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Review Article

Epidemiology of colorectal cancer

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Abstract: Colorectal cancer is currently the third deadliest cancer in the United States and will claim an estimated 49,190 U.S. lives in 2016. The purpose of this review is to summarize our current understanding of this disease, based on nationally published statistics and information presented in peer-reviewed journal articles. Specifically, this review will cover the following topics: descriptive epidemiology (including time and disease trends both in the United States and abroad), risk factors (environmental, genetic, and gene-environment interactions), screening, prevention and control, and treatment. Landmark discoveries in colorectal cancer risk factor research will also be presented. Based on the information reviewed for this report, we suggest that future U.S. public health efforts aim to increase colorectal cancer screening among African American communities, and that future worldwide colorectal cancer epidemiology studies should focus on researching nutrient-gene interactions towards the goal of improving personalized treatment and prevention strategies.

Keywords: Colorectal cancer, review, epidemiology, risk factors, screening, treatment, prevention and control

Introduction

The term colorectal cancer refers to a slowly developing cancer that begins as a tumor or tissue growth on the inner lining of the rectum or colon [1]. If this abnormal growth, known as a polyp, eventually becomes cancerous, it can form a tumor on the wall of the rectum or colon, and subsequently grow into blood vessels or lymph vessels, increasing the chance of metastasis to other anatomical sites [1, 2]. Of the cancers that begin in the colorectal region, the vast majority (over 95%) are classified as adenocarcinomas [1]. These begin in the mucus-making glands lining the colon and rectum [1, 3]. Other less-common cancers of the colorectal region include carcinoid tumors (which begin in hormone-producing intestinal cells), gastrointestinal stromal tumors (which form in specialized colonic cells known as interstitial cells of Cajal), lymphomas (immune system cancers that form in the colon or rectum), and sarcomas (which typically begin in blood vessels but occasionally form in colorectal walls) [1, 3].

Descriptive epidemiology

In the United States, colorectal cancer is the third deadliest of all cancers. In 2016 there will be an estimated 134,490 new colorectal cancer cases (70,820 in males and 63,670 in females) along with 49,190 colorectal cancer deaths (26,020 and 23,170 in males and females, respectively). Colorectal cancer ranks third, only behind prostate cancer and lung cancer, for new cases in males (8% of all new cancer cases), and behind breast cancer and lung cancer for new cases in females (8% of all new cancer cases). Similarly, only lung cancer and prostate cancer are expected to claim more U.S. male lives than colorectal cancer in 2016, and only lung cancer and breast cancer are expected to take more U.S. female lives (8% of total cancer deaths for both genders) [4]. Thus colorectal cancer remains a heavy burden on the United States population, as 1,177,556 U.S. residents were estimated to have been living with colorectal cancer in 2013 [5].

Over the last several decades, however, the U.S. burden of colorectal cancer has been decreasing. National statistics have revealed reductions in both incidence rates and death rates, while 5-year survival rates have also steadily improved. Between 1975 and 2012, the age-adjusted death rate for colorectal cancer in the United States, across all races and

both sexes, shrank by half (28.58 deaths per 100,000 in 1976 to 14.45 deaths per 100,000 in 2013) [6]. In similar fashion, age-adjusted incidence rates in the U.S., across both sexes and all races, dropped from the low-to-mid 60s per 100,000 in the 1970s and 1980s to 37.20 new cases per 100,000 in 2013 [7]. Additionally, between 1975 and 2011 (again, for all races and both sexes in the U.S.) the 5-year survival rate rose from a low of 49.8% to a high of 66.2% [8].

Public federal databases do an admirable job of describing how the burden of colorectal cancer in the U.S. has slowly lightened since the 1970s. However, other published data show that this trend is not consistent across all geographic regions, particularly when considering Eastern nations. Although the highest colorectal cancer incidence rates can still be found in North America, Europe, and Australia/New Zealand, other countries with historically low rates are now experiencing increased risk [9]. For example, Japan and Thailand are suffering rapid increases in colorectal cancer incidence [10], and incidence has been steadily increasing in Iran for the past 30 years [11]. The rates have more than doubled in Saudi Arabia since 1994 [12], about the same time that rates started to increase in the Philippines [13]. Elsewhere in the East, colorectal cancer incidence rates have also been slowly increasing, for example, in Jordan [14], as well as China, South Korea, and Singapore, all regions where cancers of the stomach and liver have typically caused the greatest concern [15].

Another observable difference between incidence of colorectal cancer in the East and West can be seen in the average age of diagnosis. In the United States and European Union, only about 2-8% of cases occur in individuals under 40 years of age [16, 17], whereas Egypt, Saudi Arabia, the Philippines, and Iran show rates of 38%, 21%, 17%, and 15-35%, respectively for this same age group [11, 13, 18, 19].

Risk factors

Environmental factors

Many studies have attributed the increased risk of developing colorectal cancer to living the "Westernized lifestyle" [10, 14-16, 20, 21]. This term encompasses obesity, sedentary behavior, and a high-meat, high-calorie, fat-rich, fiber-deficient diet, and has been linked to increased colorectal cancer risk [20, 22]. The landmark study that first connected dietary fat to risk of colon carcinogenesis took place in 1969, pioneered by Ernst Wynder and coworkers. They discovered that Japanese individuals of higher socioeconomic status (SES) were more likely to develop colon cancer than those who were less affluent, possibly due to their more Westernized diet. It was then first hypothesized that dietary fat, through its influence on bacterial flora, has an effect on colon cancer pathogenesis [21]. Building on this hypothesis, later researchers theorized that high-fat diets promote carcinogenesis by the formation of deoxycholic acid and lithocholic acid. High fat intake stimulates the production of bile acids from the liver, which after contact with anaerobic bacteria in the colon, are dehydrogenated to form these compounds [22].

Alcohol consumption and tobacco smoking also increase risks for colorectal cancer. In 2007, the International Agency for Research on Cancer (IARC) declared that there was sufficient substantiated evidence to infer that alcohol is a causal factor for colorectal cancer [23]. Research has since revealed that, when compared to non/occasional drinkers, people who consume at least 4 drinks per day are at a 52% increased risk for developing this disease [23]. Mechanistically, this carcinogenic process may reflect the impact of alcohol on folate synthesis. Specifically, alcohol entering the colon is microbially metabolized into acetaldehyde, which degrades folate *in vivo* [22, 24]. Because folate is required for DNA synthesis and repair, folate deficiency can lead to chromosome breakage, uracil misappropriation, and other DNA precursor imbalances, all of which can contribute to carcinogenesis [25]. Regarding cigarette smoking, research has revealed that tobacco smoke significantly increases colorectal cancer incidence and mortality and has been associated with a twofold to threefold increase in the risk of developing colorectal adenoma [26, 27]. This is due to the ability of the gastrointestinal tract and circulatory system to spread cigarette carcinogens to colorectal mucosa, elevating the risk of inflammation, mutagenesis, and carcinogenesis [22].

In addition to the above environmental risk factors, high blood levels of insulin, gastrointestinal inflammation, and certain meat-cooking

methods may also increase risk of colorectal carcinogenesis [22]. Hyperinsulinemia increases the risk of colorectal cancer through promotion of colon cell proliferation and reduction of apoptosis [28]. Regarding gastrointestinal inflammation and colorectal cancer, research has also revealed a link between ulcerative colitis and colorectal carcinogenesis. Evidence suggests that about 1% of all colorectal cancer cases are due to the chronic inflammation associated with ulcerative colitis, and the risk for developing cancer directly correlates to the amount of time a patient has endured the inflammatory condition [29]. Similarly, Crohn's disease, marked by intestinal inflammation, has also been shown to increase the risk of colorectal cancer, although not to the same degree as ulcerative colitis [22]. Additionally, certain methods of cooking meat may also increase the risk of developing colorectal cancer. Studies have shown that with frying, boiling, charcoal broiling, or other methods in which meat is cooked at extremely high temperatures, mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons can form, leading to the production of N-nitroso, a known human carcinogen in the colon [22, 30]. These mutagens may not be the only cause for concern, as further research has suggested that other compounds such as quinoxaline and pyridine can also increase risk of colorectal cancer, particularly distal adenomas [31].

However, in direct opposition to all these risk factors, several environmental factors actually lower the risk of developing colorectal cancer. One such protective factor is the ingestion of fish and fish oil, which has been shown not only to stifle the promotion of colonic tumors, but also to reduce the incidence of these tumors [32]. In fact, fish consumption can be so powerful a protective factor that one study documented evidence of protection against colorectal carcinogenesis even in European populations that typically consume high amounts of other meat and animal fat [33].

Another protective factor against colorectal cancer is a high intake of dietary fiber. In 1971, Denis Burkitt conducted the landmark study first linking fiber consumption to protection against colorectal cancer. He observed that colorectal cancer, as well as other non-infectious bowel diseases, were extremely rare in communities that survived on a highly fibrous diet, but were common in economically developed countries where low-fiber diets predominated [34]. Burkitt then hypothesized that a lifestyle devoid of adequate dietary fiber may be a causative factor for the increased colorectal cancer incidence seen in economically advanced nations, probably due to abnormal carcinogenic changes in the bacterial flora [34].

Additional factors documented to afford protection against colorectal cancer are: a high intake of vitamin D, a high calcium intake, habitual physical exercise, and the regular usage of aspirin. Evidence shows that taking 1000 IU/day of vitamin D can decrease colorectal cancer risk by 50%, and intake of 1250 mg/day of calcium can significantly reduce the risk of colorectal cancer [35]. Mechanistically, calcium provides this protection by decelerating colonic epithelium proliferation and by neutralizing bile acids [35]. Regarding the benefits of physical activity, studies have revealed that increasing exercise from before to after diagnosis is associated with lower total mortality [36]. One such study specifically found that regular physical exercise can reduce colorectal cancer risk by almost 25% [37]. Another study showed that those who used aspirin regularly (at least twice per week) had lower risk of colorectal cancer than those who used it less often. The hypothesized mechanism underlying this effect is the ability of aspirin to inhibit cyclooxygenase-2, an enzyme that stimulates the colorectal carcinogenic processes of inflammation and cell proliferation [38].

Genetic factors

In addition to the environmental factors above, colorectal cancer also has a significant genetic basis. Research in this area has come a long way in the last 25-30 years, thanks in part to a pioneer in this field, Professor Walter Bodmer. In 1987, Professor Bodmer made a landmark discovery when he determined that a gene called APC, which acts to help prevent cancer when functional, greatly increases colorectal cancer risk when defective. Bodmer is thus credited with saving many lives via genetic testing for faults in this gene, thereby reducing UK colorectal cancer deaths by approximately 33% [39]. Another scientist, Dr. Bert Vogelstein, received awards and recognition for his land-

mark contributions to colorectal cancer research. Since the mid 1980s, Dr. Vogelstein and coworkers have published crucial findings pertaining to colorectal tumorigenesis, documenting how the accrual of genetic changes to certain oncogenes and tumor-suppressor genes can result in colorectal tumors [40].

Many subsequent discoveries have elucidated the role of genetics in both the development and the prevention of colorectal cancer. For example, research by the UK IBD Genetics Consortium and the Wellcome Trust Case Control Consortium showed that the HNF4A, CHDH1, and LAMB1 genes (on chromosomes 20q13, 16q22, and 7q31, respectively) are linked to colorectal cancer susceptibility. This research was also the first to identify a genetic link between ulcerative colitis and colorectal cancer [41]. Additional research determined that the genetic variants miR-196a2, SNP rs60-17342, and the C allele of the SNP rs11614913 also conferred elevated risk of developing colorectal cancer [42, 43]. Genes have also been shown to affect not only the incidence of colorectal cancer, but mortality as well, as the rs4939827 SNP located on the SMAD7 gene has been linked to shorter patient survival [43].

Conversely, research has also uncovered several genetic protective factors. For example, one study found that SNP rs4779584 on chromosome 15q13 is associated with a lowered risk of colorectal cancer mortality. The same study showed that SNP rs10795668 on chromosome 10p14 is linked to lower risk of recurrence. Furthermore, this recurrence link pertained only to those treated with chemotherapy, not those treated otherwise; further, the protective effect was associated only with the variant-containing genotype, not the wild genotype [44]. Additionally, a recent study identified two genetic markers that play a role in colorectal cancer risk. One marker, the T allele in rs11-676348, is an ulcerative colitis susceptibility locus found to be protective against colorectal cancer. This locus, located on chromosome 2, is only slightly downstream of the CXCR2 gene, a gene previously linked to the development of colorectal cancer via chronic inflammation. This is significant, as rs11676348 was found to specifically afford protection against colorectal cancer tumors that had a mucinous component, were microsatellite instability-high, or associated with a Crohn's-like reaction, all of which are indicative of considerable inflammation [45]. The other marker, rs102275 (a Crohn's disease susceptibility locus on chromosome 11), was also found to be inversely related to colorectal cancer risk [45].

There is also evidence that some genes are capable of both risk reduction and protection against colorectal cancer, and new research suggests that MTHFR is among them. When researchers tested for an overall association across all populations, the homozygous TT genotype for MTHFR 677 was found to be protective against colorectal cancer [46]. Subgroup analysis, however, did not find these protective effects in all populations, as this same MTHFR 677 TT genotype was found to be a colorectal cancer risk factor for those residing in Turkey, Romania, Croatia, Hungary, Portugal, Mexico, the U.S., Taiwan, India, and Egypt [46]. Considering research linking genetics to colorectal cancer risk and protection alike, about 35% of colorectal cancer cases are influenced by genetic factors [43].

Effect of gene-environment interactions on colorectal cancer

Gene-environment interactions influence colorectal cancer risk. For example, exercise may interact with certain genes to affect colorectal cancer outcome. Level of physical activity was found to be associated with colorectal cancer survival among individuals who were PTGS2-positive, but no such association was seen among those who were PTGS2-negative [47]. Similarly, among patients with p27 expression, those who were physically active had 68% lower colon cancer mortality rates than those who were not physically active. However, these exercise benefits were absent in those without p27 expression [48].

Interactions between genetic factors and environmental factors, such as obesity, aspirin, alcohol consumption, vitamin D intake, and polyunsaturated fatty acids, have also been discovered to influence colorectal cancer risk. As body mass index (BMI) increases, so does the risk of colorectal cancer for individuals who are CTNNB1-negative (no such association is seen among CTNNB1-positive patients) [49]. However, for obese patients (BMI of at least 30), greater colorectal cancer survival was seen in those who were CTNNB1-positive, while

among non-obese patients, CTNNB1 status had no effect on survival [49].

Regarding aspirin, consistent intake has been associated with a lower incidence of colorectal cancer for individuals with the wild-type BRAF gene, and longer colorectal cancer survival for those carrying the mutated PIK3CA gene. Such associations were not seen in those with mutated BRAF or wild-type PIK3CA genotypes [50, 51]. Similarly, consistent aspirin intake was also found to decrease colorectal cancer risk in patients with high expression of 15-PGDH, whereas no such relationship was found in those with low 15-PGDH expression [52]. Also, it has been reported that aspirin reduces risk of colorectal cancer, particularly tumors with activated CTNNB1, among individuals with rs6983267 GT/TT genotypes but not among individuals with GG genotypes [53]. In addition, a recent genome-wide gene-environment interaction study identified that the chemopreventive effect of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) on colorectal cancer risk differed according to genetic variation at two single nucleotide polymorphisms (SNPs) at chromosomes 12 (rs2965667) and 15 (rs16973225) [54]. Regarding alcohol consumption, research has determined that regular alcohol drinkers with low IGF2 DMR0 methylation have an increased risk of colorectal cancer, but those with higher IGF2 DMR0 methylation ability have no such elevated risk [55].

Pertaining to vitamin D, recent research has also discovered that individuals with high blood 25(OH)D levels were less likely to develop colorectal cancer if they also had high-level intratumoral periglandular reaction as opposed to lower levels of this reaction [56]. Researchers have also revealed an interaction between marine ω-3 polyunsaturated fatty acids (PUFAs) and colorectal cancer. Those with high PUFA consumption are less likely to develop microsatellite-high colorectal cancer tumors. The risk of microsatellite-stable colorectal cancer tumors, however, is not modified by PUFA intake [57].

Screening

Screening for colorectal cancer involves testing for pre-cancerous colorectal polyps or early-stage cancer before the manifestation of symptoms, before the disease has a chance to grow or spread, and while treatment is easier to manage, less expensive, and more likely to be successful [9, 58]. In the United States, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that men and women between the ages of 50 and 75 be screened for colorectal cancer through high-sensitivity fecal occult blood testing (FOBT), sigmoidoscopy, or colonoscopy [59].

FOBT, recommended annually, tests for colorectal cancer by detecting blood in a patient's stool through the use of a chemical called guaiac or antibodies. With this method, the patient simply obtains a small sample of stool, places it in a test kit, then returns it to their health care provider for laboratory analysis. For the sigmoidoscopy, a physician inserts a thin, flexible tube into a patient's rectum to check for potentially cancerous polyps either in the rectum or the lower region of the colon. It is recommended that this test be performed every five years. Similar to the sigmoidoscopy, in a colonoscopy the doctor uses a thin, flexible, tube to check for polyps or any sign of carcinogenesis. For this test, however, a longer tube is used as the doctor will examine the rectum and the entire colon, possibly removing polyps during the test. Patients are recommended to undergo this procedure every 10 years. Although these are the three screening techniques recommended by the U.S. Preventive Services Task Force, three other screening methods (the double-contrast barium enema, the virtual colonoscopy, and the stool DNA test) are sometimes used and/or recommended by other entities [59].

Because of evidence indicating that the risk of colorectal pathogenesis and carcinogenesis increases exponentially around age 50 [49], it is strongly recommended that screening begin at age 50 for previously asymptomatic persons [59-61]. However, despite these recommendations and the strong evidence indicating the effectiveness, relative safety, and proven results of colorectal screening [61, 62], persistent issues keep screening rates low, both in the U.S. and abroad.

One such issue that can be seen in the United States lies in the unfortunate confluence of elevated risk and lower screening rates among the African American population. Compared

with Caucasian Americans, African Americans present with colorectal cancer at younger ages, have higher rates of colorectal cancer prevalence across all ages, demonstrate higher proportion of colorectal carcinogenesis prior to age 50, are more likely to die from colorectal cancer, demonstrate more metastasis-associated genetic biomarkers, and are less likely to engage in screening (56% of African Americans over age 50 follow recommended screening guidelines, compared to 62% of Caucasians) [60, 63]. Many of the aforementioned morbidity and mortality statistics can be attributed to this community's poorer nutrition, higher obesity rates, and lower rates of physical activity [51]. Thus it has been suggested that community-specific guidelines for this population should advocate for the commencement of screening prior to age 50 [60].

Another factor contributing to the low rates of colorectal cancer screening is the feasibility of establishing certain screening procedures in developing/lower-resource countries. For example, though a colonoscopy is generally considered to be a very effective and sensitive screening option, it requires significant cost, a skilled examiner, and extensive procedures, all of which may make colonoscopies virtually impossible to implement on a large scale in many developing nations [9]. Because of this, the FOBT, which is relatively inexpensive, convenient, and easy to administer, is a better option for primary colorectal cancer screening in certain geographic areas; in fact, many countries have already established a national screening program using the FOBT. Although not as sensitive as a colonoscopy, the FOBT has been shown to reduce colorectal cancer mortality by one-third, leading to the recommendation that this be the test of choice in areas where a more structural examination may not be feasible and/or possible [64].

Prevention and control

The prevention and/or control of colorectal cancer can be multifaceted. As previously mentioned, the regular consumption of fish, fiber, vitamin D, and calcium, as well as regular exercise and aspirin intake, can all help prevent the development of colorectal cancer [32-37]. In fact, the combination of dietary change along with the intake of anti-inflammatory drugs can not only prevent the growth of new polyps, but also stunt the growth of existing polyps [65]. In addition, family/community interventions can also be effective in helping to prevent colorectal cancer [66]. Family-based support for a family member with colorectal cancer, through the use of motivation and encouragement when performing prevention measures such as screening, exercising, and adopting a healthy diet, can be an effective learning tool to help with carcinogenesis prevention [66]. Another way this method can aid in prevention is through the advice of an older, trusted family member. To make this point, an example was given of how an individual, uneasy about a screening procedure, was calmed by older family members who shared their own experiences with such procedures [66]. Family-based interventions such as this, as well as screening, genetic testing, and the other aforementioned environmental preventive measures, can all play effective roles in both the prevention and control of colorectal cancer.

Treatment

The choice of treatment for colorectal cancer can depend on several factors, including the patient's health, the size of the tumor, and its location [65]. Surgery is the most common treatment option, and the type of surgery used, again, depends on variables such as the location of the cancer and the existence and extent of metastasis [65, 67]. As mentioned above, if cancer is found only in a single polyp, it can be removed during a colonoscopy [59, 65]. However, if the cancer has affected a larger area, then a bowel resection may be necessary [65]. Resection may include the partial or total removal of the colon as well as other adjacent organs (such as stomach or abdominal wall) [65].

When surgery is not necessary, treatment can include radiofrequency ablation, cryosurgery, chemotherapy, radiation therapy, or targeted therapy. Radiofrequency ablation involves the use of electrodes, inserted either directly through the skin or through an abdominal incision, to kill cancer cells. In cryosurgery, freezing techniques are used to destroy cancerous tissue. Chemotherapy treatment involves the use of drugs to hinder cancer growth or kill cancer cells [67]. A drug called 5-fluorouracil is the most common colorectal cancer chemotherapy treatment; it can be administered by a continu-

ous pump, 48-hour infusion, weekly injections, or daily injections [65]. In radiation therapy, X-rays or other radiation methods are used to exterminate carcinogenic cells. Finally, the aim of targeted therapy is to use drugs, or other methods, to attack the specific cancer cells without damaging any other tissues [67].

Conclusions

Colorectal cancer is a deadly disease that afflicts and kills many, many people across the planet, mainly in the West; however, due to Western influences, colorectal cancer is on the rise in many Eastern nations as well. Research tells us that some dietary factors, namely high meat and animal-fat consumption, can promote colorectal carcinogenesis, whereas other dietary factors, such as fish, fiber, vitamin D, and calcium, can help prevent it. Research has also elucidated a genetic link to colorectal cancer, explaining that approximately 35% of risk is due to genes, and revealing how genes can confer both risks and protective effects. In addition, genetic factors and environmental factors jointly affect the risk of colorectal cancer. Though research constantly provides new information about effective screening methods, the dissemination and application of this knowledge is still lacking in many areas and amongst certain communities. Effective treatment and prevention strategies have also been identified, tested, and documented. Research in these areas informs the public regarding how best to reduce their risk of developing colorectal cancer, and because of the increasing 5-year survival rate, provides reassurance that there are effective treatments in case they do develop this disease.

All the research found and presented here can provide a detailed, insightful, and informative look into the current situation regarding colorectal cancer. Future public health efforts in this area should focus on increasing screening rates among African Americans as well as creating educational interventions for Eastern nations. With the increase in colorectal cancer cases in the East, it is evident that residents of these nations may be adopting the Western lifestyle without understanding its health consequences. With that said, efforts should be made to increase health and nutrition education, particularly regarding the effects of meat and animal fat.

In addition, future efforts should be made to inform African Americans regarding the importance and benefit of undergoing colorectal screening by the age of 50 years, if not before. One possibly useful model might be the example of President Reagan's bout with colon cancer, an event that raised people's awareness regarding this very issue. In the wake of Ronald Reagan's fight with cancer, there was a rapid increase in the public's interest in colorectal cancer, leading to increases in screening and a subsequent sharp decline in colorectal mortality beginning in 1985 [68, 69]. If someone who is trusted and influential in the African American community comes forward and speaks about the magnitude of this issue, positive changes are likely to follow.

Finally, future studies in colorectal cancer epidemiology should focus on the interaction between genetics and nutrients. Both genetic factors and certain foods may increase or decrease an individual's likelihood of developing colorectal cancer. Thus, given a particular individual's genetic makeup, future studies should aim to discover what foods (or other lifestyle choices/behaviors) interact synergistically with that particular genotype to influence their colorectal cancer outcome. This would greatly increase our understanding of colorectal cancer epidemiology while also providing the opportunity for much more specific and personalized treatment/prevention strategies.

Disclosure of conflict of interest

None.

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