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Genetic Predispositions and Improved Risk Management of Colorectal Cancer

David Vassalluzzo[1] *

[1] Pine Crest School, Fort Lauderdale, FL, USA
*Corresponding Author: davidvass26@gmail.com

Advisor: Matthew Johnson, mjj2151@columbia.edu

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Abstract

Colorectal cancer (CRC) occurs when colon or rectum cells undergo uncontrollable growth. One cause of CRC can be attributed to mutations in the MUTYH gene. This gene codes for a protein, MYH glycosylase, that participates in a DNA damage repair pathway. Individuals with biallelic MUTYH mutations are considered to have MUTYH-associated polyposis (MAP). MAP can be characterized by the development of many adenomatous colon polyps, precursors to colorectal cancer. The failure of MYH glycosylase to perform its proper DNA damage repair function leads to hypermorphic mutations in many other genes, causing increased cell proliferation and polyposis. Genetic testing of these target genes along with early and frequent forms of detection, like colonoscopies, to detect the presence of adenomatous colon polyps are truly the keys to managing the risks of CRC. Colectomies, or the surgical removal of precancerous colon polyps, could be performed to treat CRC if necessary. Many new treatments and procedures are also being researched, including new forms of CRC detection and surgical procedures that can mitigate the effects of CRC malignancies. This inquiry aimed to determine whether or not CRC is currently being managed in this best way possible in the healthcare industry through a wide survey of reputable scientific literature. This study explored current and emerging treatment options to mitigate the effects of CRC, drawing on clinical and preclinical work in the field. Data and statistics were used to fortify and expand upon findings. The findings presented in this study reveal inefficiencies in the way CRC is managed and provide potential solutions to amending these issues.

Keywords: Colorectal Cancer, MUTYH, MUTYH-Associated polyposis, Colonoscopy, Recurrence, Screening, Chemoprevention

1. Introduction

Colorectal Cancer is a cancer of the colon or the rectum. The colon and rectum comprise the human body's large intestine and are invaluable to the digestive system. Most of the large intestine is the colon, a tube-like structure. Most colorectal cancers commence with a growth, commonly called a polyp, on the inner lining of the colon or rectum (Health. C, 2022). Some polyps eventually become cancerous, but many also stay benign. Polyps are differentiated by their likelihood to mature into cancer; polyps growing into the walls of the colon or the rectum tend to become cancerous ("What is Colorectal..."). Since many blood and lymph vessels are close to the walls of the colon and rectum, cancerous lesions could travel through those vessels and spread to other areas of the body ("What is Colorectal..."). The stage of colorectal cancer depends on how deeply the polyp or tumor has grown into the walls of the colon or rectum and whether or not it has spread to other parts of the body. Colorectal cancer can stem from many mutations or causes, including mutations to genes involved in DNA repair and cell growth.

MUTYH plays a key role in the Base-Excision DNA Repair Pathway through initiating it by excising a mispaired base (Hedge et al., 2008). It is rather common, 2,800 times per cell per day, for guanine to be damaged by a reactive

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oxygen species and become 8-oxo guanine (De Rosa et al., 2021). 8-oxo guanine can pair with adenine in addition to its normal base-pair partner cytosine. The MUTYH gene, located on Chromosome 1 of the human genome, codes for MYH glycosylase, an enzyme responsible for excising the adenine that is mispaired to the oxidized guanine derivative (Markkanen et al., 2013). MYH glycosylase is rather unique in its mechanism as it removes undamaged nucleotides (Markkanen et al., 2013). Biallelic mutations to MUTYH inhibit DNA excision repair by altering the structure of MYH glycosylase. Many mutations to MUTYH have been found to reduce the removal of adenines from A:G mismatches (Markkanen et al., 2013). This creates a buildup of adenines that are mispaired with 8-oxo guanine in many other genes, including those proven critical to preventing cancer proliferation (Markkanen et al., 2013). When MYH glycosylase activity is reduced, somatic C:G to A:T transversions occur (Markkanen et al., 2013). Current research indicates that a loss in the function of MYH glycosylase commonly leads to hypermorphic mutations that could lead to CRC across the genome, including mutations to the genes: KRAS, APC, and COX2 (Markkanen et al., 2013).

KRAS encodes for a GTP/GDP binding protein that switches between inactive and active forms depending on whether GDP (inactive) or GTP (active) is bound to it (Zhu et al., 2021). 40% of colorectal cancer patients were found to have a KRAS mutation (Zhu et al., 2021). KRAS facilitates several cell signaling pathways that are involved in cell growth and cell communication (Zhu et al., 2021). If a mutation to KRAS causes it to be "locked" in its active form, cell growth, and proliferation pathways could remain active when they are not supposed to be, leading to tumor formation (Figure 1) (Zhu et al., 2021). The prognosis in colorectal cancer patients with mutations to KRAS is relatively poor, and targeted treatments thus far have had weak efficacy (Zhu et al., 2021).

The APC gene codes for several proteins depending on where it is spliced. APC's function as a tumor suppressor largely correlates with its role in the canonical Wnt/β-catenin signaling pathway (Fang and Svitkina, 2022). When APC is mutated, this pathway remains constitutively active, producing excessive amounts of β-catenin (Fang and Svitkina, 2022). β-catenin acts as a transcription factor that activates several genes; therefore, its continued production could lead to abnormal gene transcription and tumorigenesis (Fang and Svitkina, 2022). Furthermore, APC is a microtubule-binding protein that regulates the cytoskeleton in processes such as cell migration, adhesion, polarity, division, and morphogenesis (Fang and Svitkina, 2022). Mutations to APC could lead to uncontrolled cell migration and, thus, colorectal cancer. Patients are diagnosed with Familial Adenomatous Polyposis (FAP) when both APC and MUTYH are mutated. Individuals with FAP develop several noncancerous colon polyps that, if left untreated, will become cancerous over the course of their lifetime (Figure 1).

In addition to uncontrolled cell growth, cells in CRC tumors often have dysregulated inflammation pathways. COX genes (COX-1 and COX-2) are responsible for producing prostaglandins that ultimately create cell inflammation and proliferation (Ganduri et al., 2022). COX-2 is much more commonly found to be mutated in adenomatous polyps (Ganduri et al., 2022). COX-2 functions as a regulator of cell proliferation and inflammation. In colorectal cancer patients, COX-2 tends to be overexpressed (Ganduri et al., 2022). In 50% of adenomas and 80% of carcinomas, COX-2 was found to have been overexpressed (Ganduri et al., 2022). When COX-2 is overstimulated, cell inflammation and proliferation are amplified, which can lead to CRC oncogenesis (Figure 1) (Ganduri et al., 2022).

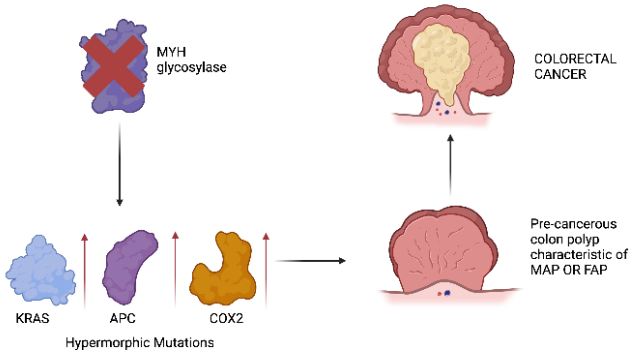

Figure 1: A Possible Carcinogenesis of Colorectal Cancer beginning with mutations to MUTYH that inhibit/inactive the function of MYH glycosylase, continuing with hypermorphic mutations to KRAS, APC, and/or COX2 that lead to the development of many precancerous colon polyps, and culminating with a CRC tumor

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The most common disease caused by mutations to the MUTYH gene is known as MUTYH-associated polyposis (MAP), a hereditary condition ("MUTYH Associated Polyposis.."). MAP is characterized by the development of many adenomatous colon polyps due to a buildup of mutations in other genes caused by the improper function of MUTYH (Figure 1) ("MUTYH Associated Polyposis.."). These polyps could become malignant if not treated, screened for, or removed in time. The number of pre-cancerous polyps developed from patient to patient varies as some may develop hundreds of polyps while others may develop around 20 adenomatous polyps ("MUTYH Associated Polyposis.."). In order to be diagnosed with MAP, both MUTYH alleles must be mutated, making it an autosomal recessive disorder (Aimé et al., 2015). People with one mutated MUTYH allele have a slightly increased risk of developing colorectal cancer ("MUTYH Associated Polyposis.."). There are clearly plenty of genetic markers that reveal whether or not a person is at high-risk of developing CRC, which is why early and efficient forms of genetic testing can be crucial to mitigating the risk of CRC.

2. Methods

This study surveys current and emerging methods used to manage the risk of CRC. It also looks at treatments that have recently been in clinical trials. The methods used encompassed a comprehensive review of scientific literature, largely focusing on clinical and pre-clinical studies related to CRC management. A very thorough review of peer-review worked was carried out to gather information on CRC management. PubMed and several other academic databases were extensively searched through with the use of keywords. More recent articles that were published within the last decade were given priority. Studies and articles were chosen if they provided intriguing insight into CRC management strategies, including genetic testing, screening techniques, surgical practices, and novel treatments. Studies were excluded if they lacked detailed methodologies, showed little traction in the clinical trial process, contained repetitive information, or had duplicative data. Data were extracted from several studies to unveil key trends and gaps in CRC management. The most important data pertained to the efficacy of treatments and screening techniques, death rates, and demographics. Findings from the literature were synthesized to point out gaps in CRC management and propose potential solutions for optimizing the way CRC is mitigated. Much focus was placed on how to integrate emerging screening techniques and chemo preventive drugs into the status quo treatment plan.

3. Current Techniques Used to Manage CRC

3.1 Testing and Screening

The best tool to manage the onset and development of colorectal cancer is through genetic testing and early and often screening as patients show a much higher chance of survival if the tumor is caught at an early stage. Many individuals are diagnosed with MAP or FAP once they have already developed CRC. People with a family history of CRC should get genetic testing around the age of 20, as individuals with MAP or FAP are widely recommended to begin colorectal cancer screening in their 20s ("MUTYH Associated Polyposis.."). The somatic c.34G>T KRAS transversion is a standard indicator of MAP, therefore, looking for this specific transversion is a common way to detect MAP (Zhu et al., 2021). KRAS plays a crucial role in MAP tumorigenesis. In individuals with MAP, keeping the colon under frequent surveillance is vital to managing the onset of cancer. One way to detect CRC is through a colonoscopy, where a doctor looks inside an individual's colon or rectum with a long device known as a colonoscope. Additionally, sigmoidoscopies can be performed and are very similar to colonoscopies, except they only survey the lower portion of the colon. Most MAP patients develop around 10 to 100 colon polyps in their lifetime, and without detection, those polyps could develop into CRC and, eventually, a malignancy (Borras et al., 2014). Individuals with FAP tend to develop more polyps over the course of their lifetime. Patients with MAP or FAP should have biannual colonoscopies beginning in their mid-to-late 20s ("MUTYH Associated Polyposis.."). Sometimes, doctors may take a biopsy of the polyps by removing a small piece of it, especially if colorectal cancer is suspected, to get more information. The material acquired through a biopsy is assessed in a laboratory to determine if the cells have

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characteristics indicative of cancer, such as a distinct size/shape or a unique arrangement relative to one another ("What do doctors look..."). Furthermore, the cells retrieved through a biopsy can be genetically tested to understand which genetic abnormalities led to polyp formation. CRC is commonly staged via CT colonography. This technique creates a 3D image of the interior of the colon, allowing oncologists to determine the tumor's size, shape, etc ("Imaging Tests for the...").

3.2 Surgical Procedures Used to Treat CRC

Surgical removals of colon polyps or tumors mainly depend on how far the growth has progressed. Some early colon cancers are treated through polypectomies and local excisions. Polypectomies involve cutting a colon polyp at its base using a wire attached to a colonoscope with an electrical current pulsing through it to remove the polyp from the colon's lining ("Colon Cancer Surgery..."). A local excision, while simple, is a little bit more substantial than a polypectomy, as it involves a numbing process followed by a deeper cut into the lining of the colon and surrounding tissue to remove a polyp or an early-stage tumor ("Colon Cancer Surgery...").

For more significant tumors, colectomies are the safest course of action. However, in individuals with MAP or FAP, colectomies may be recommended even in the presence of less severe polyps or tumors due to the genetic predisposition of these individuals to CRC. A colectomy involves removing the entire colon (total colectomy), but only partial colectomies (hemicolectomies) may be necessary, depending on disease progression or the doctor's preference ("Colon Cancer Surgery..."). Colectomies are performed in two main ways. One way is an open colectomy, where one large incision is made in the abnormal area to remove the colon ("Colon Cancer Surgery..."). The other way is a laparoscopic-assisted colectomy, where several small incisions are made to remove the colon. In this procedure, a camera is inserted into the colon through one of the incisions, and the other incisions serve as aids for the removal of portions of the colon ("Colon Cancer Surgery..."). This procedure may be more complex but confers a recovery-time advantage to patients due to the smaller incisions. In both scenarios, some surrounding lymph nodes and the colon are removed. Larger CRC tumors can lead to many digestive or bowel complications. Sometimes a stent may need to be placed in the colon to make room for fecal matter, or a procedure known as a colostomy may sometimes be necessary to create an artificial hole for fecal matter to be released ("Colon Cancer Surgery...").

3.3 The Chemotherapeutic Treatment: Oxaliplatin

Oxaliplatin is a widespread chemotherapeutic treatment for CRC and other gastrointestinal cancers. Oxaliplatin is cytotoxic, as it can damage DNA to put apoptotic stress on cells, which makes it effective in killing cancer cells. Its mechanism involves the formation of platinated DNA adducts that inhibit DNA synthesis/repair in tumor cells, eventually leading to apoptosis (Simpson et al., 2003). To maximize efficacy and toxicity, Oxaliplatin is used in conjunction with a fluoropyrimidine, normally fluorouracil (5-FU)/folinic acid (FA) (Simpson et al., 2003). The response rate, or the percentage of individuals whose tumors regressed after this chemotherapy, is about 50% (Simpson et al., 2003). Furthermore, this treatment confers a survival advantage of about five months over the other first-line treatment, irinotecan/5-FU/FA (IFL) (Simpson et al., 2003).

3.4 Limitations of Current Treatments

While current treatments are very effective, they are far from perfect. Researchers are looking for new ways to treat CRC and reduce the risks of genetic predispositions to CRC, like mutations to MUTYH. The recurrence rate of CRC in individuals who have completed colorectal cancer treatment is around 30-50% (Zare-Bandamiri et al., 2017). This demonstrates that current treatments are not entirely eliminating CRC. Furthermore, many CRC treatments have some strong adverse effects. Chemotherapies, including the one profiled earlier, kill healthy and cancer cells. Moreover, the oxaliplatin/fluorouracil (5-FU)/ folinic acid (FA) chemotherapeutic treatment has many gastrointestinal side effects, including diarrhea, nausea, and vomiting (Simpson et al., 2003). Surgical procedures such as colectomies also have many adverse effects. In addition to the side effects listed above, scar tissue formation threatens organs near

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the procedure's location and the small intestine. Furthermore, links in the gastrointestinal tract may be damaged after colectomies, and complications from the leakage of fecal matter may occur and lead to infection ("Total abdominal colectomy..."). These data demonstrate that smaller tumors/polyps that are caught earlier are much easier to treat. Early and frequent screening through procedures like colonoscopies is crucial to managing the risks of CRC and genetic predispositions to CRC, such as mutations in MUTYH.

4. New and Emerging Methods of Treating CRC

Research is constantly being done to improve the screening and treatment of CRC. Many studies focus on determining the causes of colorectal cancer to facilitate choosing the most practical course of action to treat each case of CRC. Other studies are attempting to find ways to track CRC as early as possible to mediate its effects. Much work is being done in chemoprevention by researching new drugs that can reduce tumorigenesis. Furthermore, many studies are focused on developing new treatments to address malignancies and mature CRC tumors. Plenty of work has yet to be done, but many new and emerging therapies show immense promise.

4.1 Liquid Biopsies

CRC tumors emit large amounts of circulating tumor DNA (ctDNA) into the bloodstream (Mauri et al., 2022). This has led researchers to test the viability of liquid biopsies, especially of the blood, in testing and screening for CRC. Studies have shown that in all stages of CRC, this test is highly effective and could help doctors better track the progression of CRC. The tumor DNA collected from a patient's blood in liquid biopsies could be screened for genetic markers of CRC and other abnormal genetic mutations (Mauri et al., 2022). The increased specificity of the makeup of each specific case of CRC would aid oncologists in determining the best treatments and drugs to give to patients. If doctors know the genetic abnormalities within the tumor cells, they could likely choose more targeted drugs. Questions have been raised about the feasibility of liquid biopsies in detecting CRC outside of academic settings and comprehensive cancer centers. One reason that liquid biopsies have not been readily implemented is that the amount of ctDNA that CRC tumors shed is highly variable, as the ratio of circulating free DNA and ctDNA can range from 1% to 40% (Mauri et al., 2022). This means that precise analytical techniques are required to extract ctDNA from liquid biopsy samples. That said, as research and technology improve, liquid biopsies continue to gain doctors' consideration in managing and detecting CRC.

4.2 Emerging Forms of CRC Detection

Cologuard is a non-invasive multitarget stool DNA screening test that was FDA-approved in 2014 (Tepus and Yau, 2020). Colon cells tend to exfoliate and shed into the gastrointestinal tract making it plausible for CRC to be detected through the molecular analysis of feces (Tepus and Yau, 2020). Cologuard looks for specific biomarkers in stool samples, namely, NDRG4, a tumor-suppressor, and BMP3, a regulator of cell homeostasis, DNA methylation, mutations to KRAS, and hemoglobin, to detect CRC (Tepus and Yau, 2020). Cologuard showed an 89.8% specificity and a 92.3% sensitivity in the detection of CRC (Tepus and Yau, 2020). Cologuard is currently only being used today in adults who are 45 or older ("At-Home Colon Cancer..."). However, Cologuard shows promise due to its simplicity, efficacy, and convenience.

Syndecan-2 participates in cell migration and adhesion. Studies have demonstrated that syndecan-2(SDC2) methylation frequently occurs at all stages of CRC progression (Han et al., 2019). SDC2 methylation occurs relatively early in the progression of CRC, indicating that this marker could be a very useful tool in the early detection of CRC. Additionally, SDC2 methylation can be easily detected in stool samples, a highly non-invasive technique, unlike colonoscopies and some forms of biopsies. Clinical trials have been performed to test the effectiveness of this form of CRC screening, including trials from 2018 as well as 2021. In the 2018 trial that took place in Seoul, South Korea, 245 of the trial participants were known to have CRC, and, 90.2% of those patients demonstrated the presence of SDC2 in their stool DNA (Han et al., 2019). A 2021 trial involving 1574 individuals with CRC and 1945 healthy

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individuals from three different countries (South Korea, China, and Hungary) found a .81 sensitivity and a .95 specificity when using SDC2 methylation in stool samples for the detection of CRC (Wang et al., 2022). A 2023 trial of this same test confirmed that the SDC2 methylation test had a better performance in detecting nonmetastatic CRC and adenoma that many other currently used blood tests (Zhan et al., (2023). Overall, SDC2 methylation has been a promising biomarker in the early detection of CRC (Genomictree Inc., 2022).

4.3 Chemopreventive Drugs

Many new drugs and supplements are also being researched, tested, and used to mitigate the effects of CRC. One of which is Eicosapentaenoic acid (EPA). This unsaturated fatty acid competitively binds with the COX-2 enzyme, fostering the production of apoptotic and anti-inflammatory prostaglandins and reducing arachidonic acid metabolism ("Management of familial...", 2022). While it can benefit the human body, arachidonic acid metabolism is pro-tumorigenic and pro-inflammatory; therefore, inhibiting it can reduce tumorigenesis. Clinical trials have shown a reduction and shrinking in precancerous and cancerous polyps in individuals who were given EPA ("Management of familial...", 2022). Non-steroidal anti-inflammatory drugs (NSAIDs) are some of the most promising drugs in CRC chemoprevention, especially celecoxib, sulindac, and rofecoxib ("Management of familial...", 2022). Some of these drugs are already being used, while others are still being tested. There are some well-known NSAIDs, including aspirin and ibuprofen. NSAIDs act as inhibitors of COX enzymes, especially the COX-2 enzyme, which can allow these drugs to slow or prevent tumorigenesis (Maniewska and Jezewska, 2021).The primary mechanism through which NSAIDs prevent the tumorigenesis of CRC is by suppressing prostaglandin E2, an inflammatory molecule, synthesis (Maniewska and Jezewska, 2021).. This leads to a decrease in tumor cell proliferation, angiogenesis, and survival and an increase in apoptosis (Maniewska and Jezewska, 2021).

4.4 Preventing Resistance to Oxaliplatin

As mentioned in the current treatments section, Oxaliplatin is a standard chemotherapeutic treatment used to treat CRC. As Oxaliplatin is a platinum-based chemotherapy, its use comes with many negative adverse effects. Recently, researchers have discovered a novel Pt(IV) cell-penetrating peptide conjugate (Linares et al., 2023). Samples of the use of this peptide chain *in vivo* have indicated that the addition of this peptide chain to Oxaliplatin has led to reductions in the adverse effects of this chemotherapy drug on normal tumor cells and could therefore reduce resistance to this treatment ("Validation of a therapy..."). Results from *in vivo* tests have demonstrated that platinum accumulation in the tumor's microenvironment falls significantly (about 3.5 times lower) by adding the peptide chain to oxaliplatin ("Validation of a therapy..."). The addition of this peptide chain to oxaliplatin also has additional benefits, as platinum levels dropped in organs that are usually greatly affected by chemotherapy, such as the kidneys and the liver ("Validation of a therapy..."). Moreover, the addition of this peptide has shown no loss of efficacy in preventing CRC tumorigenesis ("Validation of a therapy..."). Overall, trials on this new approach to Oxaliplatin chemotherapy in CRC have yielded promising results.

4.5 New and Emerging Surgeries to Treat CRC

Many surgeries being studied to help treat CRC malignancies and reoccurrences involve attempting to place chemotherapy as close as possible to the tumor site. One of the surgeries being studied to treat more advanced forms of CRC is called hyperthermic intraperitoneal chemotherapy (HIPEC). When CRC recurs, it tends to expand into the peritoneum, the thin lining of the abdominal cavity and organs inside the abdomen ("Colorectal Cancer Research..."). This can be very difficult for doctors to access and treat appropriately due to its anatomical location. The HIPEC procedure involves a surgery where as much of the tumor as possible in the abdomen is removed ("Colorectal Cancer Research..."). Next, while the patient is still being operated on, a heated solution of chemotherapeutic drugs is placed in the abdominal cavity ("Colorectal Cancer Research..."). This brings any residual cancer present in the abdominal cavity in direct contact with chemotherapeutic drugs, which are shown to have increased efficacy when heated

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(Ganduri et al., 2022). The early results from this treatment have been promising, as patients exhibit extended survival after undergoing this procedure ("Colorectal Cancer Research..."). However, doctors still have a lot of uncertainty about which patients should undergo this procedure.

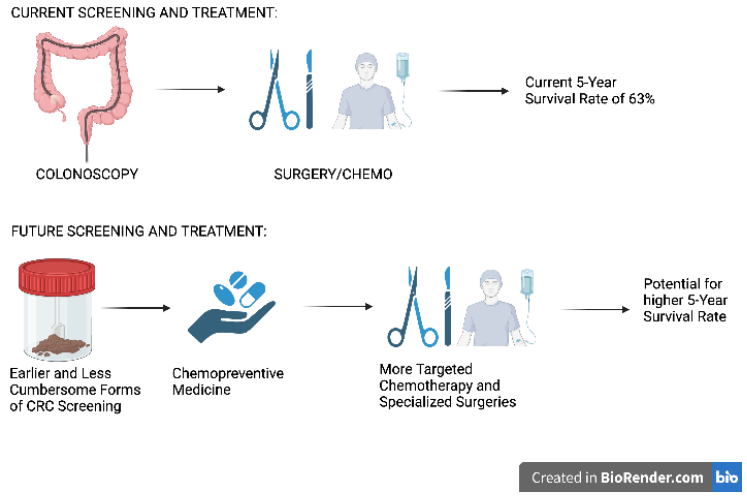

Figure 2: The Current and Proposed Future Method of Managing CRC. Describes both methods from screening and detection to treating tumors and finally to the 5-year survival rate

Another surgery being studied is known as hepatic arterial infusion chemotherapy (HAIC). The hepatic artery is the blood vessel responsible for supplying many liver tumor cells with their necessary nutrients; therefore, this surgery only has merit in patients with colorectal cancer liver metastases ("Colorectal Cancer Research..."). This surgery involves placing a port/pump near the hepatic artery ("Colorectal Cancer Research..."). A doctor can place a chemotherapeutic drug, commonly floxuridine, into the pump ("Colorectal Cancer Research..."). This brings the chemotherapy in direct contact with the liver, allowing it to target liver tumor cells specifically (Figure 2) ("Colorectal Cancer Research..."). Similar to HIPEC, doctors still have uncertainty about who this procedure should be performed on ("Colorectal Cancer Research..."). Currently, this procedure is only being done at very experienced facilities ("Colorectal Cancer Research...").

5. Discussion

Overall, the medical community has been able to make many strides in treating CRC. In the United States, the 2020 death rate from CRC was 57% less than it was in 1970.[28] This can largely be attributed to improvements in screening and testing through procedures, including colonoscopies and biopsies. Improvements are still being made in this area, with current research focusing on procedures such as detecting SDC2 methylation in stool samples or liquid biopsies. Furthermore, improvements in surgical techniques through procedures like colectomies and emerging forms of surgery like HIPECs and HAICs have made surgical resection easier. Chemotherapeutic or chemopreventive drugs have also proved helpful in treating CRC. Chemotherapeutics like Oxaliplatin can shrink tumors, and chemopreventive drugs like NSAIDS and EPA can decelerate tumorigenesis by inhibiting COX-2 and make treating CRC easier.

Although there are several viable treatment options for CRC, this problem is far from being resolved, and much work must be done. It is estimated that in 2023, 153,020 adults will be diagnosed with CRC, and 52,550 people will die from CRC in the United States alone ("Colorectal Cancer--- Statistics"). Worldwide, CRC is the second leading cause of cancer death ("Colorectal Cancer--- Statistics"). As mentioned earlier, the recurrence rate for this disease is around 30-50%. These statistics need to be improved, and that is possible. Even if effective chemotherapeutics or other drugs are introduced in the future, the easiest way to manage the risks of CRC is through early and frequent detection. As CRC progresses from a localized state to a malignancy, the 5-year survival rate rapidly declines (Table 1) ("Colorectal Cancer--- Statistics"). Even though the medical community is aware of these staggering statistics, only a little over one-third of colorectal cancers are detected when they are in the localized stage of development ("Colorectal Cancer--- Statistics"). This signals the necessity of screening for CRC both earlier and more frequently. New research can make screening more accessible and less cumbersome, motivating people to seek screening more

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regularly. Options like the SDC2 stool sample test and Cologuard offer promise, as it is much easier to test a stool sample than to conduct a relatively invasive procedure like a colonoscopy (Figure 2). Furthermore, Cologuard and the SDC2 test can be done at home, while individuals must travel to the doctor for a colonoscopy. There is also a need for campaigns aimed at encouraging individuals to screen themselves for CRC as early as possible. Research has been increasingly showing that CRC is becoming much more prevalent in younger adults (people in their 30s) (Health. C, 2022).

Another significant issue is that many people with genetic predispositions to CRC, such as having biallelic mutations in MUTYH, are not commonly diagnosed with those issues until they have already developed CRC. Research is needed to improve genetic testing to highlight individuals who must be closely monitored regarding CRC. It would make it much easier to treat individuals with genetic predispositions to CRC and increase the survival rate if those genetic markers were detected earlier in the progression of CRC or before any tumor even develops so that individuals could be screened for properly.

Table 1: Breakdown of Colon Cancer 5-Year Survival Rate and Time of Diagnosis ("Colorectal Cancer--- Statistics"). Describes the 5-year survival rate and the percentage of Colorectal Cancers Caught depending at what point CRC is in its progression.

Stage of Colon Cancer	5-Year Survival Rate	Percentage of Colorectal Cancers Caught at this Stage
Localized CRC	91%	37%
CRC has spread to surrounding tissue or lymph nodes	72%	36%
CRC has spread to distant parts of the body	13%	22%
Overall	63%	95%

Even though current treatments are quite effective in managing CRC, they are far from perfect. The 5-year survival rate is still relatively low, and CRC tends to recur frequently [28]. Tumors are sometimes resistant to chemotherapeutic drugs like Oxaliplatin, and many drugs used to treat CRC have other negative effects on the body. The Pt(IV) cell-penetrating peptide conjugate that reduces resistance to Oxaliplatin and makes it more targeted is a step in the right direction, but it is far from a solution, and research needs to continue to be aimed at making chemotherapeutic treatments more targeted (Figure 2).

The simplest way to mitigate the effects of CRC and make improvements in the statistics discussed earlier is to screen individuals as early and frequently as necessary. The earlier CRC is caught, the better the outcome will be. Even if current screening techniques like colonoscopies are somewhat cumbersome, they are essential and valuable as they can detect CRC at an early and treatable stage. Most of the resources invested in improving how CRC is managed must be used to improve screening techniques and campaign for individuals to get screened early and often.

5. Conclusion

CRC continues to bring significant challenges to healthcare despite advances in the medical community's understanding of its genetic underpinnings and improvements to screening techniques and treatments. Genetic predispositions to CRC, such as MAP underscore for early and frequent genetic testing. As CRC patients demonstrate a much higher chance of survival the earlier the tumor is detected, early and frequent screening through mediums like colonoscopies is key to managing the risks of CRC. Less invasive and more convenient emerging screening techniques like Cologuard can make CRC screening more accessible and common. If necessary, surgical procedures, like colectomies, and chemotherapeutic treatments, such as Oxaliplatin, are used to treat tumors. However, those treatments alongside emerging approaches like HIPEC, HAIC, and chemopreventive agents offer promising avenues to enhance patient outcomes. Ultimately, a multidisciplinary approach integrating genetics, diagnostics, and therapeutics will be essential in advancing CRC management and improving patient prognosis globally. With consistent communication between clinicians, pharmaceutical developers, and researchers, the medical community can continue to improve and optimize strategies for detecting CRC at an early stage and treating it.

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