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Dietary Habits and Colorectal Cancer Risk

Stacie M. Frovarp,

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Stacie M. Frovarp, RN, BSN, NP-S

University of North Dakota

PERMISSION

Title

Department Nursing

Degree Master of Science

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Abstract

According to the American Cancer Society (ACS) (2014), colorectal cancer (CRC) is the "3rd leading cause of cancer related deaths in the United States"(p. 3). Researches have hypothesized how dietary habits could increase an individual's risk of developing CRC. Diets high in red meat for example, have long been thought to produce carcinogens through cooking and digestive processes. These carcinogens damage colon DNA, leading to neoplastic changes (Raskov, Pommergaard, Burcharth, & Rosenberg, 2014). On the other hand, fiber has been suggested as having a protective nature to individuals with CRC risk. Throughout this literature review a case involving 65-year-old female from North Dakota will be explored. She presented with a chief complaint of loss of appetite, abdominal cramps, constipation, and blood in her stool. After undergoing diagnostic evaluation, she was diagnosed with adenocarcinoma of the colon. Searching the electronic databases of PubMed and CINAHL, as well as reviewing cited references from obtained articles completed a literature review. All articles were published between 2009-2015 from varying countries including United States, Japan, Europe, and Canada. In the following sections 10 studies will explore how an individual's diet could impact their risk of CRC. In conclusion, studies have shown diets high in red meats have the ability to increase an individual's risk of CRC. While diets high in vegetables and fiber can have a protective nature against CRC. The clinical benefit of this review is providing patients with this information to help lower CRC risk especially in those who have genetic predisposition.

Background

According to the American Cancer Society (ACS) (2014), colorectal cancer (CRC) is the "3rd leading cause of cancer related deaths in the United States"(p. 3). CRC is defined as an overgrowth of abnormal cells, which invade and destroy normal cells, in the colon or rectum (ACS, 2014). CRC has many risk factors including genetic predisposition and environmental exposures. To be more precise, dietary habits can cause a drastic increase or decrease in the risk for development of CRC. Dietary habits can affect the normal function of the gut by disrupting colonocyte proliferation, bacteria inhibition and growth, and introducing toxic substances to the gut wall, which induce neoplastic activity (Raskov et al., 2014).

Normally, the colon will ferment starches and proteins leftover from undigested remnants of food. The colon then extracts energy from indigestible carbohydrates, produce vitamins, absorb water and electrolytes and lastly, move waste products to the rectum (Raskov et al., 2014). There is constant proliferation of the colon mucosa and it is considered the one organ in the human body with the highest proliferation rate. It is estimated the "colonic lumen is fully renewed within 2-8 days, which is approximately 3-10 billion colonocytes per day" (Raskov et al., 2014, p. 18152). As food products pass through the colon, colonocytes are also sloughed off and are metabolized by bacteria.

Within the human gut there is a sophisticated network of bacteria called the microbiome and it is a major part of normal digestion. Food remnants within the colon are metabolized by the microbiome. Changes in colonocytes and the microbiome occur due to environmental exposures, such as diet. The microbiome also goes through changes as the body ages and tends to lose biodiversity leaving the colon susceptible to inflammatory processes with no way to combat them (Raskov et al., 2014).

Raskov et al. (2014) found dietary habits can increase the number of malignancies because the colonocytes are exposed for a prolonged amount of time to carcinogens. Due to this constant exposure the colonocytes progressively produce genetic differences, creating genetic instability. This instability along with possible genetic predisposition to mutations can increase ones likelihood of having malignant transformation. Epidemiologic data gained from numerous studies have shown there are geographical differences where risks of CRC are higher in more affluent societies due to dietary habits and lifestyle (Raskov et al., 2014).

Diets high in red meat and processed meat have shown to increase the risk of CRC by 10% for each 30 grams of meat consumed per day (Raskov et al., 2014). The undigested remnants of meat proteins will be digested by bacteria within the colon and further fermented. N-nitroso compounds (NOC) are produced after fermentation occurs. NOCs have been shown to lead to mutations in oncogenes and tumor suppressor genes within the colon (Raskov et al., 2014). Instead of being destructive, when fiber is digested and fermented there is a protective nature noted. When fiber reaches the colon, it is almost completely undigested. Fiber bulks the stool, stimulates normal gut flora growth, and diminishes the time and exposure of carcinogens to the gut (Raskov et al., 2014).

A case report will be explored in conjunction with reviewing recent studies regarding dietary habits and CRC. This case involves a 65-year-old Caucasian female from North Dakota. These symptoms had been apparent for approximately 6 weeks. No family history was known due to adoption. There were no alarming risk factors such as tobacco use, alcohol consumption, or previous exposure to radiation. Diagnosis of adenocarcinoma of the colon was found. Further exploration of this case will be presented in sections below.

The following literature review was completed to show the direct correlation between dietary habits and CRC risk. In the following sections recent studies have be examined and reviewed exploring how dietary habits can either increase or possibly lower an individuals risk of developing CRC. It is the role of the provider to educate patients and families regarding their risk of CRC. If patients and families are provided this important education regarding dietary habits and CRC risk, numbers of CRC could potentially decrease as well.

Case Report

This case involves a 65-year-old Caucasian female from North Dakota. She presented with a chief complaint of loss of appetite, abdominal cramps, constipation, and blood in her stool. Approximately 6 weeks ago she started noticing occasional cramps in her left lower quadrant (LLQ), which was associated with constipation. These cramps lasted approximately 30 minutes and were most severe following meals. She had taken laxatives to relieve the constipation, which was helped partially. When having bowel movements, bright red blood was noted in her stools and the stools were smaller in caliber than her normal. Over the past four weeks, she has had a decrease in appetite and a 12-pound weight loss. She also reports fatigue, which has been increasing.

Overall, this patient is healthy, with no past medical history. Family history is unknown due to adoption. There have been no surgeries. The only home medication is a multivitamin and she has no known allergies. This female is married and a retired teacher. She does not use tobacco and does not drink alcohol. She does not regularly exercise and her diet consists of meats such as beef, chicken, pork, but rarely fish, vegetables, fruits, and breads/pasta. She rarely visits her provider and is not up to date on screenings such as a colonoscopy, laboratory screenings, or immunizations.

A review of systems is overall negative except for what is mentioned in the history of presenting illness. She did complain of overall weakness and fatigue, some night sweats, but denies any hair loss. She did also mention some heartburn as well, denies diarrhea or the presence of hemorrhoids. No burning, frequency, or urgency with urination. No confusion, headaches, or dizziness. Denies depression and/or anxiety feelings.

Upon physical examination, this well developed female appears fatigued and distressed. Vital signs as follows, blood pressure 150/88, heart rate 72, respiratory rate 16, and temperature 97.3 degrees Fahrenheit. Her head is normocephalic, no lymphadenopathy is noted, no thyromegaly, and no JVD noted. Cardiac assessment shows regular heart rate and rhythm with no thrills, clicks, or murmurs. Lung sounds clear to auscultation to all fields with no wheezes or rhonchi. Abdominal sounds noticeably hypoactive in all four quadrants. Palpation revealed a 10x10 mass and tenderness to the left lower quadrant. Tenderness was also noted to the right upper quadrant with palpable liver edge. No edema noted to lower extremities. Cranial nerves II-VII intact.

Due to presenting illness and physical exam findings, laboratory and imaging studies were ordered. A complete blood count was ordered to evaluate blood loss from the noted bright red blood in the patients stool. This showed slight anemia with a red blood count at 4.28, hemoglobin 9.7 and hematocrit 29.9. A barium enema was ordered to evaluate the abdominal mass, constipation, and blood in her stool. This was inconclusive so a sigmoidoscopy was completed. A 17.0 cm segment of the terminal ileum and left colon was submitted and after assessment by the pathologist a diagnosis was given of infiltrating adenocarcinoma, which was poorly differentiated. Angiolymphatic invasion was identified from four of the twenty lymph nodes submitted. The adenocarcinoma was listed as Stage IIIB (T3, N2, M0). This patient was

educated on her diagnosis of adenocarcinoma of the colon, what future outcomes could look like as well as being referred to oncology and gastroenterology for management and treatment. Further treatment plans and management would occur between these providers. Palliative care would be explored after she met with oncology and gastroenterology for their consults.

Literature Review

Diets in the Midwestern region of the United States are heavily weighted with beef, pork, and chicken and extremely low on fish due to geographical distance (Food In Every Country, 2015). Some of this has changed due to the increased availability and stores being able to ship and receive fresh seafood and fish from almost anywhere in the world. Foods also typically are rotated by seasons based on availability within the Midwest (Food In Every Country, 2015). Seasons in the Midwest also have given way to more processed foods such as pickling, dried, and smoked meats (Food In Every Country, 2015). Smoked meats release heterocyclic amines (HCA), which are carcinogenic products from cooking meat at high temperatures or for long periods of time (Lee, Wang, Yang, Tao, Li, Huang, & Li, 2012). There could be many reasons as to why the patient in the case report above developed adenocarcinoma of the colon. Family history is unknown, but her Midwestern diet could have certainly sped up the process by exposing the gut to carcinogens such as HCAs. There have been many studies, which show statistically significant results of how an individuals diet may actually be a risk factor to developing CRC or how specific diet features may be protective.

It has been widely noted and researched that diets high in red meat increase an individual's risk of developing CRC, especially when there is a genetic predisposition. A very small study, only 16 participants, was completed in 2010. This study explored the possibility of inhibiting damage to colorectal DNA by diets high in red meat. Two groups of 8 participants

were created. One group ate a diet high in high-temperature red meats while another group ate the same but added inhibitors such as cruciferous vegetables, chlorophyllin, and yogurt with these meals. Urine, feces and serum were collected from volunteers at the two-week intervals to detect HCA levels and mutagenicity. HCAs are elevated in red meat and meat cooked at high temperatures and is associated with an increased risk of CRC. Rectal biopsies were also collected to detect any damage to the colon DNA. Shaughnessy et al. (2011) found urine and feces mutagenicity increased with the high temperature meats "and that consumption of yogurt, cruciferous vegetables, and chlorophyllin (CHL) altered urinary and fecal mutagenicity and reduced colorectal cell DNA damage (p. 6). The results of this study are very straightforward and show there could be a way to combat the damage HCAs does to our colorectal DNA. One very large limitation of this study is its size. If this could be reproduced in a larger population size, the results would be more statistically significant and possibly alter the development of CRC, especially in those with a genetic predisposition.

Another study examined how meat consumption increases the risk of distal colon and rectal adenomas. This randomized control trial was completed as part of a detection program for prostate, lung, colorectal, and ovarian cancer. This 10-center study was able to recruit 154,952 participants between 1993-2001 from the United States. Participants were placed into two groups, screened or non-screened. The screened participants underwent flexible sigmoidoscopy screening at baseline and then subsequently at either study year 3 or 5 (Ferruci et al., 2012). All participants were given a one-time questionnaire asking about lifestyle habits, personal history and social history, while those in the screened group completed a one-time 137-item food frequency questionnaire. These were used to explore and quantify the intake of HCAs per day for the participants. According to Ferruci et al. (2012), 1008 participants were discovered to have

distal colorectal adenoma at the 3-5 year baseline (p.610). These 1008 participants could be further broken down into "503 non-advanced, 237 advanced, and 268 were unknown for advance status"(Ferruci et al., 2012, p.610). In the top quartile for red meat consumption, 314 of the 1008 participants developed some distal adenocarcinoma of the colon. Those with high consumption of processed meat totaled 324 of 1008. Overall, the researchers felt as though this study proved a borderline positive association for CRC when red meat, processed mean, grilled meat, or nitrate and nitrite from processed meat are ingested (Ferruci et al., 2012). They felt when colorectal adenoma is separated into specific locations such as the descending/sigmoid colon and the rectum gender could play an important role as well. Men were found to have slightly higher elevated CRC risk with higher HCA intake (Ferruci et al., 2012). They also found the area in which adenoma develops could be dependent on types of meat. Ferruci et al. found a statistically significant elevated risk showed rectal adenomas occurs with higher intake of grilled meat and well or very well done meat. Even though this study showed only modest evidence for the potential increase in colorectal adenoma, it still demonstrates how red meats and particularly those cooked at high temperatures can cause damage to the colorectal DNA.

A cross sectional study completed by Ho et al. (2014), explored how genetic susceptibility played a role in colorectal adenoma development when an individual is exposed to the heterocyclic aromatic amines (HAAs) or the carcinogen produced when cooking red meat. This study yielded 336 participants who underwent a colonoscopy and completed a self-administered questionnaire. This questionnaire assessed average HAA consumption and lifestyle and social habits (Ho et al., 2014). Fasting blood samples were taken at the beginning of the study for each participant to complete genotyping along with biopsies and pathology reports from colonoscopies. Ho et al. (2014) discovered there was no significant data showing dietary

HAAs are associated with an increased colorectal adenoma risk. On the other hand, they did discover a possible link between HAA exposure, colorectal adenoma, and male gender. They also discovered individuals with genetic predisposition to neoplastic changes had tend to activate HAAs more readily as well as not having the ability to repair damaged DNA as easily (Ho et al., 2014). Again, this study did not reveal extremely strong results regarding HAAs effect on the increase in colorectal adenomas. Research is continuing to find those with genetic predisposition to colorectal cancers need to be mindful of their dietary habits and possibly decrease red meat intake to lower their risks of developing colorectal adenomas.

Wang, J. et al. (2012) further examined dietary habits in their family based case-control association study. This study was also exploring the association between HCAs and CRC risk in individuals with genetic predisposition and a close relative with CRC. Individuals were found through the USC Consortium of the Colon Cancer Family Registry (Colon-CFR). Exposure to meat was assessed using the Colon-CFR baseline risk factor questionnaire (Wang, J. et al. 2012). This study took siblings or first-degree cousins of an individual who was already diagnosed with colorectal cancer. Seven polymorphisms were examined through phenotyping. No statistically significant information was found from six polymorphisms. These polymorphisms "in genes encode for enzymes that play a key role in the metabolism of 3 main meat induced carcinogens"(Wang, J. et al., 2012). One polymorphism, GSTP1 Ile/Val, was discovered. Having this polymorphism increased an individual's risk of colorectal cancer by approximately 70% (Wang, J. et al, 2012). Another polymorphism, CYP1A2-154A>C, was noted to give the researchers their strongest evidence of a modifier to colorectal cancer risk. CYP1A2-154A>C can either have one of two alleles, A or C. Allele A equals a higher enzymatic effect when compared to C, which is slower. The results show "the carcinogenic effects of diets high in red

meat well done on the inside or outside would be greater in individuals carrying one or 2 copies of the C allele then individuals carrying 2 copies of the A allele"(Wang, J. et al., 2012). This evidence further demonstrates how closely genetic predisposition and diet are related to CRC risj. Individuals with a known family history of CRC should be educated on how to change their diets appropriately to lower their chances of developing CRC.

Humphreys et al. (2014) explored diets high in red meat in a randomized control trial exploring how dietary manipulation can create oncogenic microRNA expression. Twenty three participants were in this study which consisted of two periods of intervention that were 4 weeks in length preceded by a 4 week run in period and then separated by a 4 week washout period (Humphreys et al., 2014). Participants were placed into two groups, high red meat diet and a high red meat diet plus a high amylose maize starch. To conduct the study, at the end of each 4-week period a fecal and rectal pinch biopsy specimens were obtained. The researchers were able to show high red meat intake "significantly increased the rectal mucosa levels of miR17-92 cluster miRNAs and miR21, which are both elevated in colorectal cancers"(Humphreys et al., 2014, p. 790). The addition of high amylose maize starches is due to the fact that these have shown to modify some changes to rectal mucosal tissue. When the starch was added, there was significant reduction of miR17-92, suggesting a protective nature in reducing the risk of CRC development. It would be very interesting to see results of studies exploring potential modifiers, such as the maize starch from this study as well as the cruciferous vegetables, yogurt and chlorophyllin from the Shaughnessy et al., 2011 study. The Humphreys et al. (2014) study also had small numbers and it would be beneficial to repeat this study with a larger population to fully grasp the significance of adding starches to reduce CRC risk.

Other studies have explored the potential of dietary habits, which could protect you from the risk of developing CRC. A randomized controlled intervention study was completed by Pot et al. (2009), which involved 216 volunteers. An independent subject placed these volunteers into three separate groups, oil rich fish group, lean fish group, and dietary advice group. Fish was provided to each fish group and were instructed to eat two 150-gram portions of fish per week for 6 months. Follow up with volunteers occurred every 2-4 weeks with phone calls and checking of food diaries. For the oil rich fish group, serum levels of omega 3 polyunsaturated fatty acid VLC-PUFA were drawn at the beginning and end of the study. This substance is thought to provide the colorectal protection to individuals who eat oil rich fish, such as salmon. A food frequency questionnaire was completed by volunteers at the beginning of the study, as well as a questionnaire regarding social habits, such as physical activity, smoking and alcohol consumption. Colonic biopsies were taken at the beginning of the study as well as at the end. Pot et al. (2009) were exploring the number of mitotic or apoptotic cells in the crypts of the intestine, because apoptosis has been suggested as a marker of cancers. Overall, "fish consumption had no effect on the number of apoptotic cells per crypt after 6 months intervention compared with the dietary advice group"(Pot et al., 2009, p. 357). VLC-PUFA serum levels were all very similar at baseline and showed increase in the oil rich fish group only, which merely showed the researchers this group complied with their intervention. Therefore, this study did not support the proposed hypothesis that increasing fish consumption provides protection from colorectal cancers. Some limitations noted were fish consumption by volunteers was already at 1.5 per week, which is typically the higher end of consumption. The authors did state this was the first trial of its kind and hope this will further more research. An interesting study would include the possibility of exploring, if an individual were to change their diet from high amounts of red meat

to modifying it to having less red meat and incorporating more fish would show a decrease in CRC risk.

From the previous studies it can be suggested natural products such as vegetables, fruits, and vitamins, especially fiber have a protective nature since they have been added to high red meat diets to combat the negative effects. The next few studies explored this idea of what dietary habits are protective in nature instead of increasing a CRC risk.

A case control study completed by Chen et al. (2015) assessed dietary patterns across different geographic areas. This study noted CRC risk is higher in more developed countries rather than underdeveloped. The reasons behind this could merely be from diet alone and having highly processed foods and red meat for example available at any time. Chen et al. (2015) studied 1204 participants. In this study participants were given two questionnaires one exploring personal health the other exploring food frequency (Chen et al., 2015). From these questionnaires three dietary habits were formed, meat-diet patterned, plant-based diet and sugary diet. The meat diet had high amounts of red meat, processed meat, and processed fish. The plant-based was based on high amounts of vegetables, grains, and fruits. The sugary diet group had large amounts of sugar filled products such as pies and tarts. As in previous studies, the meat pattern diets had higher risks of CRC risk, where as the plant based diet had a more inverse relationship. Chen et al. (2015), felt as though this result, even though not strongly significant, listed the plant-based diet as having a more protective nature then only preventative. The sugary diet fell into a pattern, which showed an increased risk of CRC, much like the meat pattern diet.

Another fairly new study from 2015, explored how vegetarian diet patterns impact the risk of CRC. Orlich et al. (2015) wanted to explore how to enhance primary prevention through understanding risk factors for CRC. This study had 77,659 participants, who again took a self

administered food frequency questionnaire and were asked about 200 separate food items as well as social habits and lifestyle. "There were four vegetarian diet patterns (vegan, lacto-ovo, pescovegetarian, and semivegetarian) were combined and compared with the non-vegetarian pattern"(Orlich et al., 2015, p. E3). After an approximate 7-year follow up, 490 cases of CRC were identified out of the 77, 659 participants (Orlich et al., 2015). The non-vegetarian group had a total of 238 cancer cases followed then by lacto-ovo with 147 cases, vegan with 40 cases, peso with 35, and semi-vegetarian with 30 (Orlich et al., 2015). Orlich et al. (2015) felt as though these results were significant to state a vegetarian diet pattern shows to reduce the risk of colon cancer.

As more research is completed the protective nature of a high vegetable/ low red meat diet has more compelling research showing it can reduce an individuals risk of CRC. Another study, which indirectly studied how natural plant fiber from legumes, could potentially increase the overall health of the gut, therefore providing a protective effect against CRC. Fechner, Fenske, and Jahreis (2013) created a double blind, controlled randomized crossover trial to assess whether or not adding extra fiber onto a typical diet of participants lowered cholesterol and indirectly looking at colon health. Seventy-six participants where selected and were placed into three groups with each group given a different type of fiber to take. This study had four periods each lasting 2 weeks. There was a run in period and two intervention periods with supplementation of 25 g total dietary fiber per day added to their usual diet and a wash out period between the intervention periods"(Fechner, Fenske, & Jahreis, 2013). Fecal samples were collected and overall bowel health, such as constipation, bowel movements, and flatulence. Since this study was not directly studying CRC and reduction of risk these researchers only suggested that their findings could potentially be linked to lowering CRC due to how fiber is suspected to

work in the human gut. Fiber bulks the stool up making the oral fecal transit time shorter, meaning a shorter window of time harmful carcinogens and substances have to contact the gut wall and cause damage. When looking through their data, it does make sense, by increasing dietary fiber, even to the minimum standard 25 grams per day would help protect against CRC.

One last study examined how vitamins could potentially lower the risk of CRC in patients who had diets high in retinol, carotenes, vitamin C and vitamin E. Wang et al. (2012) recruited 1,631 participants to have their diets reviewed via a lifestyle questionnaire as well as a dietary interview examining over 148 foods and beverages. Dietary habits were then reviewed and nutrient intake was calculated from Japanese food consumption tables (Wang et al., 2012). This study had very small significant findings associated with protection from CRC. The study did show some protective nature of retinol in women, but it showed a small increase in CRC in men who had high levels of retinol intake. Wang et al. (2012) felt this study showed no evidence of reducing CRC risk with intake of specific vitamins such as vitamin C, vitamin E or carotenes. Further research would be needed to make recommendations on vitamin supplementation or selecting foods high in these vitamins to reduce the risk of CRC.

In conclusion, dietary habits have a large impact on the risks of CRC. This may be more important for those individuals who already carry an elevated risk due to a genetic predisposition. Some take-aways from this literature review would be to:

1. Diets high in red meat are associated with elevated risks of CRC. This is due to how red meat is digested by the body and carcinogens are left behind to have contact with the bowel wall. Once this happens over several years colon DNA is damaged and becomes unstable causing neoplastic changes.

2. Diets high in fish have not been shown to necessarily lower an individual's risk of developing CRC. It potentially could lessen the amount of red meat consumed, but showed no other protection from the study explored. Further studies of this kind would be needed to assess this hypothesis further.

3. Dietary intake of vegetables and fiber does show protection against CRC risk. Individuals should strive for the recommended intake of 25 -30 grams per day of fiber to lower their risk of CRC. This is hypothesized due the ability of fiber to move stool through the bowel more quickly and decreasing the time carcinogens have contact with the bowel wall and decrease the time they have to cause DNA damage.

4. The last take-away is probably one of the most important. With this information the education a provider gives to patients could potentially decrease CRC risk. Dietary habits of each patient could be examined and education given on how to change to decrease their risk of CRC. This potentially could be life changing in those individuals with elevated risks of CRC.

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