Spring 2019

Colorectal Cancer, Gut Microbiota, and Diet: What's the Connection?

Jordan Neyens

Colorectal Cancer, Gut Microbiome, and Diet: What's the Connection?

By: Jordan Neyens
Iowa State University

INTRODUCTION

Colorectal cancer (CRC) is one of the deadliest and most common cancers that humans face. It is currently the 3rd most common cause of cancer mortality worldwide, with roughly 690,000 deaths are year (Aymeric et al, 2018). CRC can be caused by many things; but it was essential that there is a balance in between the gut microbiota, diet, and the immune system of the host. It is estimated that almost a 50% decrease can be achieved by diet, physical activity, and managing weight. (AICR). The diet and health of the individual plays a large role in the gut microbiota of said individual. Other events that could happen to elevate contraction percentage of CRC include infection, stress, inflammation, and an irregular gut microbiota. Colonoscopy screenings are recommended after the age of fifty, to help catch the early signs of colorectal cancer, since it usually does not appear until the later stages of life. This does not help entirely though, since some parts of the world do not have access to screenings, or they have changed their diets significantly from traditional diets to western diets. Multiple factors play into the role the health of the gut, colon, and rectum, and it is important to know about all the factors that attribute to the diagnosis of colorectal cancer.

GUT MICROBIOTA

The intestinal tract is lined with over a thousand different types of bacteria, and trillions of different microorganisms. Depending on what microorganisms and bacteria is in abundance, can help promote or prevent CRC. Figure 1

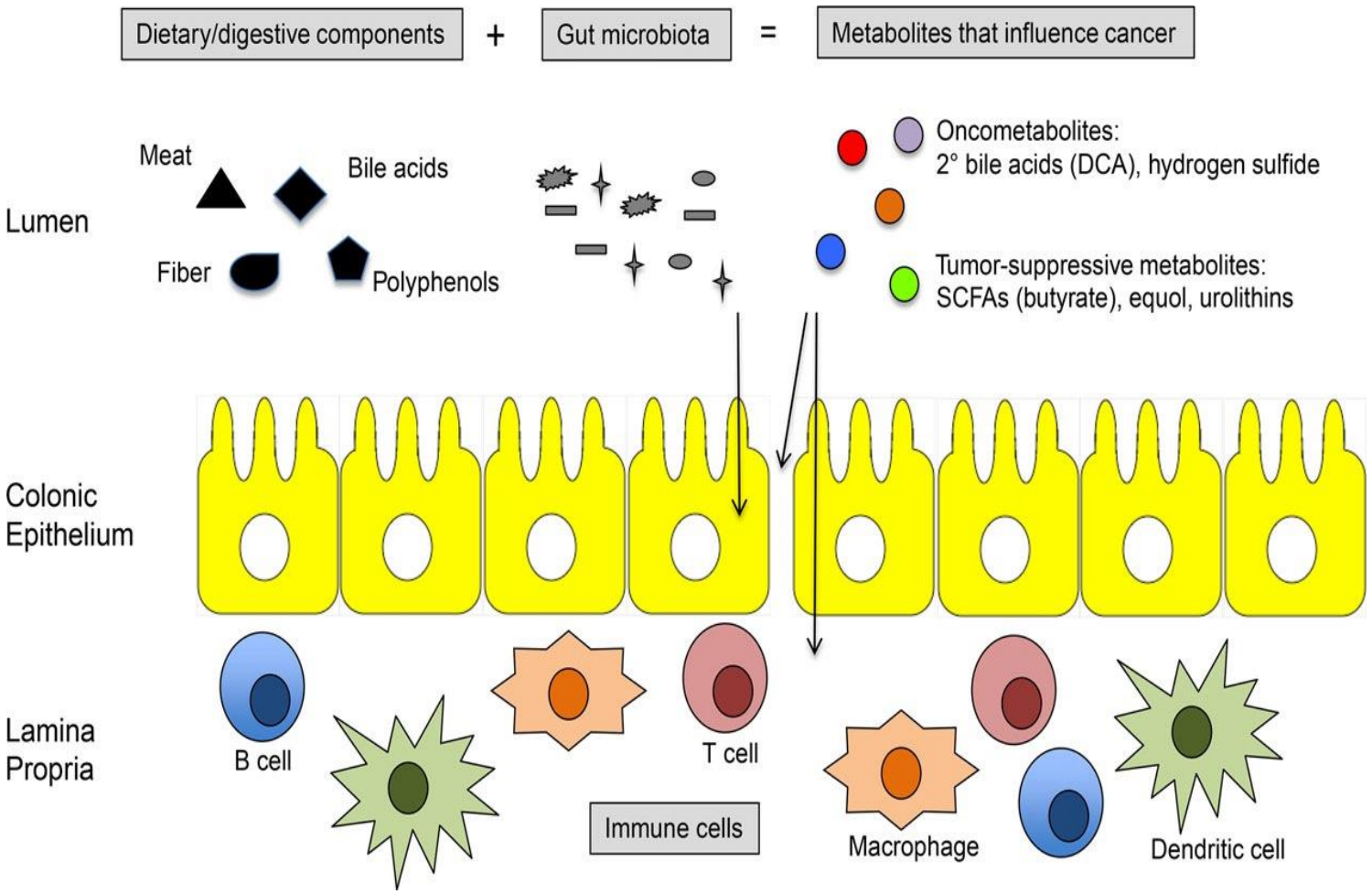

Figure 1: Above is a graphic of the colon and the different mechanisms the gut microbiota uses to influence colorectal cancer. The top row (lumen) shows how different digestive components get mixed with the gut microbiota to form certain metabolites. The oncometabolites come from meats and bile acid and promote CRC. The tumor-suppressive metabolites, butyrate for example, come from fibers and polyphenols and these help protect the colon from CRC. The bacteria of the gut microbiota can influence the colonocytes by 3 pathways depicted by the 3 black arrows. From left to right they show a direct influence of bacteria on the immune cells, then by allowing the metabolites to interrupt the colonic epithelium and lastly indirectly by influencing the metabolites that then work on the colonocytes. (Bultman 2016)

shows a schematic of what the colon looks like with all its parts. The gut microbiome is always changing based on the diet, weight, environment, etc. it can react to short term diet changes and also long-term diet changes. Short-term diet changes however, are not likely to be successful in helping prevent CRC, it must be a long-term lifestyle change for the better. The gut microbiome starts to form in utero, but a majority of it is built throughout our lifetime. Right after birth,

babies are either breastfed or formula fed. This is the start of the formation of the gut microbiota. Breastfed babies' microbiomes are a majority *Bifidobacterium*, while formula fed babies are mostly *Enterococci* in their gut (Manzat-Saplacan et al, 2015). From there, we begin to build a microbiome and add to it and change it as time goes on by what we eat and our physical daily activity. The gut extracts energy from undigested carbohydrates by the process of fermentation and the absorption of short-chain fatty acids (SCFAs), the most important being butyrate. Butyrate is extremely important for all gut related conditions, from obesity to autoimmunity to colorectal cancer.

Although diet is the main focus of this paper of what effects the gut microbiome, it is not the only thing that can change the composition of it. Sleep/mood, inflammation/infection, and skin also play roles in the microbiome. Mood is shown to have an effect on the gut, especially anger. The enteric nervous system, or the 'second brain' lies within the gut and has millions of neurons and over 30 different types of neurotransmitters (American Cancer Society 2017). The gut is also the home to over ninety percent of the serotonin in the body, making it important when it comes to melatonin production and sleeping. The microbes of the gut can also eat up or shove out bad bacteria, protecting the body against infections, not only in the gut, but across the whole body. Similarly, some microbes release compounds that help the body with immunity by lowering inflammation and not allowing the immune system to attack itself. Along with releasing agents to help fight against infection, microbes will turn oil on the skin into natural moisturizers in order to keep bacteria from entering the body that way.

When someone has CRC, the bacteria and microorganisms within the gut becomes much less diverse. This diminishing is called dysbiosis. Specifically, the bacteria *Escherichia coli*, *Fusobacterium nucleatum,* and *Streptococcus gallolyticus* are prevalent in the gut and the bacteria *Roseburia* and *Fecalibacterium,* which are butyrate producing bacteria, are scarce (Bultman 2016). *Streptococcus gallolyticus* colonization is seen as the most

significant of all bacteria seen in CRC. In one study it was seen as 1000-fold higher in tumor-bearing mice than in normal mice (Aymeric et al, 2018). This bacterium is known for being responsible for endocarditis and bacteremia in elderly patients. It is hard to determine whether the increase or decrease of these bacteria are a consequence of having CRC or if they are the cause of CRC.

DIET

The diet is one of the critical components in what defines what is present in the gut microbiome. These two components (gut microbiome and dietary components) combined create metabolites that influence cancer prevention or promotion. Although CRC incidence rates and death rates have been decreasing in the USA, this cannot be said for other Eastern countries, some rates even doubling in some Asian and European countries since the 1970s (Bultman 2016). The rates these countries have been increasing due to them adapting our Western diets. These western diets consist of a large amount of red meats, processed meats, pre-packaged foods, fats, oils, butters, deep-fried foods, and high fat diary products. This is different from a healthy diet, or eastern diet, that is low in red meats, full of fiber and whole grains, and does not include processed food of any sort. These differences can cause a huge change in the composition of the gut microbiome, and thus promoting or preventing CRC.

The overall incidence of colorectal cancer rates is lowering, but the incidence of early-onset (before the age of 50) CRC is drastically increasing. This trend upward is believed to be due to the prevalence of obesity in the United States. There has been a 51% increase in CRC incidence in patients age 20 - 49 since 1994 (Wolf et al. 2018). Obesity has the ability to activate the RAS-RAF-ERK pathway, allowing the signaling to be accelerated. This will end up causing carcinogenesis in an earlier timeframe, then if the individual was not obese.

The single most important food intake necessary for helping maintain a gut microbiome to help prevent CRC would be fiber. Fiber is shown to reduce the risk of colorectal cancer and to help

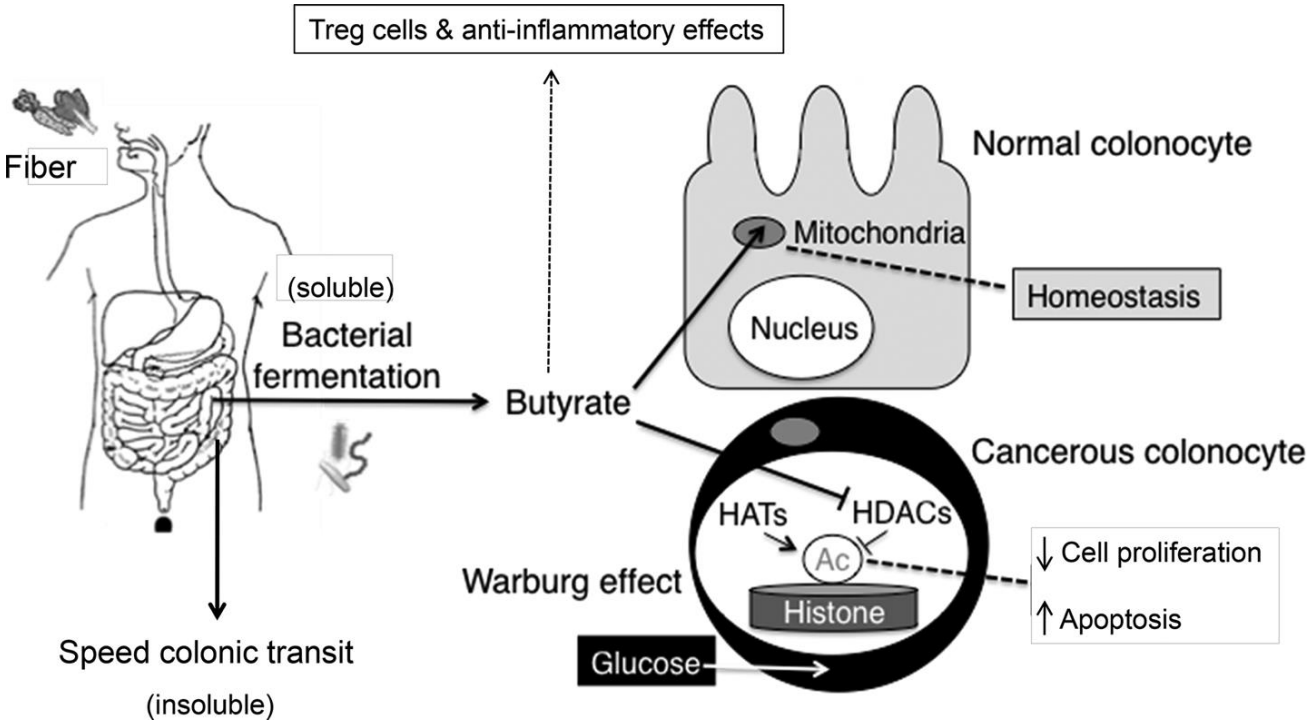

Figure 2: As fiber enters the body, it has both a soluble and insoluble pathway. The insoluble pathway is the speed colonic transit path. The soluble pathway, bacterial fermentation, leads to butyrate. Butyrate is what colonocytes use as an energy source. When colonocytes become cancerous, they feed off glucose instead of butyrate, leading there to be an excess of butyrate left in the cells. (Bultman 2016)

decrease the mortality rate after diagnosis (Mingyang et al, 2017). Dietary fiber is considered the edible part of a plant and their extracts. Fiber is not able to be digested and reabsorbed as easily as other foods, meaning it can ferment in the large intestines. Figure 2 is a picture that lays out what happens when someone ingests fiber. The first thing fiber does in the gut is speeds up colonic transit. This means the cells of the gut have less time to pick caricinogenic materials from what has be ingested. Fiber also is fermented into butyrate, an essential short-chain fatty acid (SCFAs). Without butyrate, the gut will be unable to maintain a suitable environment for good bacteria to proliferate.

THE WARBURG EFFECT

Most cells inside the human body use glucose as their main energy source. Colonocytes, or cells of the colon are one of the exceptions to this

rule. The Warburg effect is a concept that discusses the reason behind this. The Warburg effect means that cancer cells become addicted to glucose. Cells use butyrate as their main energy source in order to maintain a homeostatic environment. Butyrate is used because it can be metabolized quickly in the mitochondria so there is essentially no accumulation of it in the nucleus. When cells become cancer, they no longer want butyrate, they want glucose as their primary energy source. The used of glucose instead of butyrate isn't the problem. It's the fact that butyrate is still being transported into the cell and not being taken up and used as energy. This excess butyrate accumulates in the nucleus and functions as an HDAC inhibitor. This means that butyrate makes it so the cell cannot undergo cell proliferation or apoptosis (Bultman 2016). This idea is supported by clinical success of the drug metformin. This drug, made for diabetes, is used to lower blood glucose levels, for the prevention and treatment of CRC (Morales et al, 2015). Metformin is used also because obese individuals guts' are more likely to resemble a tumor-permissive environment.

SCREENINGS

Colorectal cancer screenings have been improving over time and it is important to keep trending in the right direction. The more physical CRC screenings are invasive and look for polyps forming on the mucosal lining of the colon. Figure 3 below shows the parts of the colon and rectum, and what is being looked for. CRC screenings did not become covered by Medicare until 1997 under the Balanced Budget Act (Montminy et al, 2019). The number of individuals that took the test significantly increased after that. Even though it is becoming more common to get tested, there is still a great percentage of the eligible population that has not been tested when they should be. There are several different ways to screen for CRC; through a colonoscopy exam, a stool sample, a barium enema, and some others.

The colonoscopy exam was first introduced in 1969 (Montminy et al, 2019). This procedure is done by inserting a long, flexible tube, the colonoscope, into the rectum. This tube has a camera on the end in order to

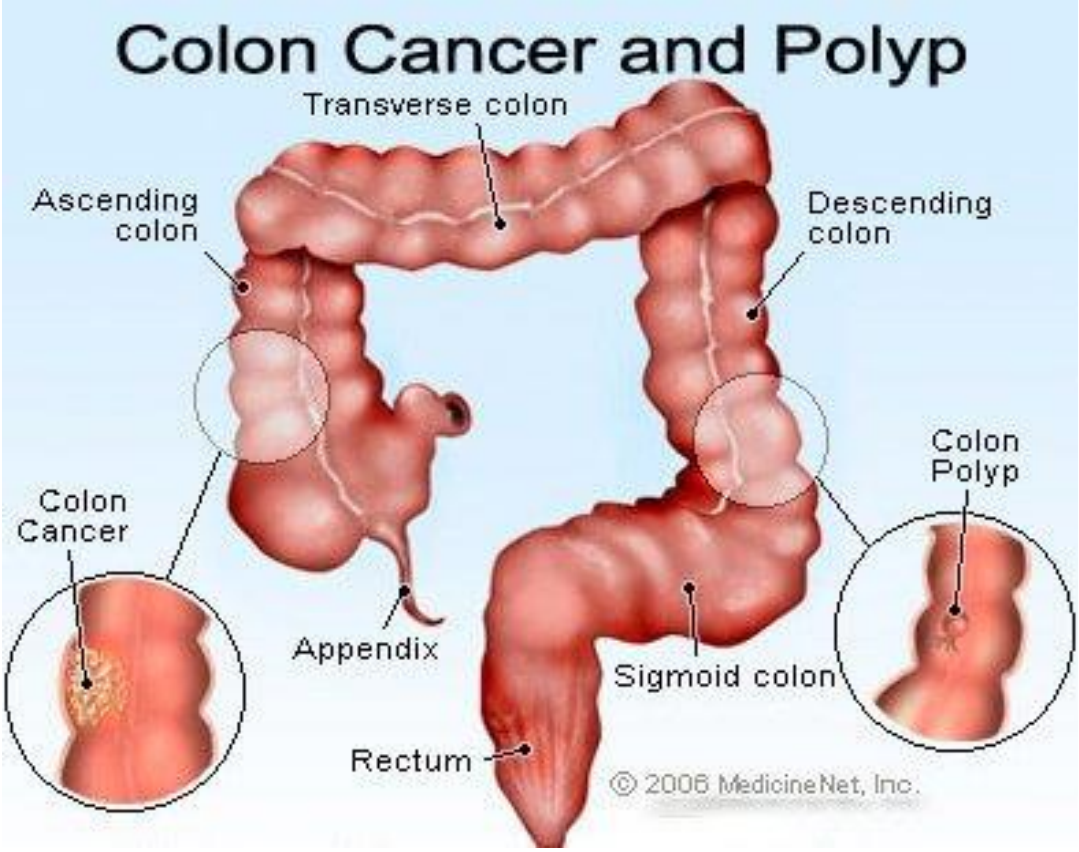

Figure 3: This image shows the rectum and colon. Colonoscopy exams are administered by inserting a tube through the rectum and throughout the colon, looking for polyps, bumps, outgrowths along the surface (medicinenet)

view the inside of the rectum and colon. If the inside looks normal, no other steps need to be taken. Small samples can be removed from the lining of the colon or rectum if anything looks abnormal. These will then be taken to have analysis done on them to make sure no cancer is present. This procedure takes less than an hour but involves drinking bowel preparation medications in order to clean out the whole GI tract. This process can be annoying for some, so that is one reason people tend to pass on the exam.

Another test, a stool sample, is way simpler for the patient. This test just requires a sample of the persons stool. From there they use gFOBT or FIT to determine if there is a problem in the rectum or colon. gFOBT was discovered first, back in 1901 (Montminy et al, 2019) and it stands for guaiac fecal occult blood test. The point of this test is to see if there is any presence of blood

within the stool, meaning there is a problem within the GI tract. The FIT test on stool was introduced in 1978 and stands for fecal immunochemical test. The most common brand of this is Cologuard and is a more sensitive test than the gFOBT, making it able to detect CRC at a lower scale. It does this by detecting human hemoglobin levels in the blood. FIT also looks for mutations within the beta-actin of the stool (Montminy et al, 2019). Although one test is better than the other, both are still used across the globe.

Barium enemas were thought of as another way to look for cancer within the colon and rectum. This procedure was done by giving a patient a double-contrast barium enema and then was evaluated two weeks later by a colonoscopy. This method was proven to be time consuming and expensive, so it is now one of the unused methods of colorectal cancer screenings.

Precancerous polyps in the lining of the gut can also be detected by using Computed Tomography Colonography, or CTC scan. This screening came out in 1994 and was thought to be a great idea because it would create 3D images of the mucosal linings of the colon. This was the case, but only for larger polyps and not the small ones that can eventually become large. For this reason, this test is not the best, but it is a close second to a colonoscopy exam.

There are other testing methods being researched at the moment. Ongoing research is looking into urine samples as a way to detect CRC. This would be done by checking the urine for certain metabolites and genes that are present in CRC cells and not in normal gut microbiome cells (Montminy et al, 2017). These tests are looking promising, besides their cost-effectiveness needs to improve.

PREVENTION

The incidence rates have risen over the last few decades, but the death rates have stayed pretty consistent. This stable death rate suggests that therapy and early detection has increased, which is a great sign. The ACS (American Cancer Society) stats that the average age of disease is 72 for women and 68 for men. 50 years old is the

recommended age to start getting tested for CRC. This is to ensure that the cancer is detected as early as possible. Some might be suggested to check even earlier than that if there is a history of colorectal cancer within the family.

Many studies have been done to see what races/genders colorectal cancer is most common within. Men are more likely to get diagnosed with this cancer than women. This is thought to be because of genetic differences between men and women. The race with the lowest incidence rate is Asian and Pacific Islanders at 32.2/100,000 (American Cancer Society, 2017). This is speaking about non-American born Asian and Pacific Islanders, because Americans have a higher rate due to their western diets and lack of low-fat in their diets.

There have also been several studies to show that racial disparities associated with CRC. African Americans seem to struggle the most with CRC. Prior to 1989, the incidence rates were higher in white males and females than African-American men and women, and now after 1989 the incidence rates are lower in white men/women than African-American men and women. African-American men also have a 52% higher death rate than that of white men (Montminy et al, 2019). This difference seems to correlate directly with the percentage of at-risk individuals being tested.

The biggest goal that seems everyone was working towards is a pledge called '80% by 2018' and was introduced by the National Colorectal Cancer Roundtable (NCCRT). This pledge was put in place to try and get 80% of eligible participants (people ages 50 or older) to get screened for colorectal cancer. The results for this campaign are not going to be released until 2020, so it is unable to determine if the 80% goal was reached. However, in 2016, the screening rates had increased, just not all the way to 80% yet. Now that it is past 2019, the new goal is to always strive for 80% nationwide colorectal cancer screenings. There are so many ways to prevent colorectal cancer, and if everyone works together, the goal of 80% screening rates can be achieved, along with healthier gut microbiomes in humans.

References

American Cancer Society, 2017a. Colorectal Cancer Screening Test. American Cancer Society, Atlanta, GA (Last revised April 6, 2017).

American Cancer Society, 2017b. Cancer Facts & Figures 2017. American Cancer Society, Atlanta, GA (Last revised April 6, 2017).

Aymeric, L., Donnadieu, F., Mulet, C., Du Merle, L., Nigro, G., Saffarian, A., . . . Dramsi, S. (2018). Colorectal cancer specific conditions promote gut colonization. *Proceedings of the National Academy of Sciences of the United States of America, 115*(2), E283-E291.

Bultman, S. J. (2016). Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. *Molecular Nutrition & Food Research,61*(1), 1500902.

Manzat-Saplacan, RM, Mircea, PA, Balacescu, L, Chira, Ri, Berindan-Neagoe, I, & Balacescu, O. (2015). Can we change our microbiome to prevent colorectal cancer development? *Acta Oncologica, 54*(8), 1085-1095

Mingyang Song, Kana Wu, Jeffrey Meyerhardt, Shuji Ogino, Charles Fuchs, Edward, Giovannucci, Andrew T. Chan, 82 - Association of Fiber Intake with Colorectal Cancer Survival, *Gastroenterology*, Volume 152, Issue 5, Supplement 1, 2017,Pages S20-S21

Montminy, Eric M., Jordan J. Karlitz, and Stephen W. Landreneau. "Progress of Colorectal Cancer Screening in United States: Past Achievements and Future Challenges." *Preventive Medicine* 120 (2019): 78-84. Web.

Morales, D. R., Morris, A. D., Metformin in cancer treatment and prevention. Annu. Rev. Med. 2015, 66, 17–29.

Wolf, A.M., Fontham, E.T., Church, T.R., Flowers, C.R., Guerra, C.E., LaMonte, S.J., Etzioni, R., McKenna, M.T., Oeffinger, K.C., Shih, Y.T., Walter, L.C., Andrews, K.S., Brawley, O.W., Brooks, D., Fedewa, S.A., Manassaram-Baptiste, D., Siegel, R.L., Wender, R.C., Smith, R.A., 2018. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J. Clin. https:// doi.org/10.3322/caac.21457.

https://www.medicinenet.com/colon_polyps/article.htm#what_do_colon_polyps_look_like_pictures