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Understanding colon cancer risk: a review of determinants and implications

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Thesis

UNDERSTANDING COLON CANCER RISK:

A REVIEW OF DETERMINANTS AND IMPLICATIONS

by

MAEGAN MAY AVERY

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Approved by

First Reader

Kimberly Bertrand, ScD
Associate Professor of Medicine

Second Reader

Emily Nowicki, PhD
Associate Professor of Natural Sciences and Mathematics
Curry College

DEDICATION

I would like to dedicate this work to my father, David Avery, who passed away of metastatic colon cancer in April 2023 after a fight with the disease that was silent until it reached the end. Dad, you have always pushed me to continue my education and research, and watching you fight this horrible disease with such dignity and bravery ignited a passion to bring the subject of colon cancer to light to help others understand the importance of assessing their risk. Your constant love and support have helped me grow into the academic I am today, and I could not have completed this research without your inspiration.

UNDERSTANDING COLON CANCER RISK:

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ABSTRACT

In 2024, the Colorectal Cancer Alliance reported that colon cancer remains in the top five most prevalent cancers within the United States, and the second main cause of cancer-related deaths. Epidemiological evidence shows that approximately half of colon cancer cases can be attributed to risk factors deemed as 'modifiable,' such as lifestyle and activity, low calcium intake, alcohol consumption, and excessive body fat. These factors promote carcinogenesis through increased inflammatory signals impacting downstream signaling pathways that regulate cellular processes for growth, survival and differentiation. High levels of inflammation are characteristics of both obesity and nonalcoholic fatty liver disease (NAFLD), though NAFLD contributes also through excess fat deposits in the liver. Conditions such as vitamin D deficiency promote tumor growth by changes in gene expression, cellular processes in the gastrointestinal system, and by promoting angiogenesis. Hyperinsulinemia, which then causes the over-secretion of hormone free insulin-like growth factor 1 (IGF-1), promotes tumor development through their anti-apoptotic effects. This thesis will discuss the contribution and roles these modifiable risk factors play in colon cancer development and the biological mechanisms underlying these associations as well as how lifestyle changes can help to reduce risk of the disease.

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INTRODUCTION

Colon Cancer

Colon cancer, defined as "a type of gastrointestinal malignancy originating from either the colon or rectum" (Mattiuzzi et.al), is the second most deadly and most frequently diagnosed cancer in the United States. In 2023, it was concluded that about 153,000 new cases of colon cancer were diagnosed, making up 7.8% of all diagnosed cancers (Menon, Cagir 2024). Men are 53% more likely to develop the disease and develop it at a younger age compared to women. Within the past several years, there has been a global increase in colon cancer incidence within individuals under the age of 50, and the prevalence of the disease in this age group is increasing more rapidly compared to those over the age of 50 (Sifaki-Pistolla et.al 2022). Interestingly, only 20% of colon cancer cases in younger people are due to a genetic pre-disposition, with most cases having no hereditary genetic cause of cancer development (Spaander et.al 2023). Colon cancer occurrence also differs between races and ethnicities within the United States, with Black Americans having the highest rate of colon cancer incidence and highest mortality rate (Carethers 2022). The reasoning for the increase in incidence among younger people and the large disparity among races has not yet been entirely discovered, though low socioeconomic status and increased intake of tobacco and alcohol are thought to be relevant to the development of the disease.

Through preventive screening and early diagnosis, the mortality of colorectal cancer has significantly decreased in the past several years (Mattiuzzi et.al). Despite this,

most cases of colon cancer are diagnosed after the onset of symptoms (Mattiuzzi et.al), with 50-60% of patients diagnosed developing metastases and 80-90% of those patients developing liver metastases that are unresectable (Benson et.al 2011). Therefore, screening is key to for early detection improving patient prognosis, or to remove potentially cancerous polyps.

The most widely accepted view of cancer is that it develops due to the accumulation of mutations in tumor suppressor oncogenes that lead to the conversion of normal cells to cancerous cells (Lao, Grady 2011). Cells containing mutations allowing for uncontrolled growth and proliferation are able to pass through cell cycle checkpoints without being flagged, leading to tumor growth. Colon cancer is a unique cancer type, as almost all cases of colon cancer begin from a precancerous, typically benign polyp that can develop further into a malignant adenoma **(Figure 1)**. Polyps are defined as protrusions in the lumen of the colon that can be adenomatous, serrated, or non-neoplastic (Meseeha, Attia 2023). Polyps are typically detected through colonoscopy as they are asymptomatic and are biopsied after colonoscopy for detection of colon cancer. Though not all polyps will become cancerous, the presence of polyps occurring before colon cancer development is what makes colonoscopies a preventative measure for colon cancer development as the disease is often asymptomatic until advanced progression (Meseeha, Attia 2023). According to the National Comprehensive Cancer Network, about 20% of colon cancer cases are associated with first-degree relatives having the disease (Benson et.al 2011). Briefly worth mentioning are the rare inherited genetic conditions that make a person more susceptible to colon cancer development, such as Lynch

syndrome and familial adenomatous polyposis that are defined by mutations and changes in the DNA mismatch repair system. The genomic classification of colon cancers and other cancers in general is difficult to determine as their role in cancer development could be through many different mutation patterns. 95% of colon cancer cases are adenocarcinomas, defined as a cancer starting in the glandular cells. Though many cases are asymptomatic as previously stated, symptoms of the disease that can alert for a patient's need for colonoscopy can include changes in bowel movements, blood in the stool, unexplained weight loss and fatigue, and iron deficiency anemia (Menon, Cagir 2024). Diagnoses are made via imaging, colonoscopy and tissue biopsy. Pathologists can also perform molecular testing for specific genetic markers consistent with colorectal cancer (WHO 2023). Progressed forms of colon cancer are prone to distant metastases, with the liver being the main site of metastasis and a small percentage of patients already having some sort of metastasis at the time of diagnosis. The metastatic patterns help to guide physicians in differentiating between a colon or rectal cancer diagnosis, which is important as the two cancer types differ in terms of staging, treatment, and surgical approaches (Tamas et.al 2015).

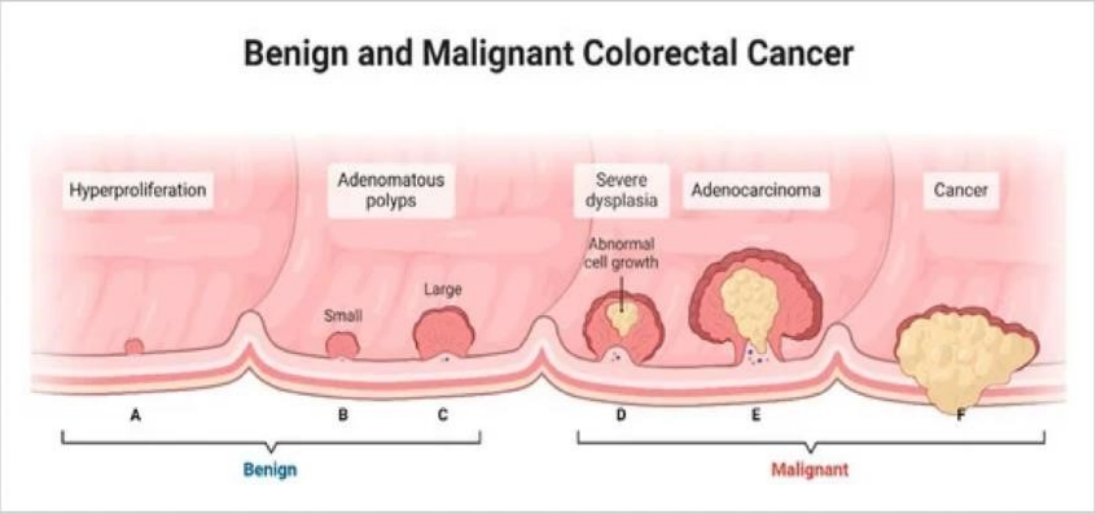


Figure 1. Gradual development of cancerous tumors in the colon. Tumors develop from benign to malignant through abnormal and uncontrolled proliferation and invasion into the lining of the colon. Image from (Gharib, Robichaud 2024).

If caught early enough, surgical resection of the tumor can be done to remove the cancer if it is limited to the colon and has no distant metastases. The use of chemotherapy in addition to surgery can kill any cancer cells potentially still present after surgical removal of the tumor to prevent recurrence of the cancer (WHO 2023). In patients with advanced stages of the disease, different types of treatment such as targeted or immunotherapy can be used in combination with chemotherapy if their cancer displays a mutation in genes coding for the BRAF or KRAS proteins, which alter the RAS/MAPK signaling pathway resulting in uncontrolled cellular proliferation. Tumors can also express genetic markers that make immunotherapy ideal to target them (WHO 2023). It is noted throughout the literature that colonoscopies are essential to early detection in order to prevent advanced silent development of the disease and that continued surveillance can prevent recurrence of the disease.

STAGE	RECURRENCE RATE
STAGE 1 - Cancer is limited to the lining of the colon.	Risk of recurrence is approximately 5% after surgical resection.
STAGE 2 - Cancer has spread through colon lining but is still limited to the colon only.	Risk increased to 10-12% after surgical resection.
STAGE 3 - Cancer has spread from colon to the lymph nodes.	Risk grows to 30% after combination of surgery and chemotherapy.
STAGE 4 - Cancer has spread beyond just lymph nodes and has metastasized to organs such as the liver.	Disease is less likely to be cured with treatment, but specialized therapies can help prevent further metastasis and improve quality of life.

Table 1. Risk of cancer recurrence after treatment based on staging of the disease. Information listed in this table is from (Berkley 2022).

For most patients, symptoms may be "silent" until the disease has grown and spread. This underscores the importance of understanding risk factors that predispose an individual to the disease. Viewing genetic predisposition or family history as non-modifiable or non-treatable risks and the lifestyle/epigenetic factors discussed in this thesis as modifiable or treatable offer a framework for educating the population on how they can potentially decrease their risk of colon cancer. There is evidence to support the idea that risk of colon cancer development can be attributed to lifestyle and dietary factors **(Table 1)**, such as lack of physical activity, smoking and high alcohol consumption, and a diet high in processed red meats (Sandler 1996). Previous research on this topic has shown that these lifestyle choices are the most crucial determinants of the risk of colon cancer development (Sandler 1996). Consensus among researchers, though, is that obesity is the largest contributing lifestyle factor putting those at risk of colon cancer, as it not only imposes its own mechanism of cancer development but can also

encompass some or all the lifestyle and dietary factors previously mentioned. While public awareness has been more focused towards changing diet and lifestyle to decrease colon cancer risk, the influence of obesity – as well as the mechanisms by which it contributes to increased colon cancer risk – has not been emphasized as strongly. Though obesity is considered a lifestyle factor, it is relevant to note the epigenetic changes to gene expression done through the obesity-induced cellular changes to DNA. The goal of this work is to recognize and highlight these mechanisms to provide a more in-depth picture to the general public of how vital these treatable factors can be when assessing colon cancer risk.

Though it can be said that obesity plays a central role in colon cancer development, there are other metabolic changes that can occur as an incidence of obesity, such as vitamin D deficiency, chronic hyperinsulinemia, and non-alcoholic fatty liver disease (NAFLD). Epidemiological data supports the association between vitamin D deficiency and increased risk of colon cancer (Pereira et.al) with non-alcoholic fatty liver disease increasing the risk as well (Po-Hsieng et.al). The combination of treatable risk factors is important to consider in addition to genetics when determining one's overall likelihood of developing colon cancer.

Table 2. Modifiable factors contributing to increased risk of colon cancer. Statistics provided by (Vallis, Wang 2022).

MODIFIABLE FACTORS	RISK
Obesity	**18-32% greater risk**
Chronic hyperinsulinemia	**Increased risk due to promotion of IGF-1**
Non-alcoholic fatty liver disease	**Increased hyperinsulinemia**
Vitamin D deficiency	**Lack of anti-tumoral actions of vitamin D**
Lack of physical activity	**44% greater risk**
Processed and red meats	**10-16% increased risk per 100g/day of red meats, 16-22% increase per 50g/day of processed meats**
Smoking	**17-25% greater risk**
Heavy alcohol consumption	**21-52% greater risk**

Introduction to Treatable/Modifiable Risk Factors

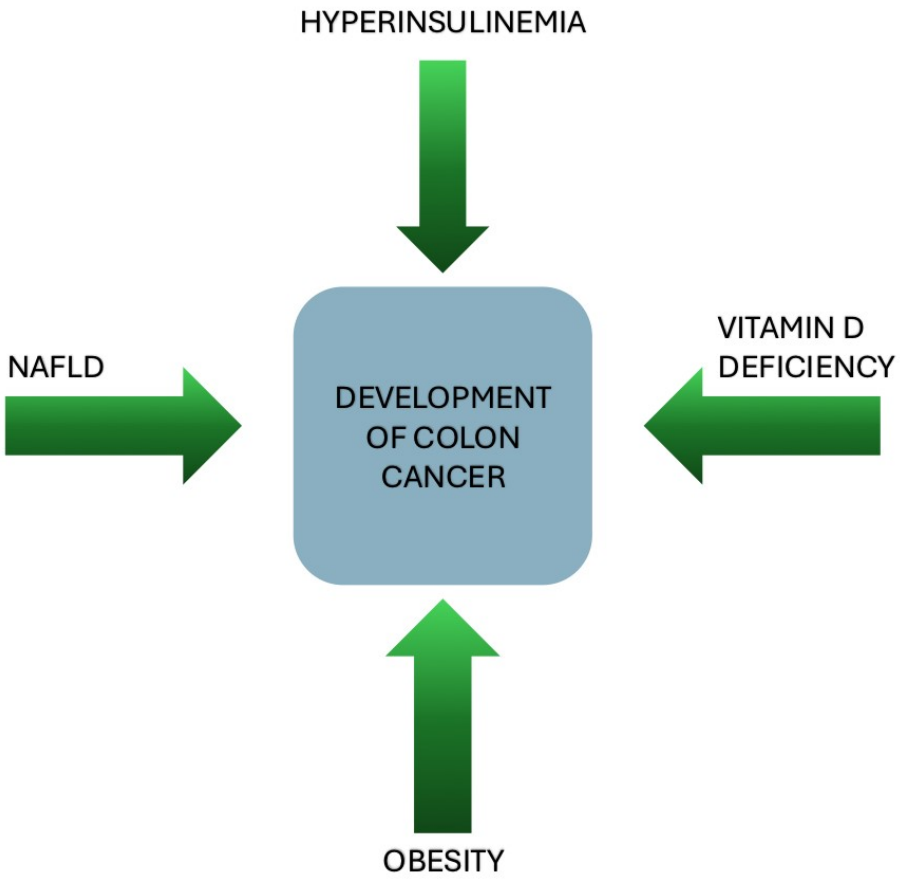


Figure 2. Treatable/modifiable risk factors related to colon cancer development. Factors such as obesity, hyperinsulinemia, vitamin D deficiency, and nonalcoholic fatty liver disease are all modifiable risk factors contributing to increased risk of colon cancer development that will be discussed throughout the chapters of this thesis.

Obesity, or the overconsumption of energy, is one of the major contributions to increased risk of colon cancer in Western countries (Giovannuci 2002) due to changes in metabolism and adipocyte function specifically, leading to a state of chronic inflammation. It is also understood that certain nutrients, such as fiber-rich foods, vitamins and minerals have anti-cancer properties when consumed by patients struggling with obesity (Zeng,

Lazarova 2011). Excess energy intake causing obesity leads to insulin resistance and hyperinsulinemia, with recent evidence showing its link to colon cancer **(Table 2)** (Giovannuci 2002). Hyperinsulinemia increases production of insulin-like growth factor 1, which can increase colorectal neoplasia, or the abnormal growth of cells within the colon, (Giovannuci 2002) that will be discussed in greater detail in further chapters.

Although the association between NAFLD and colon cancer is not entirely understood or well researched, there are several hypotheses supporting a possible association. One of these hypotheses is that hyperinsulinemia and increased growth factor, as well as the disruption of balance between adipokines leading to development of neoplasm (Po-Hsien et.al).

Recent epidemiological studies have shown that vitamin D deficiency is associated with greater risk of colon cancer (Pereira et.al). A 2022 study done by Na et.al conducted a meta-analysis of 5,706 cases of colon cancer with wide ranges of serum vitamin D levels, and found that insufficient vitamin D levels were associated with a 31% increase in risk of colon cancer development (Na et.al 2022). This is attributed to the lack of gene expression regulation that can induce cell differentiation and de-sensitizes cells to apoptosis (Pereira et.al). Deficiency of vitamin D decreases in anti-tumoral abilities in the progression of colon cancer malignancy.

Consideration of these modifiable risk factors in a patient are important so that education on colon cancer or recommendations for colonoscopy can occur. Current understanding is that leading a healthy lifestyle and/or seeking treatment of these factors can diminish the risk of not just colon cancer development, but other cancers as well. In

further chapters of this thesis, the modifiable lifestyle/epigenetic risk factors associated with colon cancer risk will be discussed in terms of mechanism and prevention, as well as ways in which treating these factors can decrease one's risk of developing colon cancer.

Specific Aims

The objective of this thesis is to review current literature to determine plausible and modifiable risk factors that increase a person's risk of developing colon cancer. I aim to draw a conclusion that ties multiple risk factors together to potentially influence and advocate for the need of early colon cancer screening, as well public education regarding ways to decrease risk of developing colon cancer.

CHAPTER ONE

Obesity

The role of obesity in the development of cancers, specifically colon cancer, is a topic that has been well-studied previously and has been proven to increase the risk of colon cancer development by 1.5-2-fold (Huang, Chen 2009). Despite this, the mechanisms that link obesity and colon cancer are not yet entirely understood. Prior research on the topic has discussed dietary factors, the inflammatory involvement of adipose tissue in cancer development, and the role of bariatric surgery in the possible prevention of colon cancer. Obesity is noted as one of the most common preventable diseases and is caused by many factors such as genetics, lack of energy expenditure, socioeconomic standing, and even psychological influence (Khanna et.al 2022). The World Health Organization has reported that as of 2022, 43% of adults were overweight, with 16% of those suffering from obesity (WHO 2024). Obesity is defined as a chronic disease characterized by excessive fat deposits negatively impacting one's health (WHO 2024). A diagnosis of obesity is made using a patient's body mass index (BMI); a number calculated by dividing the patient's wight in kilograms by their height in meters squared $BMI = \text{weight (kg)} / [\text{height (m)}]^2$ (CDC 2024). More recently, discussion around the usefulness of BMI have come up, as BMI does not paint a full picture of the impact a person's obesity has on their body, though there is no method recommended over another. More accurate measurements have been introduced, such as circumference of the abdomen, skinfold measurement to measure the thickness of the subcutaneous fat, and a person's total body water (Duren et.al 2008). All of these examples are used as a more

accurate look at the total picture caused by a person's obesity, but there is no favorable measure at this time.

In the context of colon cancer risk, the relationship with BMI has been closely studied, and it has been reported that as BMI increased by 2 kg/m^2, colon cancer risk increased by as much as 7% (Calle, Kaaks 2004). The role of obesity has been studied in many pathological processes and is known to be involved in heart disease and reproductive issues. This chapter will explore and examine the increased risk of colon cancer development in patients with obesity.

Changes and expansion of adipose tissue are characteristic in obesity, in which the adipose tissue "expands to accommodate excessive caloric intake and markedly changes its structure and cellular composition" (Fuster et.al 2017). Types of adipose tissue include white and brown, and they differ regarding morphology and location within the body. Specifically, white adipose tissue can be defined as either subcutaneous or visceral, with visceral tissue being adjacent to internal organs. Adipose tissue as an organ is known to play a role in inflammatory reactions throughout the body, mostly through the release of cytokines, chemokines and hormones (Chait, Hartigh 2020). Normally, adipose tissue plays a role in the regulation of energy and is used as storage for excess triglycerides that are mobilized to be used in times of nutrient need. Individuals with obesity are known to have excessive amounts of adipose tissue and visceral fat. Visceral fat is "highly metabolically active" and releases free fatty acids into circulation. In these individuals, when capacity for adipocytes is reached, the adipose tissue accumulates viscerally in the liver, skeletal muscle, and pancreatic beta cells (Chait, Haritgh 2020). With the expansion

of the adipose tissue in individuals with obesity, the adipocytes grow larger and larger, eventually becoming hypoxic as they move further away from blood supply (Zwezdaryk et. al 2018).

Other studies have demonstrated that the number of inflammatory macrophages can increase in this adipose tissue, causing it to become dysregulated and inflamed. Generally, the role of inflammation in the promotion of the pathological processes of cancer is due to increased cellular proliferation and damage to cellular signal pathways that regulate cell survival and growth. The chronic inflammation experienced by patients with obesity is the most favorable environment for the carcinogenesis of obesity-related cancers, specifically colon cancer. The rising amount of inflammation has been shown to be one of the most important links between colon cancer and obesity and has been evidenced using anti-inflammatory drugs reducing colon cancer risk by inhibiting COX-2, a prostaglandin (lipid compound) involved in the inflammation pathway (Heng, Lazarova 2011). Therefore, it can be concluded that obese patients with increased visceral adipose tissue experience increased amounts of inflammation, increasing the influence of these cellular processes on the development of cancer **(Figure 3).**

There are two specific hormones released by adipocytes, the cells that make up the adipose tissue: leptin and adiponectin. Both hormones play a role in regulating and promoting the expenditure of energy and have been thought to be involved in the relationship between colon cancer and obesity (Chen, Huang 2009), as well as regulating the signal pathways thought to be responsible for the growth and survival of cancerous cells.

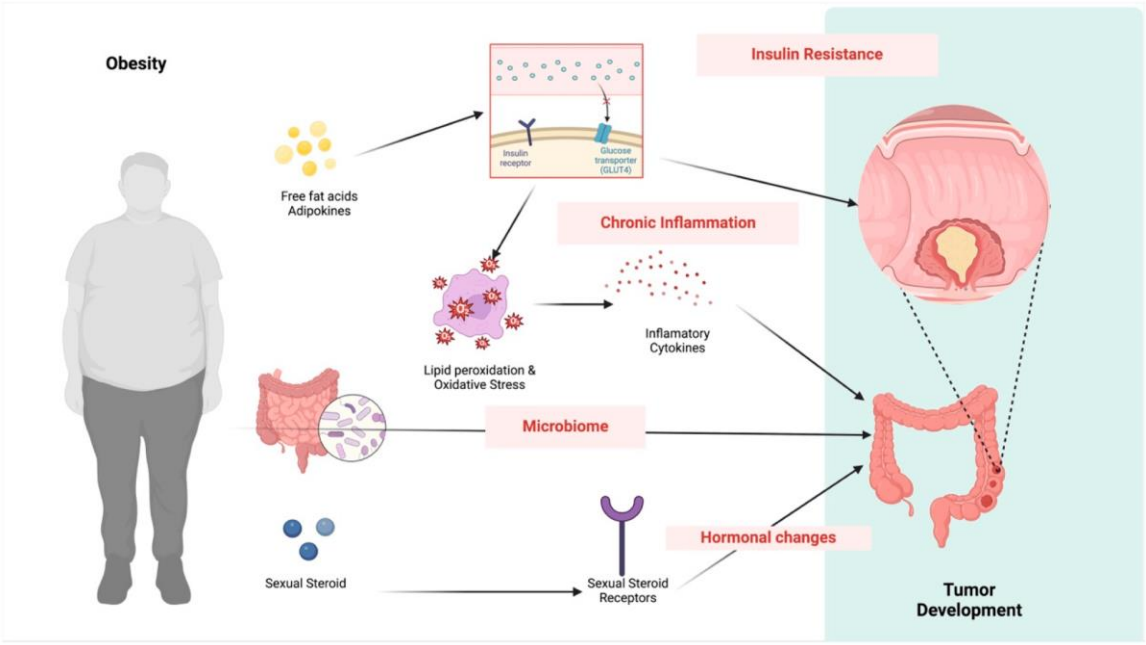


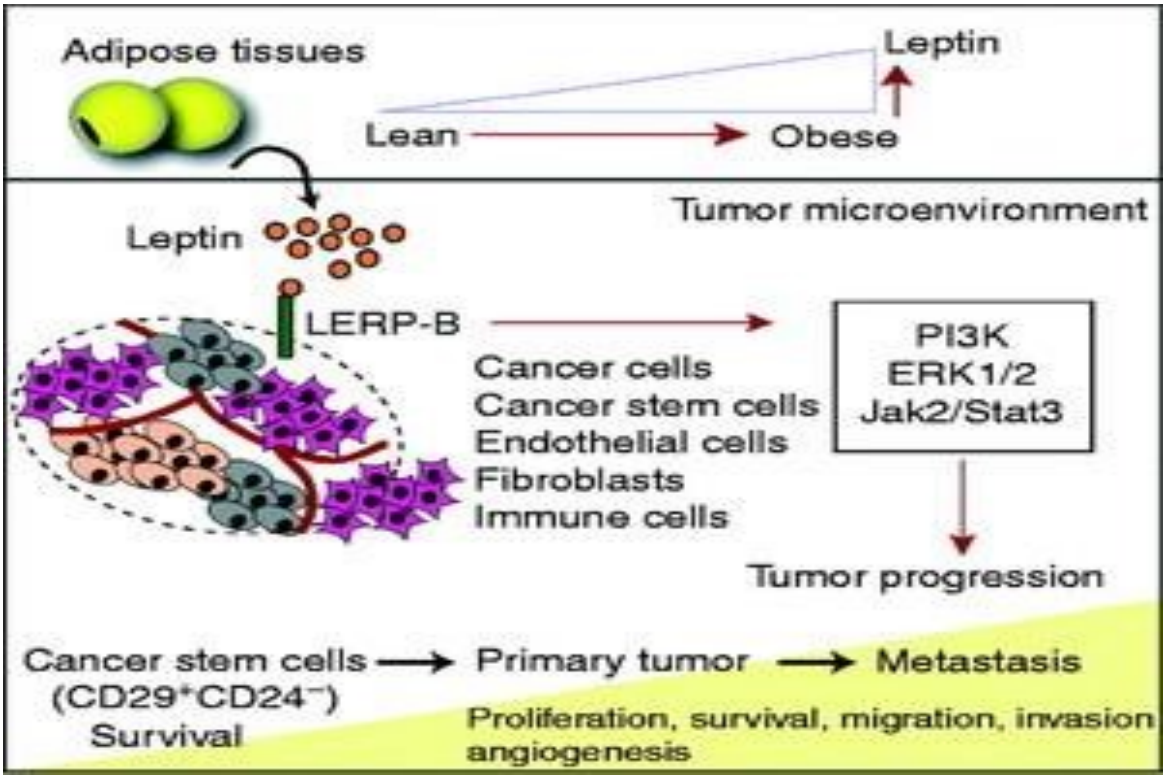
Figure 3. Mechanisms of Obesity-Related Colon Cancer Development. Several mechanisms by which obesity drives forward the development of colon cancer, such as hormonal changes and chronic inflammation. Image from (Miranda et.al 2024).

1. Leptin

Leptin is characterized as an adipokine; it is a hormone released by the adipose tissue and is involved in regulating energy expenditure, metabolism, appetite, and insulin sensitivity. Levels of leptin rise dramatically in obesity and its receptors are expressed in many tissues throughout the body (Park et.al 2015), and its release is directly proportional to the amount of fat an individual possesses (Booth et.al 2015). Leptin works to suppress appetite during the fed state by binding to its cytokine receptor, called the leptin receptor (LepR). Obese individuals become resistant to leptin over time, contributing to the dysregulation of the adipose tissue and secretion of cytokine signaling to increase inflammation and worsen the comorbidities associated with obesity (Booth et.al 2015).

In relation to cancer in general, leptin is involved in the proliferation, cellular survival and angiogenesis of cancerous cells. Leptin and its receptors are overexpressed in cancer cells located in the epithelial cell layer lining certain tissues, which aid it in communicating with cancer-promoting genes that assist in tumor growth (Booth et.al 2015). Leptin is also an activator of the PI3K/Akt pathway that favors cell proliferation, cell growth and the inhibition of apoptosis that is important for the survival of colon cancer cells **(Figure 4)**. Obese patients with excessive adipose tissue can experience overexpression of leptin, increasing the activation of these signaling pathways, and these patients can also develop resistance to this hormone (Duraiyarasan et.al 2022).

Figure 4. Ways In Which Leptin Promotes Colon Cancer Development. Taken from (Park, Scherer 2011). Increased levels of leptin in obese individuals activate signaling pathways that allow for colon cancer cell proliferation and the progression of tumors.



Research has shown that leptin and its receptors are expressed in colorectal tumors, with greater expression equating to increased aggression of the tumor (Booth et.al 2015). One study published by the International Union Against Cancer provided evidence supporting the significant increase in colon cancer risk with an increased serum level of leptin. It was determined that the risk of colon cancer development increased by 3-fold with increasing amounts of leptin, which may be the link between colon cancer tumorigenesis and obesity (Stattin et.al 2003).

2. Adiponectin

In addition to leptin, adiponectin is a second protein hormone released by the adipose tissue. Levels of this hormone are inversely related to number of adipocytes; meaning that obese patients with increased amounts of adipocytes have decreased amounts of adiponectin (Duraiyarasan et.al 2022). Similar to leptin and other hormones associated with the adipose tissue, the functions of adiponectin include sensitizing insulin receptors, increasing muscle glucose uptake while suppressing glucose production in the liver, and serving as an anti-inflammatory adipokine. Prior research has shown a correlation between low levels of circulating adiponectin and increased risk of colon cancer, with multiple studies showing the association between low circulating adiponectin and poorer outcomes of colon cancer (Chakraborty et.al 2021). Decreased amounts of adiponectin are thought to be associated with higher inflammation, therefore increasing the risk of colon cancer development in obese patients **(Figure 5)**. Receptors for adiponectin are present in both colon cancer and normal colon mucosa, so it has been thought that adiponectin could protect against the development of colon cancer, though the mechanism is not entirely known (Park et. al 2015). It is also important in stimulating the activation of p53 and the downstream cell death cascade (Duraiyarasan et.al 2022). Adiponectin has been shown to prevent or slow the development of cancer cells via the activation of apoptosis or the inhibition of the cell cycle (Booth et.al 2015). With the expansion of the adipose tissue in obese individuals, adiponectin levels decreasing result in suppression of p53 (Heng, Lazarova 2011).

In colon cancer specifically, adiponectin is recognized as a mediator of the progression of the proliferation of the cancerous cells. The relationship between circulating amounts of adiponectin and adipose tissue is inversely related to colon cancer development, such that lower levels are associated with later stage colon cancer and worse prognosis (Booth et.al 2015).

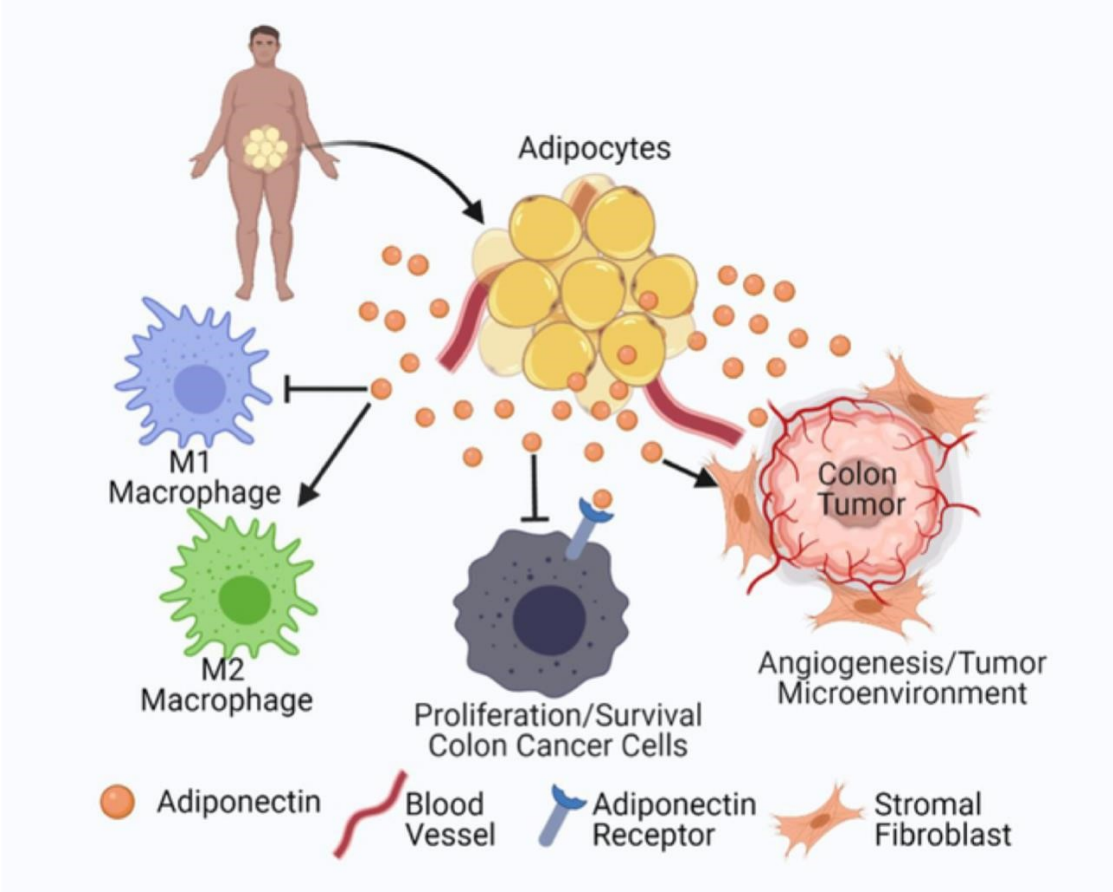


Figure 5. Role of Adiponectin in Cellular Proliferation of Colon Cancer Cells & Signaling of Inflammatory Cells. Image used from (Chakraborty et.al 2021). Role of adiponectin in the inhibition of colon cancer cell proliferation and survival as well as M1 Macrophages. Also depicts the activation of M2 Macrophages and stromal fibroblasts by adiponectin.

3. Signal Pathways

As previously mentioned, the PI3K/Akt pathway is associated with the development of colon cancer and its activation is influenced by inflammatory cytokines produced by the adipose tissue. PI3K/Akt, or the phosphatidylinositol 3-kinase/ protein kinase B pathway, regulates cellular processes such as cell growth, proliferation, protein synthesis, transcription, and apoptosis. The pathway begins when lipid kinase PI3K phosphorylates PIP2, converting it to PIP3, and PIP3 continues to phosphorylate protein

kinase B (AKT) **(Figure 6)**. Both PIP3 and AKT are essential to pathways regulating cell growth and survival and the inhibition of apoptosis. The activation of this pathway has been previously shown to lead to the development of many other types of cancer, making it a potential target for cancer therapies (Pietrzak et.al 2024). Specifically in colon cancers, the PI3K/Akt pathway is often dysregulated, and a recent study conducted in 2024 has found that colon cancer patients frequently have a mutation in the PIK3CA gene that encodes the catalytic subunit of PI3K (Pietrzak et.al 2024). The induction of these pathways due to increased amounts of inflammatory cytokines in obese patients allows for the proliferation of colon cancer cells, therefore leading to the development of colon cancer.

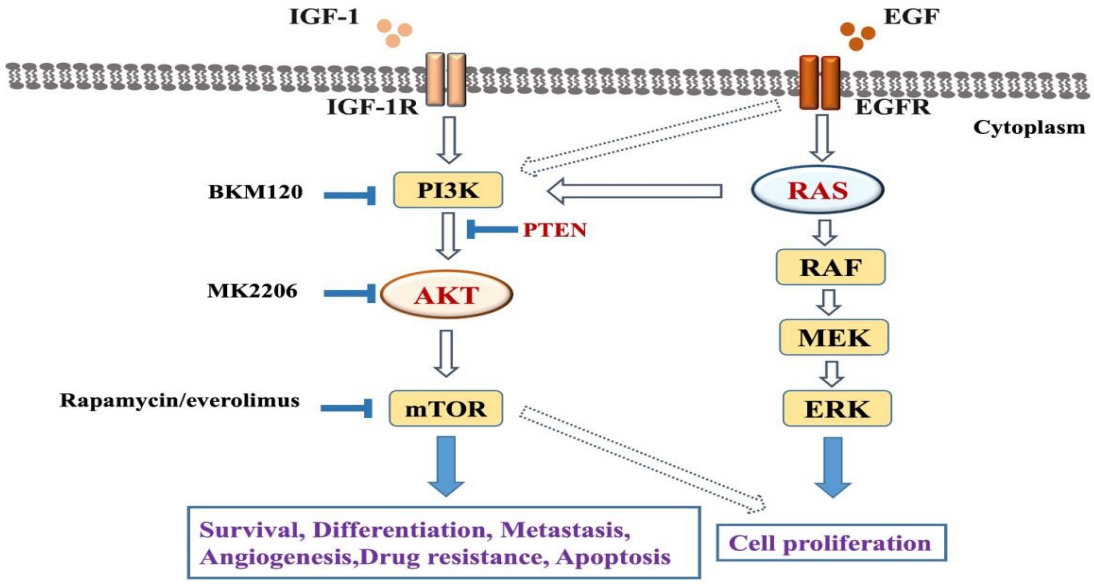


Figure 6. Effects of the PI3K/Akt Signal Pathway on cellular functions in colon cancer. Image from (Zhong et.al 2023). Different components of the PI3K/AkT signal pathway that eventually activate mTOR to increase cellular proliferation, differentiation, and angiogenesis; all crucial events allowing for development of colon cancer.

The increased amounts of leptin and decreased adiponectin present in patients with obesity can stimulate the PI3K/Akt pathway, and the downstream effects lead to

carcinogenesis (Chen, Huang 2009). It is therefore important to understand the downstream pathways to relate the role of PI3K/Akt to the carcinogenesis of colon cancer **(Figure 7)**. One of these pathways is the cell survival pathway, which can either increase proliferation or decrease apoptosis, with both of those factors being important to the ability of cancerous cells to be able to survive and replicate. Transcription factor NF-kB is a downstream target of PI3K/Akt that upregulates the further signaling pathways for cell survival (Cheng, Huang 2009). Relating to obesity, it has been noted that NF-kB is activated due to dysfunctional adipose tissue secretion of inflammatory adipokine TNF-alpha that interacts with the toll-like receptor 4 complex (Chakraborty et.al 2021). In terms of cancer, NF-kB increases the survival of cells, which in turn promotes further cancer development by increasing the resistance to apoptosis and controls the angiogenesis and invasiveness of the tumor cells (Chen, Huang 2009).

Though PI3K and Akt work together, Akt has effects downstream of PI3K due to its mediation of PI3K's effects on tumor growth and development. Downstream phosphorylation and activation of Akt has been previously associated with colon cancers, as this activation then promotes proliferation and inhibition of apoptosis, and activates mTOR to promote cell growth. (Kouveitypour et.al 2019).

Another important factor involved in the cellular survival of colon cancer cells is the inhibition of the p53 tumor suppressor gene. P53 works to cause apoptosis in cells as a response to damage in DNA (Chen, Huang 2009). Interestingly, p53 in obese patients has been proven to be a mediator of adiposity and worsens the pathology of adipose tissue (Zwezdaryk et. al 2018). Overall, studies have concluded that increased amounts of

p53 in obese patients is counter-intuitive in terms of regulating dysfunctional adipose tissue in that the secretion of inflammatory cytokines and adipokines is increased. As mentioned previously, the chronic inflammation in the adipose tissue of these patients combined with the continuous release of inflammatory markers due to increased activity of p53 creates a favorable environment for the development of colon cancers (Zwezdaryk et.al 2018).

PI3K/Akt also regulates cell cycle pathways and pathways involved in the proliferation of cells. Cellular proliferation is increased via the deactivation of glycogen synthase kinase 3 promoting cyclin D1 and pro-oncogene myc to increase the cell cycle. About 70% of patients with colon cancer have been noted to have overexpression of myc (Chen, Huang 2009). The growth of cells in terms of size as well as the synthesis of proteins is also increased by PI3K/Akt by the activation of mTOR and the kinase that regulates translation elongation. The role of mTOR in the development of many types of cancers has been developed recently due to this factor. Briefly worth mentioning is the cell cycle regulation and tumor suppression pathway p27 that is downregulated in the setting of colon cancer, and is also associated with a poorer outcome (Ogino et.al 2007). Obesity / the PI3K/Akt pathway inhibit p27, leading to even less regulation of the cell cycle.

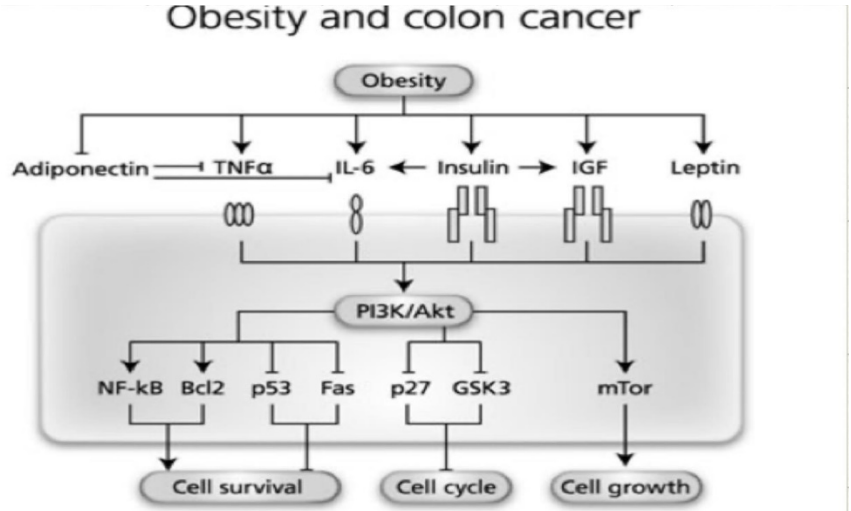


Figure 7. Overview of the Connections Between Obesity/PI3K-Akt and Colon Cancer. Links between obesity, adiponectin, and leptin, and how they all work to stimulate the PI3K/Akt pathway to promote cellular proliferation, growth and survival of cancerous cells. Image from (Huang, Chen 2008).

Though changes in the signaling pathways mentioned previously are induced via consequences of obesity, it is important to also note that dysregulation and dysfunction of these pathways can also be caused by genetic mutations. In about 20-40% of colon cancers, there are mutations in the PTEN gene that regulates the function of PI3K/Akt and leads to loss of function in tumor suppressor genes (Kouveitypour et.al 2019). There are several other signaling pathways involved in the carcinogenesis of colon cancer, and studies have shown that there is crosstalk between them to further push tumor development.

CHAPTER TWO

Hyperinsulinemia and Insulin-Like Growth Factor 1

Hyperinsulinemia, or the abnormally high amount of insulin present in the bloodstream due to resistance to insulin, is a consequence of both central obesity, or excessive fat within the abdomen and visceral fat, and type II diabetes. This condition be described in terms of insulin resistance: the non-responsiveness of cells to insulin that leads to requirement of increased amounts of it. There are three different mechanisms with which a person can become hyper-insulinemic: oversecreting insulin, the reduced clearance of it from the body, or elevated fasting insulin levels (Zhang et.al 2021). Release of insulin is meant to be a "compensatory mechanism" to maintain blood glucose levels when intake of glucose is high (Yu et.al 2022). Diabetes mellitus is a common complication that arises from obesity, therefore leading to higher circulating insulin from insulin resistance. Numerous studies have already established a connection between increased insulin and colon cancer (Yu et.al 2022) similar to that observed in obesity, and has correlated higher levels of insulin to higher risk of colon cancer. The data provided as evidence for this has been both shown in animal models as well as in epidemiological studies, and the over-exposure of cells to insulin has been shown to cause the overstimulation of cell growth and division (Saffran et.al 1997). Cancers of the breast, ovarian, prostate and lung, in addition to colon cancer, have been directly linked to insulin and IGF-1 (a hormone that stimulates cell division) that will be later discussed. Though insulin is known as a hormone that regulates blood sugar, it also has properties of growth factors such as cell growth and metabolism. Related to insulin is the hormone insulin-like growth factor axis that also works in similar ways. Insulin works on a short-

term basis, while IGF works longer term to regulate metabolism. Production and secretion of insulin, e.g., after a meal, stimulates the release of IGF- 1, a growth hormone, from the liver. Specifically, IGF-1 is a necessity for the progression of cellular growth and the cell cycle by inhibiting apoptosis (Giovannucci 2001). This chapter will discuss how hyperinsulinemia and insulin-like growth factor 1 can also contribute to the increased risk of colon cancer development.

1. Insulin and Hyperinsulinemia

Insulin acts on the GI tract, specifically the colon, to decrease blood glucose. Normal, non-cancerous epithelial cells of the colon express both insulin receptors and IGF-1 receptors. Under regular physiological circumstances, the classical targets of IGF-1 and insulin's effects include cells of the liver, skeletal muscle, adipose tissue, and the brain **(Figure 8)**. In non-pathological tissue, both insulin and IGF-1 bind with high affinity to their receptors to activate either insulin receptor 1 or insulin receptor 2, either which control cellular proliferation and apoptosis (Vigneri et.al 2015).

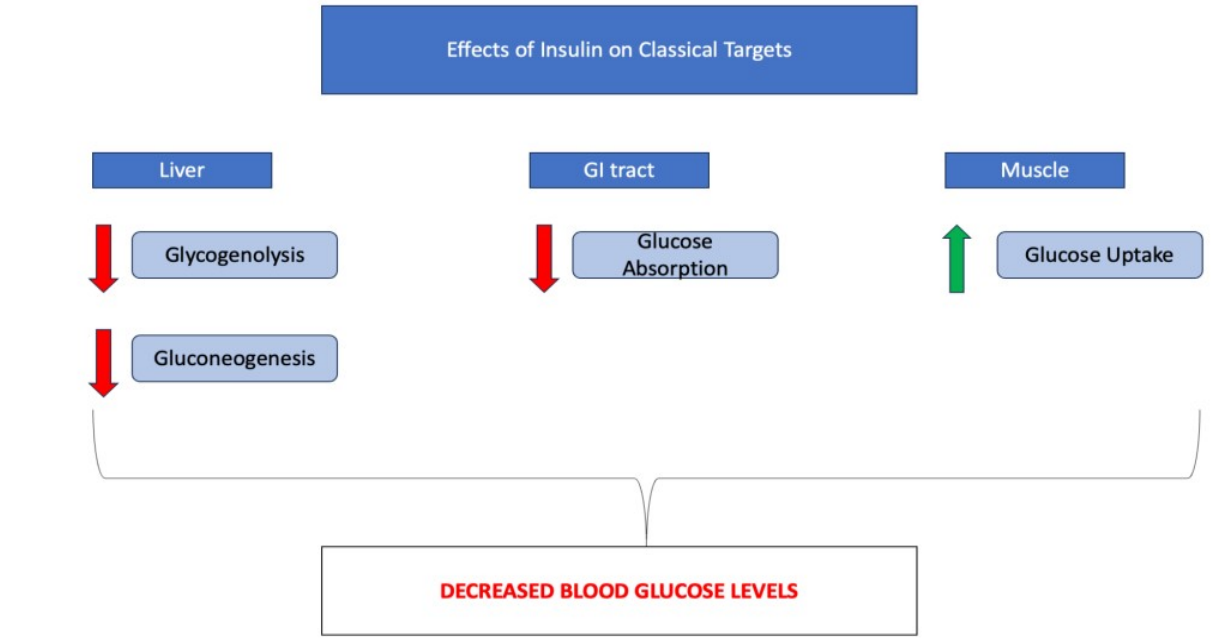


Figure 8. Effects of Insulin on Its Classical Targets. Insulin decreases gluconeogenesis (creation of glucose) and glycogenolysis (breakdown of glycogen stores into glucose) in the liver, decreases the absorption of glucose within the GI tract, and increases skeletal muscle uptake of glucose all to decrease circulating blood glucose levels.

When individuals become resistant to insulin and further over-secrete it, the excess insulin then exposes non-classical targets, such as the colon, to the effects of insulin (Zeng, Lazarova 2011). This then causes the colon to increase the expression of insulin receptors. The increase of both ligand and receptor and their binding inhibits apoptosis and stimulate the growth of cells via the downstream signaling pathway PI3K/Akt discussed previously. The theory is that unlike the classical targets of insulin's effects, cells of the colon are unable to produce the same effect of insulin as cells of, for example, skeletal muscle could. In turn, this could potentially cause increased cellular proliferation leading to accumulation of tumors (Zeng, Lazarova 2011). It has also been hypothesized that the increased amounts of insulin serve as an energy source for cellular processes that

promote carcinogenesis and tumor development and progression forward. Strong correlations between insulin and cancer have been found previously, with studies done on mice injected with high amounts of insulin eventually developing growth of aberrant crypt foci (colon cancer precursor) and increased tumor size. Another study with rats fed a high energy and high fat diet that impaired glucose tolerance/insulin resistance had similar effects (Koohestani et.al 1997). Though insulin is a hormone that regulates blood sugar, it also has properties of growth factors such as cell growth and metabolism. Related to insulin is the hormone insulin-like growth (IGF) factor axis; a signaling pathway of hormones, receptors and binding proteins that regulate physiological growth, development and metabolism (Talia et.al 2021). Insulin works on a short-term basis, while IGF works longer term to regulate metabolism. Production and secretion of insulin, e.g., after a meal, stimulates the release of IGF- 1, a growth hormone, from the liver. Specifically, IGF-1 is a necessity for the progression of cellular growth and the cell cycle by inhibiting apoptosis (Giovannucci 2001).

The binding of insulin and IGF-1 to their receptors functions as a determinant of the progression of colon cancer (Giovannuci 2001). There are two types of insulin receptors, IR-A and IR-B. IRA is considered the fetal type of insulin receptor and can recognize both insulin and a separate insulin-like growth factor with the same affinity, while insulin is the only ligand recognized by IR-B. IR-B is the receptor mainly found in the aforementioned classical targets of insulin, while IR-A is found mostly in cancerous tissues (Vigneri et.al 2015). Though the primary function of insulin receptors is to mediate the uptake of glucose, evidence suggests they play a role in modulation of

cellular metabolism (Vigneri et.al 2015). It is hypothesized that increased amounts of insulin can promote the progression of colon cancer tumors by stimulating its own receptors, receptors for IGF-1, or hybrid insulin/IGF-1 receptors (Chen et.al 2018). Overexpression of insulin receptors is a "hallmark" of the hyperinsulinemia-related cancers mentioned previously, and this overexpression is associated with poorer prognosis of disease. The overexpression is due to increased metabolic need for glucose uptake required by cancerous cells (Heckl et.al 2018). Cancerous cells have significant alterations to their insulin receptors; this includes a 2-6-fold increase of the number of insulin receptors present relative to non-cancerous cells, as well as the inability to downregulate receptor presence in response to increased amounts of insulinemia (Kilvert, Fox 2020).

As mentioned previously, tumor cells are known to specifically express IR-A. The expression of IR-A in tumor/cancerous tissue has been shown to increase in colon cancer, furthering the progression of the disease by allowing the binding of IGF-II to increase cellular proliferation (Cirillo et.al 2019). A key factor in the reasoning as to why chronic exposure to high levels of insulin and its increased binding are related to colon cancer development is the further activation of the PI3K/Akt and MAPK pathways. Adapter proteins named insulin substrates 1-4 bind the insulin receptor when it is ligand-bound. This binding attracts PI3K to phosphorylate PIP2 and PIP3, which in turn leads to the downstream phosphorylation of Akt by PDPK1 (Zhang et.al 2021). Through the downstream PI3K/Akt pathway, increased insulin can then signal cancerous cells to evade cell-cycle arrest and apoptosis via phosphorylation of apoptotic-promoting proteins

(Zhang et.al 2021). Cancer cells of any type usually have a mutation of the GTP-ase RAS protein which acts as a “switch” when activated by GTP and is part of the MAPK/ERK pathway (signal pathway involved in cellular proliferation, survival and apoptosis). Mutated RAS in cancer cells keeps the pathway constitutively active (Simanshu et.al 2018). Chronically high insulin specifically increases the amount of activated RAS available which in turn increases proliferation of cancer cells (Zhang et.al 2021).

2. Insulin-Like Growth Factor 1

When insulin is bound to its receptor, production of insulin-like growth factors from the liver is stimulated as a response. Insulin-like growth factors act as hormones that have both endocrine and mitogenic effects and have notable significance in the growth and development of cancer. There are two types of peptides: IGF-1 and IGF-2. IGF-2 will be discussed in lesser detail as it is more significantly involved in fetal development and is less important in adulthood, though it does increase with tumor development that can potentially cause increased signaling for growth. High levels of IGF-1 have been previously related to increased risk of colon cancer, similarly to insulin.

IGF-1 is synthesized in the liver and is controlled by growth hormone (GH) with circulating levels decreasing as an individual reaches puberty and adulthood **(Figure 9)**. Its main function is to stimulate cell division and control the growth of bones under the direction of growth hormone released from the pituitary. IGF-1 inhibits apoptosis that occurs when bound to its receptor. Receptors for IGF are expressed in the GI tract and can bind both IGF-1 and IGF-2 to become active. These receptors are expressed normally in healthy tissue within the colon, but the overexpression can lead to carcinogenesis.

Specifically, the IGF1R is expressed mostly in the proliferating colonic crypt cells within the colon (Gligorijevic et.al 2022). Large amounts of IGF-1 also loop back to insulin resistance discussed in the section prior. IGF-1 promotes both lipolysis and gluconeogenesis by blocking insulin signaling, therefore increasing the negative effects of hyperinsulinemia in the body (Danilowicz, Sosa 2023).

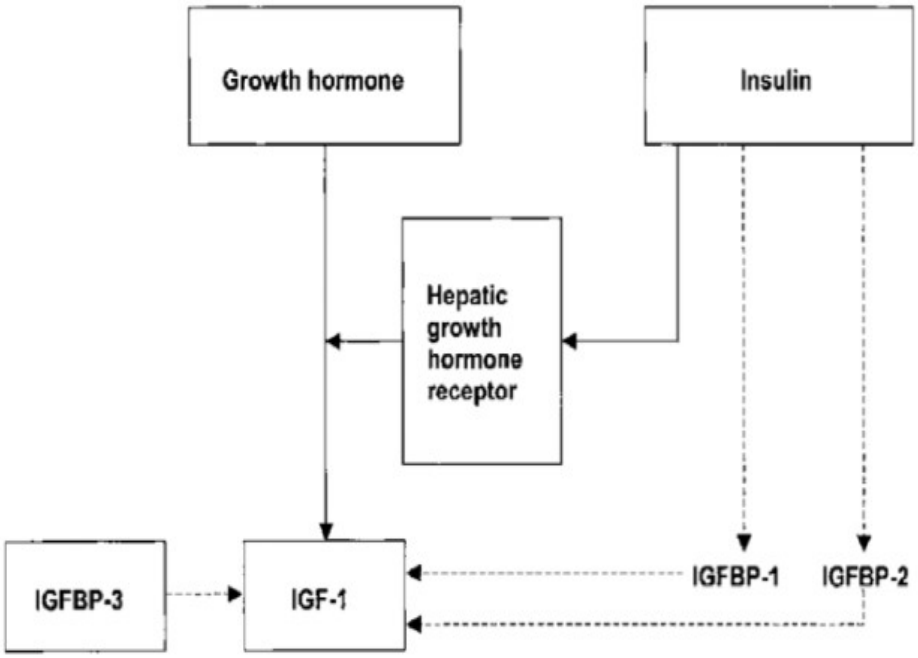


Figure 9. Stimulating Effects of Insulin and Growth Hormone on IGF-1. Both insulin and growth hormone have stimulating effects on IGF-1 through the binding proteins IGFBP-1 and IGFBP-2, as well as direct stimulation via release of growth hormone. Increased insulin can also cause increased secretion of growth hormone to raise circulating IGF-1. Image used from (Giovannucci 2001).

Also important are IGF-binding proteins that act as transport proteins to get IGF across tissues. These binding proteins act as negative regulators to control the effects of both IGF-1 and IGF-2. There are three main types of IGFBPs, but IGFBP-3 is the most abundant binding protein bound to IGF-1 in circulation. Changes in the binding of IGF-1 to these binding proteins are a key factor in how IGF-1 can influence the development of

cancerous cells. As discussed earlier, insulin can stimulate IGF-1 secretion. There are several mechanisms by which this can happen; one of which involves the reduction of secretion of IGFBP-1 from the liver via insulin stimulation. This is notable as IGFBP-1 binds IGF1 with high affinity and inhibits its actions. Hyperinsulinemia and chronic exposure to high amounts of insulin also affect the secretion of IGFBP-2 (Giovannuci 2001). Reducing these binding proteins allows for freer circulating IGF-1, leading to increased stimulation of cellular growth and inhibition of apoptosis.

To further prove the argument that IGF-1 overexpression has carcinogenic effects, studies using animal models have shown that the restriction of energy from decreasing IGF-1 levels (and insulin levels) have “anticancer” effects and are crucial in preventing cancer development (Giovannuci 2001). This study infused mice with bladder cancer deficient in p53 with energy restrictions with IGF-1, and it completely reversed the anti-cancer effects of the energy restriction treatment (Dunn et.al 1997).

A clinical example connecting colon cancer to increased IGF-1 is in patients with acromegaly, which is a metabolic disorder caused by excessive secretion of growth hormone due to a tumor of the pituitary gland that causes enlargement of the bones and tissues in the face, hands, and feet as defined by the National Cancer Institute. Cancer of the colon is one of the most common cancers in patients with acromegaly. Initially, research into the connection between colon cancer and IGF-1 was prompted due to the high prevalence of individuals with acromegaly developing the disease. In a 2019 study, it was reported that a large meta-analysis of patients with acromegaly are 2-5 times more likely to develop cancerous polyps of the colon as compared to patients without

acromegaly (Dworakowska, Grossman 2019). It was also reported in this paper that patients with acromegaly are 2-5 times more likely to develop cancerous lesions in comparison to controls. To note, insulin resistance/hyperinsulinemia are also characteristic of acromegaly, contributing to higher risk of cancer.

The excess amounts of GH/IGF-1 both have mitogenic effects as discussed prior, and long-term exposure to both hormones has been already proven to lead to development of malignant, cancerous tumors. Specific to colon cancer in acromegaly patients is the role of GH/IGF-1 in stimulation of angiogenesis and vascular endothelial growth, as well as antiapoptotic effects in human colon cancer cell lines (Danilowicz, Sosa 2023). Bowel enlargement is also a characteristic of acromegaly because of excessive growth hormone and IGF-1. This increase of IGF-1 causes the increased proliferation and blockage of apoptosis of epithelial cells within the colon, and with increased proliferation comes chances of tumorigenesis (Yamamoto, Takahashi). GH/IGF-1 are both also thought to be involved with the process of cellular migration and cellular adhesion, both of which are crucial to the development of tumors.

Overall, high IGF-1 due to hyperinsulinemia or other factors play a large role in the development of colon cancer and should be more heavily considered when determining someone’s risk of developing the disease.

CHAPTER THREE

Vitamin D Deficiency

Vitamin D is a hormone assisting the body in the utilization of calcium and phosphorus to perform many cellular and bodily functions. Vitamin D can either be synthesized by the skin upon exposure to ultraviolet radiation or can be derived from an individual's diet **(Figure 10)**. Target tissues of vitamin D include the skin, the liver and the kidneys where it is processed for different functions. Recommended intake of vitamin D by The Institute of Medicine for individuals aged 1-70 is 15 micrograms a day, with the amount increasing to 20 micrograms for those over 71 years old (National Cancer Institute 2023). In this chapter, the relationship between vitamin D deficiency and colon cancer will be explored, aiming to make possible connections between low serum vitamin D levels and increased risk of colon cancer.

In total, there are four forms of vitamin D: vitamin D3, D2, calcidiol and calcitriol. Vitamin D from the diet is usually low, therefore the primary source is through skin production of vitamin D3 via exposure of 7-dehydrocholesterol to UVB light (Pereira et.al 2023). The main and active form of vitamin D is 1,25-(OH)2D3, or calcitriol, with its main function being regulation of the calcium/phosphate balance to maintain bone integrity. Despite this, the most stable metabolite of vitamin D is the inactive form: 25(OH)D hydroxylated by the liver. This form is the most abundant within the circulation and is the biomarker used to indicate whether an individual is vitamin D deficient (Pereira et.al 2023).

Vitamin D deficiency can occur when dietary intake is low, as in people with lactose intolerance/allergy to milk, or if there is decreased exposure to sunlight (National

Institutes of Health 2024). Obesity is also associated with vitamin D deficiency, as it is a fat-soluble molecule and is taken up by the excessive adipose tissue, leaving less amounts in circulation (Tobias et.al 2023). In individuals deficient in vitamin D

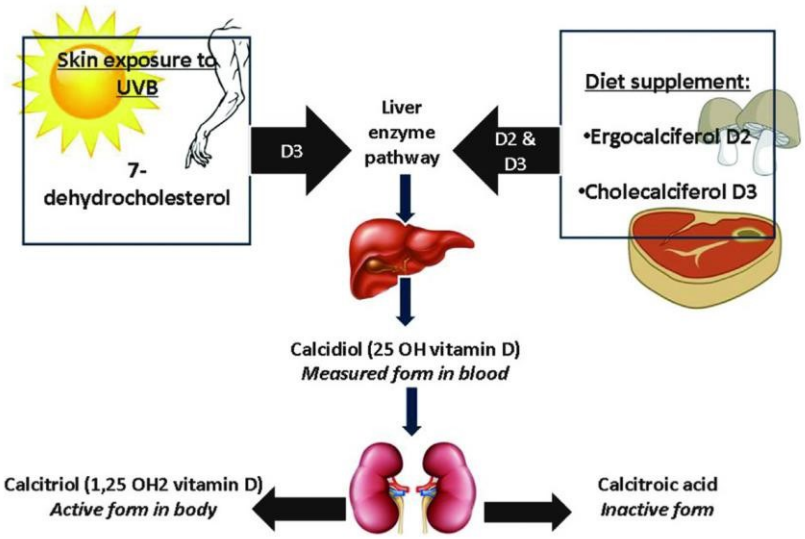


Figure 10. Sources of Vitamin D and Its Activation. Vitamin D can be supplied through the diet or by UVB exposure. It is then converted to calcitriol (active form) from calcidiol by the kidneys. Image from (Mostafa, Hegazy 2015).

that have not developed cancer, studies have suggested that supplementing with vitamin D3 (calcitriol) is more effective at raising serum 25(OH)D levels as opposed to vitamin D2 (Na et.al 2022), in turn reducing risk of cancer development. In relation to cancer, many studies conducted since 1936 to the present day have shown inverse correlations between vitamin D levels and incidence of colon cancer. Specifically, in 1980 Cedric and Frank Garland provided evidence that areas in the United States with the least exposure to sunlight had higher incidence of colon cancer/higher mortality rate (Garland, Garland 1980). Several studies since then have expanded upon the hypothesis that the lack of

exposure to natural light increases risk of developing colon cancer due to decreased vitamin D. Since then, numerous epidemiologic studies have consistently shown an inverse relationship between levels of 25(OH)D and risk of colon cancer. The hypothesized biological mechanisms underlying this association involve stimulation of apoptosis, inhibition of angiogenesis to tumor cells, and the stopping of cellular proliferation (Pereira et.al 2023).

Three cytochrome P450s are involved in the metabolism of vitamin D: CYP27A1, CYP27B1, and CYP24B1, with CYP27A1 being the one to hydroxylate vitamin D to 25(OH)D, and CYP27B1 converting 25(OH)D into calcitriol. The responsiveness of cells to the actions of vitamin D is dependent on the actual amount of calcitriol within the cell's nucleus and the amount of vitamin D receptors present, which is determined by the activity of both CYP27B1 and CYP27A1 (Ferrer-Mayorga et.al 2019). CYP24A1 acts as a regulator by converting the increasing calcitriol to an inactive form. This regulator CYP450 has been shown to be overly expressed in cancerous tumors causing large decreases in serum vitamin D levels, with colon cancer tumors tending to possess a genetic mutation directly correlating with the increase of CYP24A1 (Na et.al 2022), providing further evidence in favor of the hypothesis that vitamin D has potential anti-cancer effects.

Researchers and scientists at the Dana-Farber Cancer Institute report that supplementing chemotherapy with high doses of vitamin D can slow disease progression in patients with colon cancer, even in patients with metastatic disease (Dana-Farber Cancer Institute 2019). A small clinical trial was conducted in which 139 patients

suffering from metastatic colon cancer were split in half, with one group receiving a high dose of vitamin D and the other group receiving a low dose. Results showed that that the group receiving the higher dose had better survival. This same study notes the benefits of supplementation being less effective in obese individuals (Dana-Farber Cancer Institute 2019).

The binding of vitamin D to its receptor regulates the cellular processes mentioned above. Vitamin D receptors are highly expressed through the GI system, and calcitriol maintains the epithelial barrier of the intestine by promoting the differentiation of epithelial cells (Na et.al 2022). In the intestine, calcitriol binds its receptor and promotes expression of calcium-binding protein calbindin to enhance calcium absorption through the intestinal lining and into the bloodstream. Non-cancerous colon epithelial cells are among the cell types that express the vitamin D receptor (Pereira et.al 2023). Studies of cancerous colon cells have shown that early stages of colon cancer do express the vitamin D receptor, and that it is lost or becomes resistant to vitamin D in more advanced stages (Pereira et.al 2023).

As discussed above, vitamin D3 (calcitriol) is involved with the process of cellular proliferation and differentiation upon binding to its receptor (Pereira et.al 2023). The entire mechanism is not yet completely understood, but it is thought that calcitriol modulates genes p19, p21, p27 and p53 that are involved in the cell cycle. Research on this topic has shown that calcitriol regulates the degradation of p27, with the decrease in degradation inhibiting cellular proliferation and stimulating apoptosis. The cell cycle is then further halted by the inactivation of the kinase-dependent complex, keeping cells

stuck in the G1 phase (Ferreira de Almeida, Machado- Coimbra 2019). This accumulation of cells unable to progress through the rest of the cycle is also caused by the expression of inhibitory genes and kinase inhibitors that downregulate both cyclin A and cyclin F (Pereira et.al 2012). The arrest of cells at the G1 phase is an important and crucial piece in preventing the progression and division of cancerous cells. Calcitriol's ability to promote differentiation of colon cancer cells and control the regulators of this process is also important in cancer prevention. Calcitriol upregulates specific genes responsible for both intestinal epithelial markers and cytoskeleton/adhesion proteins (Ferreira de Almeida, Machado- Coimbra 2019). It is crucial to maintain a tight barrier through these proteins to protect against the invasion of cancerous cells into healthy tissue.

The next mechanism by which calcitriol may work to decrease risk of colon cancer is through the stimulation of apoptosis. Used in some cancer therapies, research has shown that administration of active vitamin D activates apoptotic pathways and prevents angiogenesis in cancerous tumors. Though this function of vitamin D is important in preventing cancer development and aiding the inhibition of its development, large amounts of vitamin D are required to induce apoptotic effects. Like how cell proliferation is halted, the stimulation of apoptosis involves regulation of genes involved in this process. Calcitriol uses expression of mitochondrial proteins that prevent BCL-2 (an anti-apoptotic protein) from dimerizing with BAX (a pro-apoptotic protein). The dimerization of BCL-2 and BAX prevents BAX from inserting into the mitochondrial membrane and releasing cytochrome c to initiate the caspase pathway that leads to

apoptosis. The inhibition of BAX due to calcitriol is what eventually allows for apoptosis to continue (Pereira et.al 2012). Over-expression of BCL-2 is a 'hallmark' characteristic of tumors, as introduces genetic mutations that protect the carcinogenic cells and promote destabilization of genes (Skrajnowska, Bobrowska-Korczak 2019). Research done on the apoptotic effects of vitamin D in GI cancers have also shown other mechanisms through which apoptosis can be induced; down regulating ERK and AkT both can block cell growth and induce apoptosis (El-Sharkawy, Malki 2020). In conjunction with the cellular proliferative effects of calcitriol, apoptosis has been shown to be induced via the up regulation of p21 and p27.

Moreover, treating colon cancer cells with vitamin D leads to the activation of proteins called cystatins that inhibit the cysteine proteases of the cathepsin family (Skrajnowska, Bobrowska-Korczak 2019). This is a crucial mechanism, as cathepsin B is heavily involved in the metastasis of tumors and other transformative pathways and enters the nucleus of the cell to further activate apoptosis.

Vitamin D / calcitriol also plays a preventative role against angiogenesis; the process by which new blood vessels form from existing ones, that is crucial for tumors to be able to obtain the nutrients needed to grow. Yet another noted anti-cancer function of vitamin D / calcitriol is the inhibition of angiogenesis, which is done through several mechanisms. Vascular endothelial growth factor is a protein required for angiogenesis, and calcitriol can decrease its expression by inhibiting the transcription, and therefore, expression of hypoxia-inducible factor 1 (Na et.al 2022).

Calcitriol has also been shown in cancer cells to block gene transcription of Interleukin-8 (IL-8) to stop angiogenesis, as a function of IL-8 attracts inflammatory markers to the site of the tumor, promoting angiogenesis (Skrajnowska, Bobrowska-Korczak 2019). This can also be done either directly through endothelial cells of the tumor, or indirectly by decreasing amounts of COX-2 generated (Skrajnowska, Bobrowska-Korczak 2019). As mentioned above, calcitriol is involved in the regulation of vascular endothelial growth factor, and thrombospondin 1. Both proteins act in opposition to each other to control angiogenesis in tumor cells and have heavy implications in diseases like cancer, and calcitriol controls both to maintain homeostasis. In colon cancer cells specifically, calcitriol downregulates the expression of DKK4 (a protein involved in the WNT signaling pathway that is also involved in cellular proliferation and differentiation) that has been discovered to be upregulated in colon cancer cells/tumors to prevent angiogenesis (Pereira et.al 2012).

The influence of vitamin D on the changes to the gut microbiome made by colon cancer is a question that could be crucial in understanding the whole process by which colon carcinogenesis is promoted. In healthy individuals, the microbiome of the colon includes *Bifidobacterium, Akkermansia, Bacteroidetes* and *Enterobacter,* though there are changes throughout a person's life due to diet, lifestyle and age. The genera of microorganisms included in a healthy microbiome work to maintain homeostasis through vitamin production, metabolism of food ingested, and immunomodulation, relating to prior remarks regarding the influence of the immune response on colon carcinogenesis. In recent years, it has been discovered that alterations in the gut microbiome are involved in

certain diseases, especially in colon cancer due to the high density of bacteria within the colon (Rinninella et.al 2021). Studies comparing fecal samples between patients with colon cancer and healthy individuals has shown numerous microbial genres that are consistent among colon cancer patients, most of which are considered to push the progression of colon cancer by increasing inflammation (Rinninella et.al 2021). The mechanism by which the microbiome is changed in people with colon cancer has yet to be determined. Research has provided evidence that there are increased amounts of pathogens and microbes associated with disease due to decreased butyrate-producing microbes that are used as a beneficial energy source for cells of the colon and help to defend against pathogens (Rinninella et.al 2021). Men with higher circulating 1,25(OH)D tend to possess butyrate-producing bacteria. Thus, current evidence suggests that deficiency in vitamin D further exacerbates the imbalance of the gut microbiome and promotes its further dysbiosis.

As mentioned previously, vitamin D works as an immunomodulator, regulating immune response. Introduction of pathogenic and disease-associated microbes to the colonic mucosa elicits an immune response, which is where vitamin D and its receptor play a crucial role. Discussed previously was the involvement of calcitriol and its receptor in maintaining the tight junctions in the colonic epithelial barrier to prevent invasion of cancerous cells and potential other pathogens. To further expand on this topic, calcitriol works to maintain this strong barrier with the help of *Akkermansia muciniphila,* which helps maintain the integrity of the barrier by sealing the tight junctions and promoting the secretion of anti-inflammatory cytokines (Na et.al 2022). Studies of

vitamin D deficiency in mice have also provided evidence of imbalanced gut microbiome, increased permeability of the gut epithelial barrier, and inflammation that can increase insulin resistance (Rinninella et.al 2021). As bacteria do not express the vitamin D receptor, regulation of vitamin D has to be done by the host. Since pathogenic bacteria downregulate the expression of vitamin D receptors, this further exacerbates the pro-cancer effects in individuals deficient in vitamin D (Ferreira de Almeida, Machado-Coimbra 2019). Therefore, it can be concluded that deficiency in vitamin D progresses colon cancer cells' ability to form malignancy not only by inhibiting apoptosis and disrupting tight junctions, but also by inducing significant alterations in the gut microbiome, which plays an equally critical role in driving cancer progression as discussed above.

CHAPTER FOUR

Non-Alcoholic Fatty Liver Disease

Like the topics already discussed, nonalcoholic fatty liver disease is a consequence of obesity found in about one of every four people globally. Nonalcoholic fatty liver disease, or NAFLD, represents a range of metabolic disorders of the GI tract involving the accumulation of fat in the liver (steatosis) of individuals consuming little to no alcohol. Individuals with NAFLD possess extreme insulin resistance and inflammation, often due to obesity as 90% of NAFLD cases are attributed to obesity (Muhidin et.al 2012). The disease itself is typically asymptomatic, and when left untreated can drive the progression of other disorders such as liver cirrhosis and hepatocellular carcinoma **(Figure 11)** (Chakraborty, Wang 2021). Due to the disease's relation to obesity and other cancer-associated factors, there is interest in the involvement of NAFLD and colon cancer. To date, studies have been able to relate the incidence of NAFLD with poor survival rate of colon cancer due to the increased likelihood of adenomatous polyp development (Chakraborty, Wang 2021). This makes sense as the liver of NAFLD patients (already compromised with excessive fat) is the most common site of metastasis of colon cancer due to the venous drainage of the colon draining directly into the portal vein, directing blood flow to the liver; a compromised liver would therefore make it easier for tumors to progress and spread. Though the exact link between NAFLD and the development of colon cancer is not entirely known at this time, the mechanisms are thought to be similar in terms of risk to obesity, hyperinsulinemia and vitamin D deficiency.

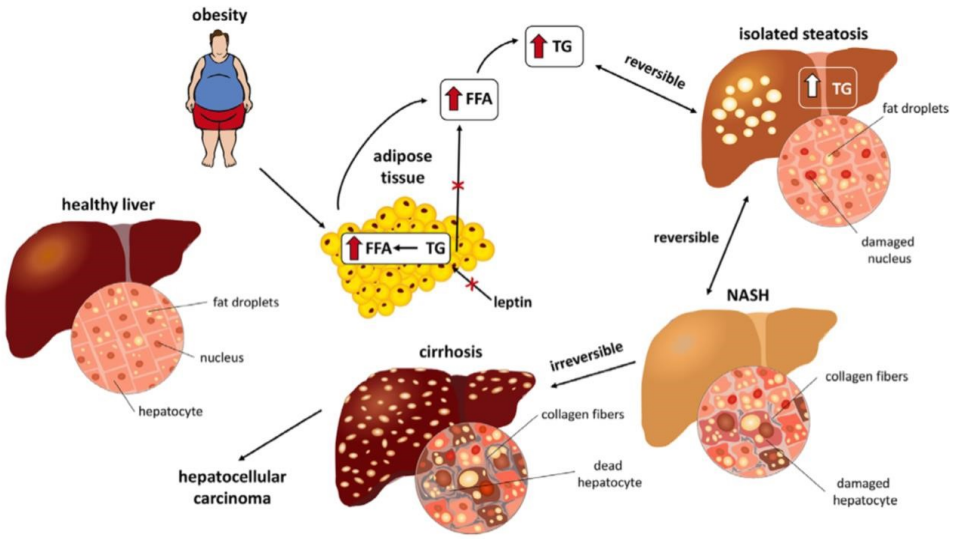


Figure 11. Progression of Severity of Fat Deposits in NAFLD. The development in severity of NAFLD through small amounts of fat deposits in the liver, eventually leading to irreversible cirrhosis and hepatocellular carcinoma, all linked to obesity in an individual. Figure from (Korinkova et.al 2020).

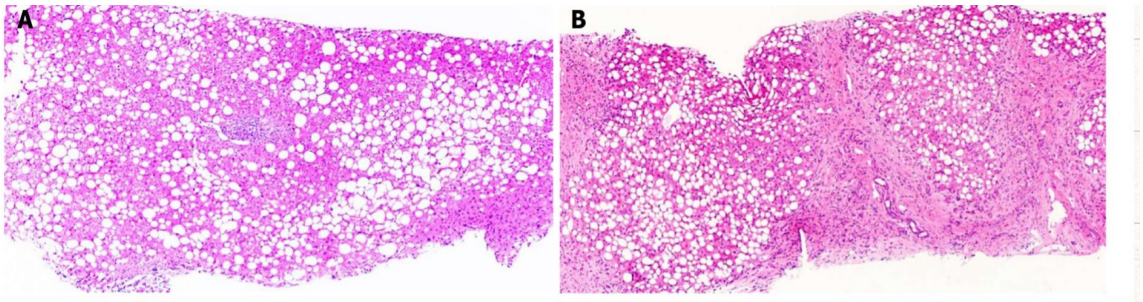


Figure 12. H&E Stain of Liver Biopsy from Healthy Liver and Cirrhotic Liver. Image A depicts a liver biopsy of a 45-year-old male with simple liver steatosis with no inflammation or fibrosis. Image B depicts liver biopsy of a 48-year-old male with cirrhosis of the liver due to NAFLD with marked areas of fibrous tissue. Image and description used from (Li et.al 2018).

Studies have found that individuals with NAFLD are at much higher risk of developing premalignant polyps within the colon, as well as possible cardiovascular and reproductive complications. Cancers attributed to the consequences of NAFLD include

colon, prostate, breast, stomach and liver cancer. Several epidemiological and clinical studies have shown associations between colon cancer and NAFLD. For example, a study conducted by Yang et.al showed the number of metastases in the liver of mice with NAFLD and colon cancer was greater than the actual size of the tumors, providing evidence that NAFLD creates a favorable environment for migration and growth of colon cancer tumors to the liver (Yang et.al 2024). Further, most studies have concluded that patients with more severe fibrosis of the liver have the highest incidence of colon cancer as compared to those with less severe steatosis, due to fibrosis representing the stage before cirrhosis (Zeng et.al 2022). More severe cases of NAFLD have greater contribution to development of adenomas in the colon as compared to early stages of fatty liver disease. The incidence of colon cancer in patients with more severe NAFLD has been found to be 1.61 times higher as compared to those with less liver fat or simple steatosis, with the incidence of advanced colon cancer being 2.64 times higher with more severe cases of NAFLD (Zeng et.al 2022). Interestingly, individuals with more severe NAFLD were found to be more likely to develop cancerous tumors within the left colon compared to the right colon, though the reasoning for this has yet to be determined. A study by Allen et.al was the first to hypothesize that NAFLD was a bridge to colon cancer from obesity. In their study, obese individuals without NAFLD had a significantly lower risk of cancer development as compared to those with NAFLD. Also, it was noted that incidence of colon cancer in people with NAFLD and obesity was significantly increased in males, but not in females.

Although the mechanisms by which NAFLD contributes to development of cancer is not entirely known currently, there are several hypotheses in the literature. Just as increased deposition of fat and adipose tissue in obese individuals leads to chronic inflammation, the continuous deposition of fat into the liver can also lead to inflammation **(Figure 12)**. This chronic inflammation has been found to be the essential driving force behind the development of cirrhosis and hepatocellular carcinoma (Chakraborty, Wang 2021). This contribution of excess fat deposits, in addition to systemic inflammation caused by obesity, is detrimental in that it even further promotes pathogenesis of colon cancer. Inflammatory cytokines and neutrophils get "trapped" within the tissue of the liver and are thought to facilitate the awakening of dormant cancerous tumor cells and lead them to their proliferation (Chakraborty, Wang 2021). Having access to neutrophils and other inflammatory cells in a liver infiltrated with fat gives cancer cells the perfect place to metastasize. A 2014 study determined that increased C-reactive protein (CRP), a blood marker of systemic inflammation, was positively correlated with mortality in colon cancer patients, therefore suggesting that high inflammation is associated with the metastasis of colon cancer and worsens the individual's outcome (Goyal et.al 2014). This same study also suggested an association between the high inflammation in the liver of those with NAFLD and the ability of colon cancer cells to metastasize to the liver and hypothesized that decreasing this inflammation in NAFLD patients could decrease or prevent the likelihood of colon cancer metastasizing to the liver (Chakraborty, Wang 2021). In order to support the extreme needs of continually proliferating cancer cells for fat, there is resulting increased uptake of free fatty acids and as well as an increase in

cholesterol synthesis. By doing so, it becomes easier for cancer cells to invade and metastasize within different tissues by promoting inflammation (Crudele et.al 2024). Another hypothesis is that hypoxic conditions cause the adipocytes deposited in the liver to send out inflammatory cytokines to stimulate angiogenesis to the fat cells, allowing them to grow and proliferate (Muhidin et.al 2012). As discussed in chapter one, the pro-inflammatory state caused by fat tissue is what leads to both promotion of cancer cellular proliferation as well as hyperinsulinemia.

Since fat tissue is involved with NAFLD, it makes sense that the risks posed by the disease are like the risks associated with excess adipose tissue from obesity. Individuals with NAFLD experience decreased levels of adiponectin as compared to healthy, non-obese patients. It has been established that adiponectin has anti-cancer effects such as growth inhibition. With low adiponectin levels, TNF-alpha will not be inhibited, also leading to increased angiogenesis to tumor cells and proliferation. Leptin levels are also changed with NAFLD as it works counterintuitively to adiponectin (Adolph et.al 2017). Under circumstances with which adiponectin is decreased, leptin exerts its pro-cancerous effects to increase colon cancer cell proliferation (Adolph et.al 2017). Further, the higher the serum leptin levels are, the more severe the fatty liver disease (Adolph et.al 2017), therefore increasing the risk and likelihood of colon cancer development, as risk increases with increased severity of NAFLD (Wu et.al 2023).

As mentioned prior, the liver is the most common site of metastasis for patients with metastatic colon cancer. Liver metastases are the highest contributors to mortality from the disease, with about 50% of colon cancer patients developing metastases in the

liver (Zeineddine et.al 2023) and only 10-20% of these patients can undergo surgical resection (Zhang et.al 2024). A recent study investigated the role of NAFLD in the metastasis of colon cancer and the mechanisms with which it is facilitated. It was noted in the study that mild cases of NAFLD often go missed and undiagnosed by physicians due to lack of specialized MRI needed to diagnose the disease. It was also found that 25% of people in the United States have NAFLD, and the prevalence of the disease is increasing (Truong, Noureddin 2022). The missed diagnosis of NAFLD in asymptomatic patients could be considered a large contributor to the disease-related increased risk of colon cancer, as the disease is allowed to progress to a point that colon cancer cells are able to proliferate, and tumors are able to spread. Researchers in this study hypothesized that NAFLD plays a contributing role in the development of aggressive colon cancer metastases to the liver. The researchers fed a high fat diet to mice with active metastases of colorectal cancer so that they would develop a fatty liver. It was discovered that cells from the fatty liver would release extracellular vesicles containing genetic material, therefore sending pro-metastatic signals throughout the body (Wang et.al 2023). These extracellular vesicles contain microRNAs that stimulate proliferation and migration, factors established as important to the development of cancer cells. It was found that the fatty liver within the mice induced suppression of the immune system by inhibiting CD8 T cell function, therefore allowing for migration of colon cancer tumors because the fat allows for reprogramming of the CD8 T cells that creates a favorable environment for the cancer to grow (Wang et.al 2023). Ultimately, the study was able to show that NAFLD

provides an environment that can support colon cancer metastases and therefore worsen the outcome of colon cancer.

Other research has shown that lipid deposits within the liver could possibly promote colon cancer development and metastasis by upregulating the Beta2-adrenergic receptor and toll-like receptor 4 expression to activate the STAT3 signaling pathway (Zhang et.al 2024). For example, it was found that NAFLD activates toll-like receptor 4 in the macrophages within the liver that promotes IL-1beta and VEGF towards the growth of colon cancer. Further detailed in this same study was the increase in palmitate synthesis in liver-metastasized colon cancer cells that is facilitated by NAFLD. Palmitate is the building block for lipids such as triglycerides and phospholipids, and this study demonstrates the epidermal growth factor receptor (EGFR) as the substrate for palmitate synthesis (Zhang et.al 2024). Overall, several different mechanisms have been hypothesized regarding how NAFLD increases risk of both developing colon cancer and metastasis of colon cancer.

A final mechanism proposed by Chen et.al in 2021 colon cancer cells use fatty acid transporter 1 to obtain lipolytic products and their growth is promoted via mitochondrial oxidation (Chen et.al 2021). These researchers proposed that excess fat deposits in the liver creates a pro-metastasis environment for colon cancer cells to migrate to the liver remodeling of the extracellular matrix (Chen et.al 2021). Though there is very little evidence to further support the mechanisms described in this study, the conclusion is the same as the other studies; excess fat within the liver is associated with colon cancer and its metastasis.

DISCUSSION

The complex task of understanding the risk determinants and factors associated with colon cancer is crucial for developing an effective prevention plan. The factors discussed in this thesis and their roles in colon cancer development are well defined within the literature.

In chapter one, I reviewed evidence that colon cancer risk is increased by 7% as a patient's BMI increases by 2 kg/m^2. It is imperative to stress the importance of maintaining a healthy weight and the value it has on reducing health risks as the rate of obesity steadily climbs throughout the world. The question can then be posed: can weight loss or decrease in BMI reduce risk of colon cancer? Does lifelong obesity pose a greater risk, and can that risk still be decreased with weight loss and healthy weight maintenance? Epidemiological research in the Iowa Women's Health Study found that intentional weight loss of over 20 pounds, regardless of obesity status, was associated with a reduction in incidence of colon cancer by 9% (Parker, Folsom 2003). Results in this study also provided evidence that weight loss through diet change in women specifically was successful in decreasing chronic inflammation and in down-regulating inflammatory pathways that contribute to cancer development (Pendyala et.al 2010). Together, these findings validate the hypothesis that weight loss in obese people thereby lowers colon cancer risk. In contrast to the studies done previously that provide evidence linking weight loss and decreased colon cancer risk, more recent work discusses the importance of preventing persistent and long-term obesity and staying at a healthy, non-obese weight when considering colon cancer risk. A population-based study by Seo et.al

in 2023 noted that life-long obesity can play a role in colon cancer development, and a higher BMI elicits a higher mortality rate (Seo et.al 2023). Mainly, this study focused on a population of obese individuals and non-obese individuals and tracked their associated risk of colon cancer in 4-year intervals. Results from the study showed that persistent obesity increased risk for colon cancer, and those individuals who went from obese to non-obese by losing weight had lowered their risk of colon cancer (Seo et.al 2023). Despite the results of the study, it is noted that weight loss itself should not be the only factor considered when evaluating colon cancer risk decrease, but preventing long-term obesity and maintaining a healthy weight are more relevant in terms of colon cancer prevention (Seo et.al 2023).

Though lifestyle and diet changes do induce weight loss, bariatric surgery is more effective for weight loss in morbidly obese patients. Bariatric surgery refers to a group of surgical procedures designed to modify the digestive system to restrict the amount of food eaten or absorbed with the goal to decrease health conditions in those suffering from morbid obesity, as defined by the National Cancer Institute. The hypothesized mechanism by which bariatric surgery reduces risk is through improved metabolic effects and reduced inflammation due to a decrease in adipocytes (Villarreal-Calderon et.al 2021). However, epidemiological evidence to support this hypothesis has been mixed, with some studies showing decreased risk and other showing increased risk of colon cancer development. A 2024 meta-analysis of previously published research by Liu et.al concluded that obese women status-post bariatric surgery had a 54% decrease in colon cancer risk following the surgery compared to those who have not had the surgery (Liu

et.al 2024), showing that bariatric surgery may reduce colon cancer risk; however, there was no evidence of an association among men. A separate study from Hussan et.al found that men in comparison to women had an increase in incidence of colon cancer following bariatric surgery (Hussan et.al 2022). Other studies have found anywhere from a 27 - 44% lower risk of colon cancer in patients, male or female, who have had bariatric surgery (Hussan et.al 2022). Though the idea of weight loss through surgery is logical in terms of decreasing colon cancer risk, this conflicts with most of the literature and research; most published work reflects a higher incidence of colon cancer following bariatric surgeries. This is a potential bias in these studies, as the patients recommended for bariatric surgery are considered morbidly obese, so it remains possible that their obesity remains the real factor increasing risk. Research by D'Amato et.al has shown a gradual and significant increase in colon cancer risk 10 years following bariatric surgery, with these patients having nearly a 2-fold increase in risk (D'Amato et.al 2023). The reasoning for this remains unclear, but one idea is that the malabsorption of nutrients influences the gut microenvironment (Pararas et.al 2023). Yet another population-based study done by Tao et.al in 2019 explored the incidence of colon cancer in a large group of individuals with an obesity diagnosis from 1980 to 2015 (Tao et.al 2019). Results from this study concluded that there was an increase in colon cancer incidence following the procedure compared to those without the surgery. Again, the mechanism by which this occurs is not yet known, but investigating the cellular changes in the GI tract that occur with bariatric surgery could potentially be beneficial to consider (Tao et.al 2019). More work should be done to determine the actual impact of bariatric surgery on risk of colon

cancer to determine how effective of a preventative measure it could be in terms of lowering colon cancer risk through decreasing obesity.

Losing weight can also impact the pro-cancer effects of chronic hyperinsulinemia. The relationship between obesity and increased circulating levels of insulin and IGF-1 have been discussed in detail in prior chapters. Resolving issues pertaining to obesity does influence insulin and IGF-1. Because high IGF-1 levels are directly correlated by high insulin levels, lowering insulin has a positive effect on IGF-1 amounts. The same study done by Pendyala et.al intentional weight loss reduced inflammatory markers and molecules involved in the PI3K/AkT signaling pathway, therefore decreasing the likelihood of cancerous tumors developing in the colon (Pendyala et.al 2010). The nuanced topic of weight loss drugs for diabetics decreasing colon cancer risk is gaining more attention in the literature, with ongoing research investigating their impact. GLP-1 receptor agonists such as Ozempic and Mounjaro are prescribed to individuals suffering from obesity and type II diabetes to assist with the disease, as well as for intentional weight loss. In one study, patients taking GLP-1s had anywhere from a 44% to 50% decreased incidence of colon cancer (depending on the status of their weight) as compared to those treating their diabetes with insulin (Wang et.al 2023). This represents a crucial potential breakthrough in treating risk factors contributing to increased colon cancer risk.

Vitamin D deficiency is more prevalent in obese individuals and can therefore be a hypothesized mechanism by which colon cancer risk is increased within the obese population (Shanmugalingam et.al 2014). The percentage of these individuals suffering

from both obesity and vitamin D deficiency can range anywhere from 22% to 96% depending on location and population (Zakharova et.al 2019). To date, more research is needed to conclude that vitamin D supplementation is effective in decreasing colon cancer risk in obese individuals. In contrast, increased circulating vitamin D levels are known to be correlated with decreased risk for colon cancer in non-obese individuals, and research has shown a 24% decrease in colon cancer incidence with vitamin D supplementation in those with normal body weight (Berzigotti 2023). Overall risk reduction has been associated with increased dietary intake of vitamin D, with one study providing evidence of the 'protective' value of dietary vitamin D over supplemental (Kim et.al 2022). Recent clinical studies have been conducted under the hypothesis that vitamin D supplementation to prevent colon cancer development or reduce risk is less effective with increasing BMI (Kim et.al 2021). Peixoto et.al report that their study yielded lower colon cancer incidence in healthy-weight individuals treated with vitamin D in comparison to individuals with a higher BMI (Peixoto et.al 2022), suggesting that being obese plays a role in the effectiveness of vitamin D supplementation.

The most common site of metastasis in colon cancer is the liver, and NAFLD can increase the aggressive tendency of cancer cells to migrate to the liver via signals from extracellular vesicles and immune responses. This is like how adipocytes in visceral fat leads to development of the cancer cells themselves. In 2023, Wang et.al made a connection between NAFLD and liver metastasis, stating that patients with NAFLD may require different treatment for metastatic colon cancer than those who do not suffer from the disease (Jaber 2023). About 50-90% of individuals with obesity also have NAFLD

(Divella et.al 2019), though NAFLD has about 15-30% occurrence in the general population of those with normal weight (Divella et.al 2019). Because of this correlation, the major way to treat NAFLD is through weight loss. Medical professionals suggest patients try to eat a healthier diet with less fat and to increase exercise, as even a 3-5% decrease in body weight can help reverse the effects of excess fat throughout the body, especially in the liver (Mayo Clinic 2024) to decrease the likelihood of cancer development. At this time, there are no medications to cure NAFLD, but progression of disease may be halted by the weight loss, overall decreasing the risk of colon cancer development.

Upon review of the literature, it can be concluded that although all factors discussed present their own risk of colon cancer development, vitamin D deficiency, NAFLD and hyperinsulinemia can all be viewed as mediators along the pathway from obesity to cancer. Obesity represents the primary etiological factor contributing to colon cancer development, while the other factors discussed throughout this thesis act as consequences of obesity that only further exacerbate the risk. Therefore, addressing and treating obesity remains a crucial step in decreasing risk of colon cancer development, in addition to treatment of the other metabolic risk factors discussed in prior chapters.

Targeting the modifiable factors contributing to increased colon cancer risk are vital to decrease the incidence and prevalence of the disease. As reviewed, there is well-established evidence that factors associated with obesity, vitamin D deficiency, NAFLD and hyperinsulinemia are associated with increased risk of colon cancer. Though the current research provides clear evidence linking the modifiable risk factors discussed

throughout this paper, more work should be done providing the public with this information to educate those most at risk. Further research would be relevant to implement and assess targeted interventions to help the public understand their risk of colon cancer development and encourage them to take the preventative actions necessary to lower the prevalence of this disease.

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