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The Contribution of Allostatic Load to Colorectal Cancer Outcomes

By

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CHAPTER 7: A DESCRIPTION OF FINDINGS FOR GENERAL AUDIENCES

7.1 Why write this chapter?

At the Carbone Cancer Center, most of our research is conducted with the goal of reducing the burden of cancer. However, accomplishing this goal will take more than just researchers. Teams of many different people from many different backgrounds need to collaborate to solve the complex issues related to cancer. It is essential that we as scientists can communicate our research so that we can work together on these big problems. I am beyond excited to have the opportunity to write a chapter of my dissertation for a general audience with support, editing, and guidance from the Wisconsin Initiative for Science Literacy (WISL). The goals of the WISL align marvelously with my belief that writing and communication matter and make our science both stronger and more meaningful. To my fellow scientists, I hope this chapter can be an example for sharing your work with the public. To everyone else, I hope this chapter will help you better understand cancer, generally, and my research, specifically. At the end of this chapter, readers can find a set of resources to learn more about cancer and some opportunities to advocate for better cancer research and treatment, for yourself and others.

7.2 What does stress have to do with cancer?

Cancer is a disease of uncontrolled growth that disrupts a body's normal processes. Every cell in your body has an internal instruction manual, called DNA. Damage to this DNA can cause a cell to ignore the signals that tell them to stop growing. Normally, cells die when they get old or damaged. Cancer cells, however, continue to grow and divide. This rapid growth causes a mass of cells called a tumor. When cancerous cells break away from the original tumor, they can travel through the body to start tumors in other places. The process of damaged cells accumulating more damage, allowing them to invade nearby bodily tissue and spread to other parts of the body, is called tumor progression.

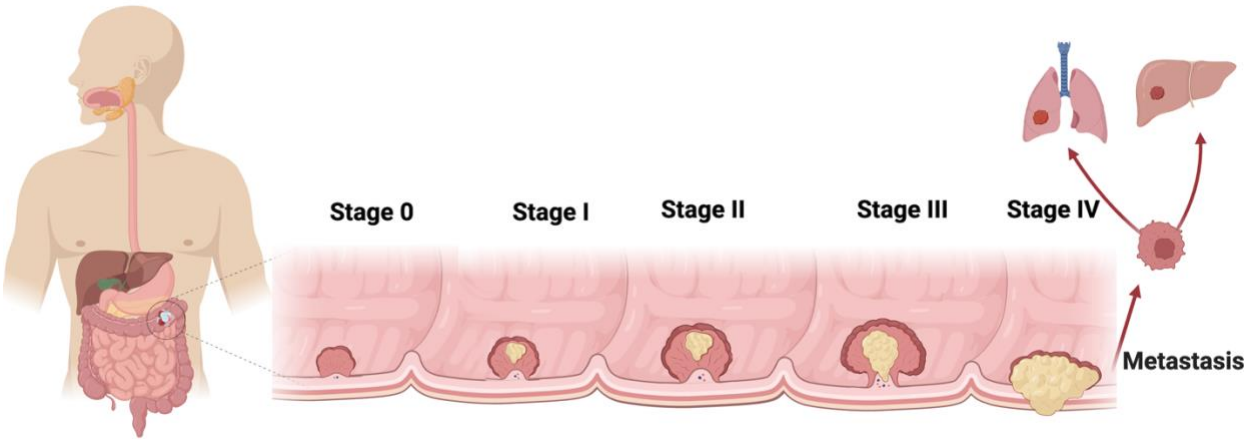

Figure 1. The different stages of colorectal cancer progression.

Created in BioRender. Walts, Z. (2026) https://BioRender.com/ke7gf2t

I study colon and rectum (or colorectal) cancer, the second most deadly cancer in the U.S. Luckily, colorectal cancer is preventable. When tumors first start to grow, they are called "polyps" (Figure 1). Most polyps do not become cancerous, but some do. Screening tests are used to find cancer at an early stage, done when you have no cancer symptoms. For colorectal cancer, colonoscopy screening is used by doctors to examine the colon for polyps, signs that cancer may be developing. The potentially cancerous polyps can be removed during colonoscopies, stopping cancer before it starts. Although colonoscopy doesn't prevent all cancers, it can also improve survival by catching cancer early. Five years after diagnosis, about 90% of patients with early-stage colorectal cancers are still alive compared to about 15% of those with late-stage cancers.

National organizations track colorectal cancer screening (including colonoscopy), diagnosis, and deaths.[237] More than half of all colorectal cancers can be explained by behaviors, including smoking, diet, physical inactivity, and cancer screening. However, modifiable factors do not act alone.[238] Social and environmental factors, such as the resources in one's neighborhood and discrimination from medical professionals, impact whether people can access everything from cancer screening to healthy foods. Social, environmental, and modifiable factors together help us understand why colorectal cancer mortality is 30% higher for Black than

white individuals. It also shows us that we can change disparities. By making screening free and accessible, covering treatment, and hiring staff to support patients, Delaware almost completely eliminated differences in colorectal cancer mortality by racial identity.[239]

As I learned more about racial mortality disparities, I noticed a tool called “allostatic load.” Allostatic load measures the impact of stress on your body by measuring health of the cardiovascular, immune, and metabolic systems. These systems are activated by the brain when facing stress. Increasing your heart rate and blood pressure can prepare you to run away from a threat, but if these systems are activated very often or for a long time, the systems may be harmed. Over time, the consequences of stress can be made worse by social and environmental factors, like poor healthcare access, or smoking. As a result, high allostatic load is more common among Black and low-income Americans.[240] Symptoms of depression, another consequence of stress, is also more common in these groups.[241]

Some researchers focus on understanding how cancer works in animals like mice to give us clues about how cancer might work in humans. Mouse studies reveal that stress may directly impact colorectal cancer. Mice exposed to chronic stress have different levels of certain gut bacteria[83] and different cellular environments.[84] Because of these changes, stressed mice had more tumors and these tumors were more likely to spread. Importantly, these biological pathways have not yet been studied in humans.

Epidemiologists, like myself, use large data sets that include information collected from many people to understand how much the factors identified by other researchers influence outcomes in human cancer patients. Studies show that high allostatic load increases mortality risk twofold in the month after colorectal cancer surgery, as well as increasing the number of surgical complications,[48] and major cardiac events.[44] These findings help us to start thinking about the things we could do to reduce the risk of death for colorectal cancer patients.

Through both its impact on tumor progression identified in mice studies, and through its direct impacts on mortality identified in epidemiologic studies, stress is likely to create poor

outcomes for colorectal cancer patients (Figure 2). My dissertation uses epidemiological research methods to ask an important question that I believe is central to understanding why sccolorectal cancer impacts some groups more than others:

How does chronic stress impact colorectal cancer, and how might we use our understanding of chronic stress to improve patient outcomes?

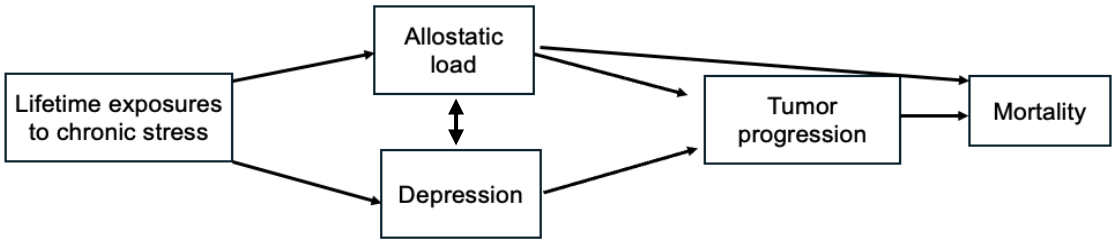

Figure 2 – Conceptual model of the relationship between allostatic load and colorectal cancer

7.3 So what did I do?

My project was defined by three specific hypotheses, broken into three papers.

Because both depression and allostatic load can be caused by stress, we would expect that those with high allostatic load are more likely to also have depression. In previous studies, this relationship is strong, increasing our confidence that allostatic load is measuring some aspect of stress. However, this has not been studied in some populations. **This led to my first question: Are those with high allostatic load more likely to have depression in our unique sample?**

Previous research also consistently finds that high allostatic load increases the risk of mortality for cancer patients, but, again, this has not yet been studied in some populations. **This led to my second question: What is the impact of allostatic load on colorectal cancer mortality in our unique sample?**

Finally, many scientists hypothesize that allostatic load could be used in cancer clinics to identify whether patients need additional services, such as financial support, cardiovascular

disease monitoring, or post-surgical observation, to improve their outcomes. However, no one has worked with staff of cancer clinics to understand how using allostatic load might benefit patients. **This led to my third question: How might allostatic load improve the current processes cancer clinics use to support colorectal cancer patients?**

I chose my dissertation project because of biases that I identified in the existing research about allostatic load and colorectal cancer outcomes. Biases can make it more difficult to accurately estimate how a certain factor, like allostatic load, impacts cancer. Observational data is the type of data most commonly used by epidemiologists. “Observational data” is information collected by measuring health, behaviors, and events in their natural setting without intervening or controlling the subjects of the research. Observational data is different from experimental data. In an experiment, researchers might compare two very similar groups where only one group received a treatment in order to see how the treatment impacts the patients. Researchers often exclude people with common diseases like diabetes, obesity and depression from these studies to reduce the chance that these conditions will impact the findings of the experiment. While experimental data is a great tool to understand exactly how a treatment works, the highly controlled environment makes it difficult to translate these findings into the real world. This is where observational data shines. Because we are watching people in their natural settings, our findings are much more likely to reflect how exposures, like allostatic load, impact outcomes in the real world.

The three major categories of bias in observational data are **selection bias**, **information bias**, and **confounding bias**. From the beginning, I hoped that by addressing these biases, I could help change allostatic load from a research tool to a clinical tool. If allostatic load can identify colorectal cancer patients who are at higher risk for heart disease and surgical or other complications, maybe we can deliver targeted services to reduce those risks.

Most studies are based on primarily white samples, even though Black and low-income populations experience higher allostatic load and worse cancer outcomes. Additionally, few

existing studies focus on colorectal cancer, despite the disease's established disparities by racial identity and socioeconomic status. This is an issue of **selection bias**. **Selection bias** occurs when there are differences between who participates in a study and who does not. One way to overcome **selection bias** is to see whether what we know from previous studies can be observed in different groups of people. In my research, I use data from the Southern Community Cohort Study (SCCS). which is unique because it includes a high number of people historically excluded from other studies, including those who live in rural areas, identify as Black, and report low income. Addressing **selection bias** improves our confidence that allostatic load is a useful tool for patient populations that face health disparities.

Information biases occur when the data we collect about participants is inaccurate. All SCCS participants filled out a survey about their demographics, behaviors, and health history when they entered the study. Standardized surveys combat **information bias** by ensuring that questions are delivered to all participants in the same way. Many participants used computers to complete surveys, combatting **information bias** by ensuring that social pressure from an interviewer won't change the way someone answers questions. Some participants also provided blood samples when they entered the study. The baseline data collected and managed by the staff of the SCCS and their partners and doctor's offices across the Southeastern US allowed me to calculate each participant's allostatic load before cancer developed, making sure that the impact of cancer or its treatment did not impact our data (Figure 3). To collect data about who developed incident, or new, cancers and when, we used government-maintained data registries. We also used government data registries to collect data on who died and when after enrolling in the SCCS. The rigorous procedures of government surveillance data from state cancer registries and the National Death Index made sure that we had high-quality diagnosis and mortality data for all participants.

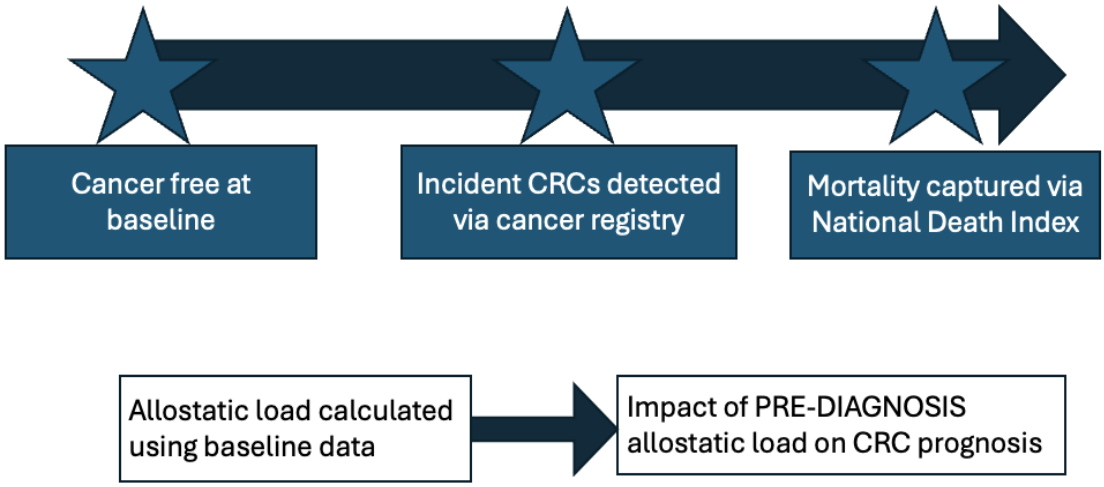

Figure 3 – Timing of Southern Community Cohort Study data collection made sure that I could achieve my study objectives

I calculated allostatic load using a combination of biomarker data from blood samples and health history data from surveys. Blood biomarkers are simply markers of bodily function which are found in the blood. For example, A1C is a protein in the blood that interacts with sugar present in the blood stream. Doctors measure A1C to understand how your body regulates sugar. I chose to use an existing definition of allostatic load which includes 10 biomarkers from across the cardiovascular, metabolic, and immune systems. Each biomarker was assigned a score: “1” for “high-risk” or “0” for “low-risk.” I added together the number of biomarkers at potentially dangerous levels for each participant, in order to get a score that describes the total health of systems associated with the stress response.

Another common type of bias is **confounding bias**. Confounding occurs when an observed association has an alternate explanation. When this third, hidden factor is linked both to the exposure and the outcome under study, it can blur the results, making it look like the exposure has either more or less of an impact on the outcome than it truly does. For example, if you were to survey a group of people about whether or not they carried matches, we might find

that, after 10 years, those who carried matches were more likely to develop lung cancer. However, it might be clear to you that people who carry matches are more likely to smoke cigarettes. In this example, cigarette smoking, not carrying matches, is the true reason for the increased risk of lung cancer.

I handled **confounding bias** in two ways. First, I included variables known or suspected to be related to both the exposure and outcome under study in our statistical models. Discussions with my dissertation committee members and reading other research articles helped me decide what to include. In the first study, I included variables related both to depression and stress such as age, sex, race, insurance status, education and marital status. In the second study, I included variables related both to stress and mortality such as age, cancer stage at diagnosis, previous cancer, family history of colorectal cancers, sex, race, insurance status, colorectal cancer screening participation, smoking status, and alcohol intake. Including these variables in my models uses statistics to make our participants more similar. By holding these potential “alternate explanations” constant, I can more directly see how allostatic load is related to depression and mortality. Another important way to combat **confounding bias** is to investigate how the relationships between exposure and outcome might vary across groups. I used statistical tests to detect differences in associations by race, sex, socioeconomic status, and treatment.

In Project 1, I wanted to extend confidence in allostatic load as a measure of stress to racially and socioeconomically diverse populations. To do this, I used baseline data from an existing sub-sample of 939 SCCS participants, including both those who would later be diagnosed with colorectal cancer and those who never developed colorectal cancer. I used a statistical measure called an odds ratio to describe the association between allostatic load and depression. An odds ratio shows how much more (or less) likely an event is to happen in one group compared to another group. An odds ratio above 1 would show that patients with high allostatic load are more likely to have depression. We ultimately found that those with

depression had higher odds of also having a high allostatic load score (odds ratio: 1.74). Statistical tests showed that the relationship between depression and allostatic load was the same in men and women, in Black and white participants, and whether participants did or did not later develop colorectal cancer.

In Project 2, my goals largely remained the same. This time, I wanted to extend the confidence in allostatic load as a predictor of mortality to colorectal cancer patients in the SCCS. To do this, I focused on a subset of the 1058 participants who have, to date, developed colorectal cancer after enrolling in the study. Like I mentioned, about a quarter of participants provided the blood samples required to measure most allostatic load biomarkers. As a result, my sample included 303 participants who both 1) had baseline measurements of allostatic load and 2) had developed colorectal cancer after entering into the SCCS. This time, I used a measure called a hazard ratio to show how fast or slow mortality occurs in one group compared to the other. A hazard ratio above 1 shows that patients with high allostatic load are at higher risk of mortality. I found those with a high compared to a low allostatic load prior to their cancer diagnosis had a higher mortality risk after being diagnosed with colorectal cancer (hazard ratio: 1.81).

I found some variation in this association. Among those with later stage disease, which had already metastasized at the time of diagnosis, high allostatic load was associated with a 173% higher mortality risk compared to those with low allostatic load (hazard ratio: 2.73). Allostatic load was not associated with mortality for those who did not receive surgery. In those with an education of less than high school, high allostatic load was associated with almost a two-fold increase in mortality (hazard ratio: 1.76). In those with annual household income of less than $15,000 at baseline, high allostatic load was associated with over two-fold increase in mortality (hazard ratio: 2.24). However, among those with an education of high school or more or an annual household income of $15,000 or more, allostatic load was not related to mortality

risk. This is a clue that resources such as income or education might help participants manage the impact of stress on mortality.

In Project 3, I wanted to understand the potential benefits and challenges of using allostatic load in the clinic. With another graduate student trained in interview-based research and my dissertation chair, we conducted three focus groups with clinical staff at the University of Wisconsin Carbone Cancer Center. These groups included 3 oncologists, 3 patient navigation nursing staff, and 3 patient intake nursing staff. We talked to different kinds of providers and both myself and my fellow student researcher read the focus group transcripts to identify themes. If the three groups of clinical staff said similar things and the two readers identified similar themes, it reduces the chance that personal biases are impacting our conclusions. We learned that it is standard clinical practice to use surveys to help identify the needs of individual cancer patients. However, some patients are less likely to complete these surveys and may not always understand what they need for successful treatment. Simply put, the ways we identify colorectal cancer patients who need additional support are not working for everyone. Although everyone agreed that more specific research about allostatic load is needed before it can be used in the clinic, our participants also agreed that identifying patients with high allostatic load might help us catch high-risk patients who are missed by surveys.

There are two major lessons that I hope readers will take away from my work. First, allostatic load is a promising objective tool to identify colorectal cancer patients who are at increased risk of mortality. Second, collecting focus group interview data can improve the clinical potential of a new tool. When you understand the needs of clinicians facing patients every day, we are more likely to develop tools that will support improved patient outcomes.

I hope that by reframing the way we approach cancer care to be more holistic, considering how stress can impact cancer outcomes and how social systems like education interact with this relationship, that I can help to push our clinics towards taking care of the whole person, not just the cancer.

7.4 Creating a new epidemiology: Opportunities to include communities in cancer research and advocacy

In late 2023, exhausted from a months-long battle for my doctors to take my symptoms seriously, I read in my medical record that my doctor described me as “weepy and easily upset.” This deflated me completely. I was reduced to my worst moments and left with the feeling that my doctor considered me unreasonable, or too demanding. My knowledge about medical science was central to my healing journey. By listening to my symptoms, I knew something in my body was wrong, and I knew which kinds of doctors specialized in treating my symptoms. Armed with this trust in myself and medical science, I continued to advocate for myself until I found someone who could treat my symptoms, even when some doctors dismissed me.

This is not everyone’s experience. My insurance allowed me to meet several different doctors until I found one who could help me. My flexible schedule, being a graduate student, allowed me to schedule appointments at any time of day. These are two among the many reasons that I am no longer in debilitating pain. Not all patients have the time, resources, knowledge, or desire to advocate. As a scientist, and as a patient, patient advocacy is necessary to create health solutions that work for everyone. There are many opportunities to use community members’ thoughts, priorities, and expertise to make epidemiology research work better for patients.

Community Advocacy Boards

Twice during my dissertation research, I presented my findings to the Statewide Community Advisory Board at the University of Wisconsin Carbone Cancer Center. First, to propose my hypotheses and then to share my findings. Meetings with the Community Advisory Board helped me to understand the importance of education, insurance, and income in determining colorectal cancer outcomes. Patients can join community advocacy boards to voice their priorities. Community insight helps researchers focus on relevant questions, conduct trustworthy studies, and share findings with the community.

Please find a list of Community resources from the Carbone Cancer Center

- Cancer Research Summaries for the General Public are designed to help community members understand cancer research.
    - To see these summaries, visit the following webpage: https://cancer.wisc.edu/resources-for-the-community/
- Information on Community Advocacy Boards at Carbone Cancer Center show community members in Wisconsin how to get involved in research.
    - Visit the following webpage for more information: https://cancer.wisc.edu/community-outreach-and-engagement/community-advocacy-board/

Other opportunities to engage with cancer research and advocacy

Beyond Community Advocacy Boards at the Carbone Cancer Center, many national organizations are working to bring the patient voice and lived experience into science by collecting data from groups who are under-represented in research, supporting funding for cancer research, and training research advocates.

- Queer cancer patients and caretakers can take the OUT Survey to help inform the research priorities for these populations: https://www.cancer-network.org/out-surveys/
- The American Cancer Society's Cancer Action Network advocates for evidence-based public policies to reduce the cancer burden for everyone by engaging volunteers across the country to make their voices heard by policymakers at every level of government: https://www.fightcancer.org/
- Learn more about becoming a cancer research advocate at Progress for Patients, an online advocacy education program and community working to help patients, advocates, and caregivers acquire the necessary tools to effectively communicate with drug researchers, developers, and regulators: https://progressforpatients.org/

Patient advocacy, support and resources for patients and their families.

Patient advocacy and patient support empower individuals and their families to navigate complex healthcare systems, foster informed decisions, and provide essential emotional and practical help, leading to better outcomes and experiences.

- The U.S. Centers for Medicare & Medicaid Services offer some resources to find patient advocates who can help you navigate the healthcare system: https://www.cms.gov/medical-bill-rights/help/guides/patient-advocate
- The Cancer Hope Network matches cancer patients or family members with trained volunteers who have undergone and recovered from a similar cancer experience: https://cancerhopenetwork.org/
- Access support groups organized by the Colorectal Cancer Alliance, including BlueHQ, their online support hub: https://colorectalcancer.org/resources-support/community-support/online-communities-colorectal-cancer-patients-and-families
- The American Cancer Society holds many support groups and offers many educational resources, with options for everybody. Access online and nationwide cancer support services, e-mail-based discussion groups, and online classes: https://www.cancer.org/support-programs-and-services/online-communities.html
- The Cancer Network maintains a list of LGBTQIA+ welcoming care providers, from cancer screening to survivorship: https://www.cancer-network.org/cancer-treatment-screening-providers/