, and Environmental Factors. *Obesity*. 2014;22(3):868-874. doi:10.1002/oby.20502
206. Reidpath DD, Burns C, Garrard J, Mahoney M, Townsend M. An ecological study of the relationship between social and environmental determinants of obesity. *Health Place*. 2002;8(2):141-145. doi:10.1016/S1353-8292(01)00028-4
207. Conroy SM, Shariff-Marco S, Yang J, et al. Characterizing the neighborhood obesogenic environment in the Multiethnic Cohort: a multi-level infrastructure for cancer health disparities research. *Cancer Causes Control*. 2018;29(1):167-183. doi:10.1007/s10552-017-0980-1
208. Wang A, Wheeler DC. Catchment Area Analysis Using Bayesian Regression Modeling. *Cancer Inform*. 2015;14(S2):71-79. doi:10.4137/CIN.S17297.
209. Vanderweele TJ, Vansteelandt S, Robins JM. Effect decomposition in the presence of an exposure-induced mediator-outcome confounder. *Epidemiology*. 2014;25(2):300-306. doi:10.1097/EDE.0000000000000034
210. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30. doi:10.3322/caac.21442
211. Singh GK, Siahpush M. Widening rural-urban disparities in all-cause mortality and mortality from major causes of death in the USA, 1969-2009. *J Urban Heal*. 2014;91(2):272-292. doi:10.1007/s11524-013-9847-2
212. Office of Disease Prevention and Health Promotion. Healthy People2020 Cancer Objectives. https://www.healthypeople.gov/2020/topics-objectives/topic/cancer/objectives. Published 2010. Accessed October 23, 2018.
213. National Colorectal Cancer Roundtable. 80% By 2018. http://nccrt.org/what-we-do/80-percent-by-2018/. Accessed October 23, 2018.
214. Joseph DA, Meester RGS, Zauber AG, et al. Colorectal cancer screening: Estimated future colonoscopy need and current volume and capacity. *Cancer*. 2016;122(16):2479-2486. doi:10.1002/cncr.30070
215. Butterly L, Olenec C, Goodrich M, Carney P, Dietrich A. Colonoscopy Demand and Capacity in New Hampshire. *Am J Prev Med*. 2007;32(1):25-31. doi:10.1016/j.amepre.2006.08.026
216. Ballew C, Lloyd BG, Miller SH. Capacity for Colorectal Cancer Screening by Colonoscopy, Montana, 2008. *Am J Prev Med*. 2009;36(4):329-332. doi:10.1016/j.amepre.2008.11.021
217. Mao L, Nekorchuk D. Measuring spatial accessibility to healthcare for populations with multiple transportation modes. *Heal Place*. 2013;24:115-122. doi:10.1016/j.healthplace.2013.08.008
218. Fransen K, Neutens T, De Maeyer P, Deruyter G. A commuter-based two-step floating catchment area method for measuring spatial accessibility of daycare centers. *Heal Place*. 2015;32:65-73. doi:10.1016/j.healthplace.2015.01.002
219. McGrail MR, Humphreys JS. Measuring spatial accessibility to primary health care services: Utilising dynamic catchment sizes. *Appl Geogr*. 2014;54:182-188.

doi:10.1016/j.apgeog.2014.08.005
220. Luo W, Whippo T. Variable catchment sizes for the two-step floating catchment area (2SFCA) method. *Heal Place*. 2012;18(4):789-795. doi:10.1016/j.healthplace.2012.04.002
221. Wan N, Zou B, Sternberg T. A three-step floating catchment area method for analyzing spatial access to health services. *Int J Geogr Inf Sci*. 2012;26(6):1073-1089. doi:10.1080/13658816.2011.624987
222. United States Department of Agriculture. 2010 Rural-Urban Commuting Area (RUCA) Codes. https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/documentation/. Published 2016. Accessed November 14, 2018.
223. Esri, Tom Tom North America Inc., United States Postal Service. USA Zip Code Areas. https://www.arcgis.com/home/item.html?id=8d2012a2016e484dafaac0451f9aea24. Published 2019. Accessed November 14, 2018.
224. James C V., Moonesinghe R, Wilson-Frederick SM, Hall JE, Penman-Aguilar A, Bouye K. Racial/Ethnic Health Disparities Among Rural Adults — United States , 2012 – 2015. *Morb Mortal Wkly Rep*. 2017;66(23):1-9.
225. Josey MJ, Eberth JM, Mobley LR, et al. Should Measures of Health Care Availability be Based on the Providers or the Procedures? A Case Study with Implications for Rural Colorectal Cancer Disparities. *J Rural Heal*. 2018;0:1-8. doi:10.1111/jrh.12332
226. National Cancer Institute N. *Cancer Trends Progress Report*.; 2017. https://progressreport.cancer.gov/.
227. de Moor JS, Cohen RA, Shapiro JA, et al. Colorectal cancer screening in the United States: Trends from 2008 to 2015 and variation by health insurance coverage. *Prev Med (Baltim)*. 2018;112(April):199-206. doi:10.1016/j.ypmed.2018.05.001
228. Berkowitz Z, Zhang X, Richards TB, Nadel M, Peipins LA, Holt J. Multilevel small-area estimation of colorectal cancer screening in the United States. *Cancer Epidemiol Biomarkers Prev*. 2018;27(3):245-253. doi:10.1158/1055-9965.EPI-17-0488
229. National Cancer Institute, National Cancer Insititute NI of EHS. *CANCER AND THE ENVIRONMENT*.; 2003. http://www.nih.gov.
230. Sallis JF, Saelens BE, Frank LD, et al. Neighborhood built environment and income: Examining multiple health outcomes. *Soc Sci Med*. 2009;68(7):1285-1293. doi:10.1016/j.socscimed.2009.01.017
231. Bell J, Mora G, Hagan E, Rubin V, Karpyn A. *Access to Healthy Food and Why It Matters: A Review of the Research*.; 2013. http://thefoodtrust.org/uploads/media_items/access-to-healthy-food.original.pdf.
232. Ma Y, Yang Y, Wang F, et al. Obesity and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies. *PLoS One*. 2013;8(1). doi:10.1371/journal.pone.0053916
233. Sanchez NF, Stierman B, Saab S, Mahajan D, Yeung H, Francois F. Physical activity reduces risk for colon polyps in a multiethnic colorectal cancer screening population. *BMC Res Notes*. 2012;5(1):312. doi:10.1186/1756-0500-5-312
234. Vanderweele TJ, Vansteelandt S. Conceptual issues concerning mediation,

interventions and composition. *Stat Interface*. 2009;2(4):457-468. doi:10.4310/SII.2009.v2.n4.a7
235. National Center for Health Statistics. About Tobacco Use Information. https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm. Published 2017. Accessed January 17, 2019.
236. Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion C for DC and P. Alcohol and Public Health. https://www.cdc.gov/alcohol/faqs.htm. Published 2018. Accessed January 17, 2019.
237. US Census Bureau. American Community Survey. https://www.census.gov/programs-surveys/acs/news/data-releases.2011.html. Published 2011. Accessed January 28, 2019.
238. Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. 2013;18(2):137-150. doi:10.1037/a0031034
239. Vanderweele TJ, Chiba Y. Sensitivity analysis for direct and indirect effects in the presence of exposure-induced mediator-outcome confounders. *Epidemiol Biostat Public Heal*. 2014;11(2):1-16. doi:10.2427/9027
240. Pearce J, Hiscock R, Blakely T, Witten K. The contextual effects of neighbourhood access to supermarkets and convenience stores on individual fruit and vegetable consumption. *J Epidemiol Community Health*. 2008;62(3):198-201. doi:10.1136/jech.2006.059196
241. Cummins S, Flint E, Matthews SA. New Neighborhood Grocery Store Increased Awareness Of Food Access But Did Not Alter Dietary Habits Or Obesity. *Health Aff*. 2014;33(2):283-291. doi:10.1377/hlthaff.2013.0512
242. Li F, Harmer P, Cardinal BJ, et al. Built environment and 1-year change in weight and waist circumference in middle-aged and older adults: Portland neighborhood environment and health study. *Am J Epidemiol*. 2009;169(4):401-408. doi:10.1093/aje/kwn398
243. Gordon-Larsen P. Food Availability/Convenience and Obesity. *Adv Nutr*. 2014;5(6):809-817. doi:10.3945/an.114.007070
244. Schoenberg MH. Physical Activity and Nutrition in Primary and Tertiary Prevention of Colorectal Cancer. *Visc Med*. 2016;32(3):199-204. doi:10.1159/000446492
245. Boehmer TK, Lovegreen SL, Haire-Joshu D, Brownson RC, Brownson R. What Constitutes an Obesogenic Environment in Rural Communities? Send reprint requests to. 2006;20(6):411-422. http://journals.sagepub.com/doi/pdf/10.4278/0890-1171-20.6.411.
246. Josey MJ, Moore S. The influence of social networks and the built environment on physical inactivity: A longitudinal study of urban-dwelling adults. *Health Place*. 2018;54:62-68. doi:10.1016/j.healthplace.2018.08.016
247. Christakis N a, Fowler JH. The Spread of Obesity in a Large Social Network over 32 Years. *N Engl J Med*. 2007;357(4):370-379. doi:10.1056/NEJMsa066082
248. Comstock SS, Hortos K, Kovan B, McCaskey S, Pathak DR, Fenton JI. Adipokines and obesity are associated with colorectal polyps in adult males: A

cross-sectional study. *PLoS One*. 2014;9(1). doi:10.1371/journal.pone.0085939
249. Kim YJ, Kim YJ, Lee S. An association between colonic adenoma and abdominal obesity: A cross-sectional study. *BMC Gastroenterol*. 2009;9:1-6. doi:10.1186/1471-230X-9-4
250. Tran S, Gibbs A, Murray IC, et al. Obesity Increases Prevalence of Colonic Adenomas at Screening Colonoscopy: A Canadian Community-Based Study. *Can J Gastroenterol Hepatol*. 2017;2017:1-8. doi:10.1155/2017/8750967
251. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer*. 2010;116(3):544-573. doi:10.1002/cncr.24760
252. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*. 2012;62(4):220-241. doi:10.3322/caac.21149
253. National Cancer Institute N. *Facing Forward: Life After Cancer Treatment*.; 2006.
254. Cost Helper Health. Colonoscopy Cost. https://health.costhelper.com/colonoscopy.html. Accessed December 26, 2018.
255. Palmer NRA, Geiger AM, Felder TM, Lu L, Case LD, Weaver KE. Racial/ethnic disparities in health care receipt among male cancer survivors. *Am J Public Health*. 2013;103(7):1306-1313. doi:10.2105/AJPH.2012.301096
256. Ford ME, Sterba KR, Armeson K, Malek AM, Knight KD, Zapka J. Factors Influencing Adherence to Recommended Colorectal Cancer Surveillance: Experiences and Behaviors of Colorectal Cancer Survivors. *J Cancer Educ*. August 2018. doi:10.1007/s13187-018-1398-5
257. McDougall JA, Banegas MP, Wiggins CL, Chiu VK, Rajput A, Kinney AY. Rural Disparities in Treatment-Related Financial Hardship and Adherence to Surveillance Colonoscopy in Diverse Colorectal Cancer Survivors. *Cancer Epidemiol Biomarkers Prev*. 2018;27(11):1275-1282. doi:10.1158/1055-9965.EPI-17-1083
258. Surveillance Epidemiology and End Results Program. SEER*Stat Tutorials: Calculating Age-adjusted Rates. https://seer.cancer.gov/seerstat/tutorials/aarates/definition.html. Accessed December 2, 2018.
259. Salloum RG, Hornbrook MC, Fishman PA, Ritzwoller DP, O'Keeffe Rossetti MC, Elston Lafata J. Adherence to surveillance care guidelines after breast and colorectal cancer treatment with curative intent. *Cancer*. 2012;118(22):5644-5651. doi:10.1002/cncr.27544
260. Standeven L, Price Hiller J, Mulder K, Zhu G, Ghosh S, Spratlin JL. Impact of a Dedicated Cancer Center Surveillance Program on Guideline Adherence for Patients With Stage II and III Colorectal Cancer. *Clin Colorectal Cancer*. 2013;12(2):103-112. doi:10.1016/j.clcc.2012.09.006
261. Rolnick S, Hensley Alford S, Kucera GP, et al. Racial and age differences in colon examination surveillance following a diagnosis of colorectal cancer. *J Natl Cancer Inst Monogr*. 2005;1524(35):96-101. doi:10.1093/jncimonographs/lgi045
262. Ellison GL, Warren JL, Knopf KB, Brown ML. Racial differences in the receipt of bowel surveillance following potentially curative colorectal cancer surgery. *Health Serv Res*. 2003;38(6 Pt 2):1885-1903.

doi:http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291475-6773/issues
263. Pollitz K, Lucia K, Keith K, et al. *Coverage of Colonoscopies Under the Affordable Care Act's Prevention Benefit*.; 2012.
264. Barnett JC, Vornovitsky MS, Davis KE, et al. Health Insurance Coverage in the United States: 2015. *United States Census Bur*. 2016;257(September). https://www.census.gov/content/dam/Census/library/publications/2016/demo/p60-257.pdf.
265. Zullig LL, Jackson GL, Weinberger M, Provenzale D, Reeve BB, Carpenter WR. An examination of racial differences in process and outcome of colorectal cancer care quality among users of the veterans affairs health care system. *Clin Colorectal Cancer*. 2013;12(4):255-260. doi:10.1016/j.clcc.2013.06.004
266. Herzig DO, Buie WD, Weiser MR, et al. Clinical Practice Guidelines for the Surgical Treatment of Patients With Lynch Syndrome. *Dis Colon Rectum*. 2017;60(2):137-143. doi:10.1097/DCR.0000000000000785

APPENDIX A

CODES TO IDENTIFY COLONOSCOPY

Table A.1. CPT, HCPCS, and ICD-9 codes to identify colonoscopy in outpatient dataset

Code	Description
G0105	Colorectal cancer screening; colonoscopy on individual at high risk
G0121	Colorectal cancer screening; colonoscopy on individual not meeting the criteria for high risk
44388	Colonoscopy through stoma
44389	Colonoscopy through stoma with biopsy
44390	Colonoscopy through stoma with foreign body removal
44391	Colonoscopy through stoma with control of bleeding
44392	Colonoscopy through stoma with hot biopsy
44393	Colonoscopy through stoma with ablation of tumor(s), polyp(s) or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
44394	Colonoscopy through stoma with snare
44397	Colonoscopy through stoma with transendoscopic stent placement
45355	Transabdominal colonoscopy via colotomy
45378	Colonoscopy
45379	Colonoscopy with foreign body removal
45380	Colonoscopy with biopsy
45381	Colonoscopy with submucosal injection
45382	Colonoscopy with control of bleeding
45383	Colonoscopy with ablation of tumor(s), polyp(s) or other lesion(s) not amenable to removal by hot biopsy, forceps, bipolar cautery or snare technique
45384	Colonoscopy with hot biopsy
45385	Colonoscopy with snare
45386	Colonoscopy with dilation
45387	Colonoscopy with transendoscopic stent placement
45391	Colonoscopy with endoscopic ultrasound
45392	Colonoscopy with endoscopic ultrasound with FNA
45.21	Transabdominal endoscopy of large intestine
45.22	Endoscopy of large intestine through artificial stoma
45.23	Colonoscopy
45.25	Endoscopic biopsy of large intestine
45.41	Excision of lesion or tissue of large intestine
45.42	Endoscopic polypectomy of large intestine
45.43	Endoscopic destruction of other lesion or tissue of large intestine
48.24	Endoscopic biopsy of rectum
48.36	Endoscopic polypectomy of rectum

APPENDIX B

PREVALENCE ESTIMATES OVER TIME

Table B.1. Prevalence (%) of 1-year surveillance colonoscopy by race and sex over time

	Overall	Men		Women	
Year	Population	White	Black	White	Black
2002	57.0	58.2	49.2	60.4	51 .0
2003	58.9	59.2	44.9	67.6	51.2
2004	53.8	55.0	51.7	56.3	45.7
2005	57.5	60.1	47.9	61.1	49.9
2006	55.2	57.5	43.7	61.7	49.6
2007	55.7	60.0	44.1	61.9	41.6
2008	53.8	58.9	46.5	52.8	48.1
2009	55.5	55.2	59.8	54.1	55.8
2010	53.8	55.3	45.2	58.5	50.4
2011	58.2	58.5	47 .0	62.3	64.1
2012	55.4	52.1	47.6	61.7	58.9
2013	54.2	55.9	52.9	53.2	53.9