Colorectal Cancer: Epidemiology, Risk Factors, and Health Services

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ABSTRACT

Colorectal carcinoma is the third most common cancer in the United States in both men and women but still remains the second leading cause of cancer-related deaths. The risk of developing colorectal cancer increases with age. Additional risk factors include family history of colorectal cancer, heredity conditions such as polyposis and hereditary nonpolyposis colorectal cancer, and personal history of inflammatory bowel disease, polyps, and cancers. Health services is a new scientific discipline that examines the quality of care, often at the population level, and may examine parts or the entire spectrum of care.

KEYWORDS: Colorectal cancer, epidemiology, risk factors

Objectives: Upon completion of this article, the reader should be familiar with the epidemiology and risk factors of colorectal cancer.

This article addresses the epidemiology of colorectal cancer, including the described risk factors for its development. In addition, we provide a brief discussion of the health services issues as they relate to colorectal cancer. Both topics are essential public health factors regarding improving the care and outcomes for this cancer.

Colorectal carcinoma is the third most common cancer in the United States in both men and women but still remains the second leading cause of cancer-related deaths. Worldwide, colorectal cancer is the fourth most common cancer and affects both men and women equally. In 2003, more than 146,000 cases of colorectal cancer were diagnosed in the United States, and the American Cancer Society estimated that ~56,730 would die from this disease.[1] The substantial mortality associated with this cancer makes it the leading cause of gastrointestinal cancer deaths. In adults in the United States, the incidence of colorectal cancer and mortality rates from this disease have steadily declined over the past two decades.[2,3] The lifetime probability of developing colorectal cancer is 1 in 17 for men and 1 in 18 for women.[4] Although large differences exist in survival depending on the stage of the disease, if colorectal cancer is diagnosed at an early stage, 5-year survival rates have been reported to be as high as 90%.[5–7]

EPIDEMIOLOGY

Age

The risk of developing colorectal cancer increases with advancing age. More than 90% of the people diagnosed with the disease are older than 50, with the average age at the time of diagnosis being 64. In the United States it is the most common cancer in the population older than 75. People between the ages of 65 and 85 are six times more likely to develop colorectal cancer than people

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younger than 50.[8] Patients older than 70 present mostly with early-stage disease, whereas younger patients, usually in their 40s, present with much more aggressive disease for a given stage of presentation.[9]

Gender

The role of gender in the development of colorectal cancer remains unclear. In the United States and worldwide, the incidence in men and women is equal.[10] In a study by McArdle and Hole, looking at outcomes in 3200 patients after colorectal surgery for colorectal cancer, female patients tended to be older at presentation, with 40% of the patients being over the age of 75, compared with 30% of male patients presenting over the age of 75.[11] Women had more right-sided tumors, whereas men had more tumors in the left side of the colon. Although women presented more in an emergency setting than male patients, no differences in postoperative mortality were seen between the sexes; however, the overall 5-year survival and disease-free survival following curative resection were significantly higher in women than men, 55.2% versus 49% ($p < 0.001$) and 67.3% versus 64%, respectively.

Race

Several studies have demonstrated a racial difference in colon cancer survival. African American have a higher incidence of colorectal cancer and lower survival rates than other racial groups.[12–14] Data from the population-based cancer registries that form the Surveillance Epidemiology End Results (SEER) Program of the National Cancer Institute demonstrated that the incidence of colorectal cancer in Caucasian men and women between 1975 and 2000 declined after 1985, and in the year 2000 the incidence was 20% to 25% lower than it was in 1985.[15] However, during the same time period, the incidence in African American men increased and between 1985 and 2000, they had an incidence rate that was 12.3% higher than that of Caucasian men; moreover, the rate in African American women was 17.5% higher than in Caucasian women. When comparing survival rates, the 5-year survival rate for patients with localized colorectal cancer (stages 1 and 2) in Caucasians was 90% compared with 83% for African Americans. For patients with a stage 3 and 4 colon cancer, survival rates were similarly disproportionate: 63% in Caucasians and 53% in African Americans.

An explanation for this disparity in survival rates in African Americans compared with Caucasians has been suggested by some groups to be lack of health care coverage for African Americans compared with Caucasians.[16–18] Studies have shown that there are statistically significant differences in the rates at which physicians performed screening tests in African Americans, with physicians performing less digital rectal examinations, fecal occult blood testing, and colonoscopy.[19,20] The decreased survival rate could also be attributed to the fact that a greater proportion of African Americans present with more advanced disease, which has also been ascribed to lower screening rates, less access to health care, and differences in treatment options.[21,22] Adjuvant chemotherapy and radiation are used much less in African American patients than in Caucasians.[23] These findings were not seen in colorectal cancer patients who received treatment in the Veterans Affair Health Care System, which provides equal access to health care to all its patients.[24] Minimal to no survival differences were seen in survival rates stage for stage in African Americans compared with Caucasians. From these studies it seems evident that the differences in survival seen in African Americans in some studies may be linked to socioeconomic issues rather than differences in the biology of colorectal tumors in African Americans. This issue of disparity in care is addressed later in the health services section of this article.

RISK FACTORS

Family History

Colorectal carcinoma usually occurs in one of three patterns: sporadic, inherited, or familial. Sporadic disease is usually seen in ~70% to 75% of cases. Approximately 20% to 25% of cases occur in patients who have other family members who have also had colon cancer. A patient is considered as having a significant family history of colon cancer if a first-degree relative has been diagnosed with colon cancer or colon polyps before the age of 60 or if two or more first-degree relatives have been diagnosed with colon cancer or colon polyps at any age. There have been studies with conflicting outcomes concerning the increased risk of colorectal cancer in first-degree relatives of patients with the disease, ranging from no increased risk to a 6.3-fold increased risk to as high as an 8-fold increased risk in first-degree relatives.[25–27] St John et al quantified the risk of colorectal cancer in 7493 first-degree relatives of 523 patients with colorectal cancer from a practice of one surgeon.[28] Their study concluded that the odds ratio for colorectal cancer was 1.8 in patients who had one family member affected with the disease and 5.7 in patients having two affected relatives. The magnitude of risk was higher if the affected family member was younger than 55 years, and the risk to relatives was greatest if the affected family member was younger than 45 years at the time of diagnosis. Furthermore, their study concluded that the risk of cancer was independent of the gender of the affected individual, the site of disease, or the type of cancer. Many studies have been done to determine whether there is a genetic mutation for familial colon

cancer; in particular, research has focused on understanding the pathogenesis of familial colon cancer seen in Ashkenazi Jews.[29,30] The lifetime risk of individuals of European Jewish descent is reported to be between 10% to 15%. Laken et al were the first to describe the I1307K APC germline mutation in Ashkenazi Jews, which is found in ~6% of the individuals and ~10% to 12% of Jewish people who have colon cancer.[31] This and other studies concluded that a healthy Ashkenazi Jew with the I1307K APC mutation has an 18% to 30% lifetime risk for developing colon cancer.[32–34]

Familial Adenomatous Polyposis

Of the 5% to 10% of inherited colorectal cancers, most are related to the increased risk from hereditary polyposis syndromes or hereditary nonpolyposis colon cancer (HNPCC). Familial adenomatous polyposis (FAP) is the best characterized of the hereditary polyposis syndromes and is thought to be present in 1% to 2% of all patients diagnosed with colorectal cancer. The genetic mutation associated with FAP is a germline mutation in the APC gene, which is a tumor suppressor gene located on the long arm of chromosome 5q21. The APC gene is referred to as the "gatekeeper" of colonic neoplastic progression and promotes apoptosis in colonic cells. It regulates β-catenin microtubule proteins, which regulate cell signal transduction and growth, and is thought to inhibit β-catenin–induced cellular proliferation.[35] Thus, a mutation in the APC gene, which results in a truncated protein, prevents apoptosis and allows β-catenin–stimulated cell growth. The rapid growth of cells that lack the APC function increases the likelihood of genetic transformation of an adenomatous polyp becoming malignant. FAP is inherited as an autosomal dominant trait and is characterized by hundreds to thousands of adenomatous polyps throughout the gastrointestinal tract but more commonly in the colon. The polyps in the colon usually occur early in life, and patients can present with clinical symptoms between the age of 16 and 60. If they do not undergo a prophylactic colectomy early, all affected individuals develop colorectal cancer by the age of 40. Commercially available genetic tests for FAP that test for truncation of the APC protein identify the APC mutation in ~80% of patients. Sieber et al reported that ~7% to 8% of patients who have the FAP phenotype, and in whom the APC germline mutation cannot be detected, may carry the MYH gene mutation.[36] The MYH gene is a base excision repair gene located on chromosome 1p and has been linked to colorectal cancer.

Other syndromes known to involve a germline mutation in the APC gene include Gardner's syndrome and Turcot syndrome. Gardner's syndrome is characterized by extracolonic manifestations such as osteomas of the mandible and skull, dermoid tumors, and mesenteric fibromatosis. Studies has demonstrated that the colonic adenomatosis, duodenal polyposis, and the risk of colon and gastric cancer associated with Gardner's syndrome are identical to those in FAP.[37,38] Turcot syndrome is associated with central nervous system tumors.

Attenuated Familial Adenomatous Polyposis

Attenuated familial adenomatous polyposis (AFAP) is a clinical entity that is associated with variant APC mutations in some patients, but some patients have also been found to have missense mutations. The risk of developing AFAP in one's lifetime is unknown. AFAP is distinct from FAP and is characterized by few to 100 polyps, later onset (15 years later than FAP), and a significant but lower risk of colorectal cancer. It has been suggested that these are the patients who tend to have "rectal sparing" of the polyps. If testing using the germline APC mutation is negative in patients suspected of having AFAP, genetic testing for the MYH mutation should be considered.

Hereditary Nonpolyposis Colorectal Cancer

Patient with HNPCC do not have a large number of polyps as seen in patients with FAP. HNPCC is also known as Lynch syndrome and cancer family syndrome. It is inherited as an autosomal dominant trait and can be caused by a mutation in one of several DNA mismatch repair (MMR) genes. These genes function by maintaining the fidelity of DNA replication by identifying and excising single-base mismatches and insertion-deletion loops during DNA replication. The MMR system serves a DNA damage surveillance function by preventing incorrect base pairing or avoiding insertion-deletion loops by slippage of DNA polymerase. Compromise of cells with these functions may lead to accumulation of mutations resulting in the initiation of cancer. Inactivation of DNA MMR genes facilitates the accumulation of spontaneous point mutations, deletions, and insertions in short repetitive DNA sequences termed microsatellites. These genetic alterations constitute microsatellite instability and are found in the majority of tumors (> 90%) from patients with germline mutations in the MMR genes. Six different proteins are required for the complete MMR system: hMSH2, hMLH1, hPMS1, hPMS2, hMSH3, and hMSH6. The genes *hMSH2* and *hMLH1* have been thought to account for most of the mutations seen in patients with HNPCC.[39]

HNPCC constitutes ~5% to 10% of all colorectal cancers and confers up to an 80% lifetime risk of developing colon cancer, a 61% risk of developing endometrial cancer, a 9% risk for ovarian cancer, and a < 10% risk of developing other extracolonic cancers.[40] The average age at diagnosis is in the mid-40s, and

patients are more likely to develop right-sided colonic cancers. They are also at risk for developing synchronous or metachronous lesions. The following criteria for defining families with HNPCC were established by the International Collaborative Group and are referred to as the Amsterdam criteria: there should be three relatives with an HNPCC-associated cancer, one of the three relatives should be a first-degree relative of the other two individuals, two successive generations should be affected, at least one relative should be diagnosed before the age of 50, FAP should be excluded, and the tumor should be verified by pathology.

Colonic Polyps

Studies have shown that a history of colonic adenomatous polyps places a patient at an increased risk for developing colorectal cancer.[41,42] Colorectal polyps can be benign or malignant; benign polyps included hamartomas, hyperplastic, inflammatory, and mucosal. It is well known that colorectal cancers arise from adenomatous polyps, which have three histologic variants: tubular, tubulovillous, and villous adenomas. Tubular adenomas represent $\sim$75% to 85% of adenomatous polyps and have $<$ 5% chance of harboring a malignancy. Tubulovillous adenomas represent 10% to 15% of polyps and usually 20% to 25% harbor a malignancy. Villous adenomas constitute 5% to 10% of the remaining polyps and 35% to 40% of the polyps are malignant.

The size and degree of villous features are also predictive of the risk of malignancy within the polyp. Polyps larger that 2 cm have $>$ 40% chance of being malignant, and 35% of polyps with severe dysplasia have been found to be malignant after complete excision. It has been suggested that the transformation from adenoma to carcinoma takes $\sim$ 10 years.[43] It is estimated that nearly 40% of Americans aged 50 years or older harbor adenomatous polyps. Although there is no direct evidence that the majority of colorectal cancers arise from adenomas, adenocarcinomas are generally considered to arise from adenomas, and when patients with adenomas were observed for 20 years, the risk of cancer at the site of the adenoma was 25%, which is much higher than that expected in the normal population; furthermore, excision of adenomatous polyps is associated with a significantly reduced incidence of colorectal cancer.[44]

Inflammatory Bowel Disease

Patients with inflammatory bowel disease (IBD) have an increased risk for developing colorectal cancer. No genetic basis has been identified to explain the predisposition of patients with both Crohn's disease and ulcerative colitis to develop colorectal cancer. The mortality rate of patients with known IBD who have been diagnosed with colorectal cancer is higher than that for sporadic colorectal cancer. The risk is related to the duration and anatomic extent of the disease. This is supported by the knowledge that the risk of colon cancer increases with longer duration of IBD, increased anatomic extent of disease, and the presence of other inflammatory manifestations such as primary sclerosing cholangitis; furthermore, certain drugs that are used to treat IBD, such as 5-aminosalicylates and steroids, may prevent the development of colorectal cancer. The risk of colorectal cancer in patients with IBD has been reported to be between 7% and 14% in multiple studies after a disease duration of 25 years.[45,46] Some studies have reported the risk to be as high as 30% in patients who have had IBD for greater than 35 years.[47,48]

Bernstein et al looked at a cohort of 5529 patients with IBD, of whom 2857 patients had Crohn's disease and 2672 had ulcerative colitis.[49] There was a significantly increased incidence rate of colon cancer for patients with both Crohn's disease (IRR [incident rate ratio] = 2.64) and ulcerative colitis (IRR = 2.75) compared with the non-IBD population. This increased incidence rate was higher among IBD patients who were younger than 40 years and greater in males than females. An increased risk of rectal cancer was also seen in patients with ulcerative colitis but not in patients with Crohn's disease; however, there was an increase in the number of small bowel cancers in patients with Crohn's disease and not with ulcerative colitis. These results were corroborated by Bansal and Sonnenberg, who reported on 11,446 patients with IBD in the Department of Veterans Affair, of whom 371 developed colorectal cancer.[50] This group was compared with 52,243 patients without IBD who developed colorectal cancer. Patients with IBD who developed colorectal cancer were, as a group, 7 years younger than the group who did not have IBD. The type of IBD, gender, and race did not significantly influence the development of cancer. A history of nonsteroidal anti-inflammatory drug (NSAID) use in patients with and without IBD was associated with a protective role against colorectal cancer compared with patients in both groups without a history of NSAID use. A strong association of developing colorectal cancer was also seen in patients with IBD who had primary sclerosing cholangitis.

Behavioral Risk Factors

Several components of diet and behavior have suggested to be risk factors for colorectal cancer. Dietary factors such as high consumption of red meat such as beef and pork has been associated with an increased relative risk of advanced colorectal cancer compared with that in patients who do not consume these meat products.[51,52] Conflicting results have been reported on the role of diets high in fruits, vegetables, and fiber and colorectal

cancer.[53–55] It has been suggested that calcium may inhibit carcinogenesis by inhibiting colonic epithelial hyperproliferation. In placebo-controlled trials involving 930 patients with a history of colorectal adenomas, it was demonstrated that calcium supplementation reduced epithelial hyperproliferation and reduced the formation of new adenomas.[56] Although these lifestyle factors may be potential means of preventing colorectal cancer, there are differences in opinion regarding the evidence for some of these dietary factors as well as their role in protecting patients with a genetically increased risk for colorectal cancer.

Long-term cigarette smoking (30 to 40 years) has been shown to be associated with colorectal cancer. Although studies in the 1970s and 1980s reported no association between tobacco and colon cancer, most studies did not include smokers who had used tobacco for more than 20 years. It has becoming increasingly evident that long-term heavy smokers, such as those who began smoking heavily at a younger age, are at greatest risk for developing colon cancer.[57–59] The population attributable risk of colorectal cancer from tobacco use has been 21% in men and 12% in women. Tobacco smoke has known carcinogens including heterocyclic amines, nitrosamines, and polycyclic hydrocarbons. These compounds have been known to interact with the APC gene in animal models.

HEALTH SERVICES

A relatively new scientific discipline is health services. Among other things, health services researchers examine the quality of care, often at the population level, and may examine parts or the entire spectrum of care. One important factor in this regard is the receipt of appropriate care and treatment. For colorectal cancer, much work has been performed addressing issues for screening, treatment, and surveillance. The following is a brief discussion of health services issues pertaining to colorectal cancer.

Screening

The U.S. Preventive Services Task Force (USPSTF) and American Cancer Society strongly recommend that clinicians screen all men and women 50 years of age or older who are at average risk for colorectal cancer. The individuals who are considered at high risk because of a history of suggestive familial polyposis or hereditary nonpolyposis colorectal cancer or those with a personal history of ulcerative colitis may need to be screened earlier than age 50.[60]

Although there is ample evidence that colorectal screening is necessary for early detection and can lead to decreased incidence and mortality,[61–63] screening rates continue to be low in the United States.[64] Effective screening methods are recommended by numerous national organizations and are readily available, but according to the Centers for Disease Control and Prevention (CDC) and the National Health Interview Survey, only 45% of men and 41% of women aged 50 years or older had undergone a sigmoidoscopy or colonoscopy within the previous 10 years or had used a fecal occult blood test (FOBT) home test kit within the previous year in 2000.[64] In 2000, screening rates in many states were below the Healthy People 2010 target of 50% for both FOBT and sigmoidoscopy.[65] A more recent study has shown little improvement. Etzioni et al conducted an analysis using the 2001 California Health Interview Survey to evaluate the rates of colorectal cancer test use, predictors of the receipt of tests, and reasons for nonuse of colorectal cancer tests. According to their study, nearly 54% of those who participated in the survey reported undergoing a recent colorectal cancer test. However, men were more likely to have undergone a test than women in both age groups: 50 to 64 and older than 65 years. The study found the most important predictors of colorectal cancer testing were insurance coverage and having a usual source of care.[66]

An important health services issue deals with existing disparities (e.g., race or ethnicity, age, education level) in access to health care between different groups in the population. For example, Etzioni et al found that Caucasians and African Americans in California were more likely to be tested than individuals from other ethnic groups, that is, Latinos and Asian Americans. For instance, Latinos younger than 65 years were significantly less likely to have undergone recent testing than Caucasians (RR [relative risk], 0.84; 95% confidence interval, 0.77–0.92).[66] In another study, according to the Behavioral Risk Factor Surveillance System of the CDC, the prevalence of never having any colorectal cancer screening decreased with age in both women and men. In a study population of 61,865, more than half of women and men aged 50 to 54 reported underuse of colorectal cancer screening compared with about one third of the women and men aged 80 and older. Having less than a high school education, no health insurance, or negligible use of preventive services (not having regular health checkup visits) were also associated with underutilization of any colorectal cancer screening test.[67]

According to the "Annual report to the nation on the status of cancer, 1975–2000," the prevalence of sigmoidoscopy or colonoscopy among white men ranged from 33.5% to 63.5%, and the same prevalence for white women ranged from 38.3% to 62.1%. Prevalence estimates for black men and women had more variability.[68] According to the National Cancer Institute, in 2000, 33% of people ages 50 and older had an FOBT within the past 2 years and this number includes 21% of Hispanics, 31% of blacks, and 35% of whites. Thirty-nine percent of people in the same age group had ever

had a colorectal endoscopy, including 28% of Hispanics, 33% of blacks, and 41% of whites.[65]

Focusing on patients' preferences and increasing knowledge about the various screening tests can serve to increase the number of colorectal screenings performed annually.[69,70] Health services research is essential in this regard. These various studies and surveys reiterate the importance of tailoring public heath interventions for specific groups of the population to increase the utilization of any colorectal cancer screening test, resulting in decreased incidence of and mortality from the cancer.

Treatment

It is well accepted that adjuvant treatment for colorectal cancer should be given to stage 3 or 4 colon cancer and stage 2 to 4 rectal cancer.[71,72] As with screening rates, health services researchers have shown that underuse and disparities exist for the receipt of appropriate treatment for colorectal cancer. A population-based study conducted by Ayanian et al found that rates of chemotherapy and radiation use were strongly associated with age; older patients were significantly less likely to receive chemotherapy and radiation therapy than younger patients. Unmarried patients and those with greater comorbidities were also significantly less likely to receive chemotherapy, and African Americans and patients initially treated in low-volume hospitals compared with those treated in high-volume hospitals were less likely to undergo radiation therapy. According to the study, reasons for not providing appropriate treatment were patient's refusal, comorbidity, or lack of clinical indication.[73] Furthermore, another study performed by Baxter et al found significant predictors of radiation therapy associated with gender, race, and age. Although they found the use of radiation therapy to increase over time, disparities continued to exist between genders and different racial and age groups. According to their study, female, African American, and older patients were significantly less likely to receive radiation therapy.[74] Finally, Govindarajan et al found that African Americans have a poorer prognosis and were treated less frequently with chemotherapy and radiation compared with Caucasian patients.[75]

Much of the ongoing work looking at underuse and disparities in colorectal cancer treatment is attempting to evaluate the factors (mutable and nonmutable) that may be addressed. Whereas some studies have suggested that the providers are the reason for disparate use, others have reported that people of certain races and ethnicities are more likely to refuse the recommended treatment.[76] If this is true, perhaps intervention studies to ensure that adequate informed decisions take place are needed.

In truth, there are probably several factors that are associated with the type of treatment and care received for colorectal cancer. When specific barriers can be removed, it appears that differences in outcomes disappear between different groups in the population. This has been illustrated in a couple of studies. For example, a population-based study of elderly individuals with both Medicaid and Medicare coverage was conducted in Tennessee. Several important factors known to create disparities in the care and treatment of colorectal cancer, such as race, age, and stage at diagnosis, as well as comorbidities, were examined, and the study found that with equal access care (Medicaid and Medicare) there was no significant difference in outcomes among the subjects. This study concluded that the lack of difference in outcomes among the subjects can be attributed to the equal access to care that existed among the subjects because they all had the same medical coverage.[77] Another study looked at temporal trends in the survival of colorectal cancer patients treated in the Veterans Affairs (VA) Health Care System between 1987 and 1998. The study showed that survival for both Caucasian and African American patients improved over time and the racial disparity that exists for treating colorectal cancer in other health care systems was not significant in the VA system. This study likewise showed that equal access to care and receipt of treatment can lead to improved outcomes regardless of socioeconomic and demographic factors.[78]

It seems apparent that there is a clear need to increase screening rates throughout the country to reduce the incidence and mortality from colorectal cancer. Also, disparities in access to appropriate treatment for colorectal cancer do exist and need to be addressed to improve the quality and delivery of care for colorectal cancer.

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