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Obesity and obesity-related inflammation and metabolic conditions appear to influence the recurrence, disease-free survival, and mortality of patients with colorectal cancer.

The Effects of Obesity and Obesity-Related Conditions on Colorectal Cancer Prognosis

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Background: Colorectal cancer is the second-leading cause of cancer death in the United States among men and women combined. Refinements in screening, staging, and treatment strategies have improved survival from this disease, with over 65% of patients diagnosed with colorectal cancer surviving over 5 years after diagnosis. In the prognosis of colorectal cancer, clinicopathological factors are important. However, modifiable prognostic factors are emerging as significant contributors to cancer outcomes, including obesity and obesity-related inflammation and metabolic conditions.

Methods: This report reviews the literature on obesity and obesity-related inflammation and metabolic disturbances and colorectal cancer outcomes (recurrence, disease-free survival, and/or mortality). A PubMed search was conducted of all English-language papers published between August 2003 and 2009 and cited in MEDLINE.

Results: Primary research papers were reviewed for colorectal cancer outcomes related to obesity, inflammation, or metabolic conditions. An association between body size and colorectal cancer recurrence and possibly survival was found; however, reports have been inconsistent. These inconsistent findings may be due to the complex interaction between adiposity, physical inactivity, and dietary intake. Circulating prognostic markers such as C-reactive protein, insulin-like growth factor, and insulin, alone or in combination, have been associated with prognosis in observational studies and should be evaluated in randomized trials and considered for incorporation into surveillance.

Conclusions: The literature suggests that obesity and obesity-related inflammation and metabolic conditions contribute to the prognosis of colorectal cancer; however, comprehensive large scale trials are needed. Interventions to reduce weight and control inflammation and metabolic conditions, such as diabetes, need to be evaluated and rapidly translated to behavior guidelines for patients.

Introduction

In 2009, approximately 146,000 individuals were diagnosed with colorectal cancer in the United States, and more than 49,000 individuals died of this disease.¹ This

makes colorectal cancer the second leading cause of cancer death in the United States among men and women combined.¹ Despite refinements in screening, staging, and treatment strategies, over 35% of patients

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diagnosed with colorectal cancer die within 5 years of diagnosis. Only 40% of patients with colorectal cancer are diagnosed at a localized stage, for which 5-year survival rates are greater than 90%. The majority of patients are diagnosed with either regional or distant spread, and the 5-year survival rates at these stages are approximately 68% and 11%, respectively.²

At the same time, the number of colorectal cancer survivors in the population continues to increase. This trend is accelerated by the increasing compliance to screening and the availability of more effective colorectal cancer treatment regimens. In 2002, the National Cancer Institute and the Centers for Disease Control and Prevention estimated that there were 10.1 million survivors of all cancers in the United States, a number that has tripled since 1971.³ Among these are more than 1 million colorectal cancer survivors. Unfortunately, most survivors remain at risk for colorectal cancer recurrence (about 30% for all stages) and continue to endure posttreatment effects during survivorship.

At the time of cancer diagnosis and during surveillance, prognostic factors are utilized by clinicians to predict the probable course of disease in each patient and the likely outcome of the disease. The current gold standard for cancer prognosis is clinicopathological staging. However, outcome is independently influenced by other factors: histological characteristics of the tumor, patient age, presentation of disease, and performance status. Recently, molecular testing for mutations has proven effective in predicting tumor response to chemotherapy.⁴ However, while clinicopathological factors are important, modifiable factors are emerging as key predictors of patient prognosis. One such factor is obesity, which is modifiable. Cancer patients are increasingly interested in what lifestyle-related measures can be taken to optimize their recovery, to prevent recurrent or secondary tumors, and to assist in their return to an active, healthy life.⁵ Therefore, a review of modifiable prognostic factors for colorectal cancer is needed. Obesity and obesity-related inflammation and metabolic conditions have been proposed as modifiable prognostic factors in colorectal cancer. This report reviews the evidence regarding the effects of obesity and the resulting chronic inflammation and metabolic disturbances on colorectal cancer outcomes (recurrence, disease-free survival, and/or mortality).

Methods

We conducted a PubMed search of all English-language papers cited in MEDLINE that were published between August 2003 and 2009. The following search terms were used: colorectal cancer, outcomes, prognosis or mortality and obesity, energy balance, diet, inflammation, diabetes, metabolic syndrome, insulin, resistance, and growth factor. The query retrieved 1,533 primary papers and 405 review articles. Primary research papers were included if they reported data on colorectal cancer outcomes related to obesity, inflammation, or metabolic conditions. Papers that focused primarily on

surgical or treatment outcomes, treatment trial results, or prognostic biomarkers not directly related to obesity were excluded.

Obesity and Colorectal Cancer Outcomes

The worldwide prevalence of obesity is rising with epidemic proportions.⁶ Obesity, which is a strong risk factor for several chronic diseases, is modifiable through increased physical activity, improved dietary habits and, if necessary, medical intervention. Being overweight or obese at the time of colorectal cancer diagnosis appears to be predictive of poor cancer outcomes. Women with stage II or III colon cancer who had a body mass index (BMI) at diagnosis of ≥ 30 kg/m² were 1.34 times more likely to die of their cancer (95% confidence interval [CI], 1.07–1.67) compared with women who had a BMI below 30 kg/m², whereas obese women were only marginally at risk for disease recurrence (hazard ratio [HR] = 1.24; 95% CI, 0.98–1.59), and obese men did not have an altered overall or disease-free survival.⁷ The Million Women's Study in the United Kingdom did not report a significant association between women's BMI measured before colon or rectal cancer diagnosis and colorectal cancer mortality.⁸ In contrast, among stage II and III rectal cancer patients, having a BMI ≥ 30 kg/m² at first treatment visit was predictive of having a local rectal cancer recurrence among men but not women. BMI was not significantly associated with overall survival from rectal cancer for either gender.⁹ Dignam et al¹⁰ reported that very obese patients (BMI > 35 kg/m²) with Dukes B and C colon cancer had the greatest risk of colon cancer recurrence (HR = 1.38; 95% CI, 1.10–1.73) or death due to colon cancer (HR = 1.36; 95% CI, 1.06–1.73), whereas obese patients (BMI 30–34.9 kg/m²) did not have significantly poorer disease-free or colon cancer-specific survival compared with normal-weight patients (HR = 1.06; 95% CI, 0.93–1.21 and HR = 1.04; 95% CI, 0.88–1.24, respectively).¹⁰ In this large study, the associations did not differ between males and females and were independent of dose modification or completion of chemotherapy. In a recent study of 1,053 patients with stage III colon cancer, Meyerhardt et al¹¹ observed no association between BMI or weight change 6 months after treatment and colon cancer outcome (disease-free survival and overall survival). This study was based on self-reported weight and height for all analyses and utilized cumulative BMI instead of BMI at the start of chemotherapy. Park et al¹² reported that among a cohort of Korean cancer survivors, male colorectal cancer survivors with a BMI ≥ 25 kg/m² were 3.45 times more likely (95% CI, 1.50–7.93) to have a second colorectal cancer compared with colorectal cancer survivors with a BMI < 23 kg/m². However, in this same cohort a BMI > 25 kg/m² was not independently associated with overall or cancer-specific mortality.¹³

BMI is a relatively crude measure of body size and does not take into consideration the known significance of fat distribution. Central obesity has been linked to greater prevalence of obesity-related metabolic aberrations.

tions. Using digital images of presurgical computed tomography (CT), proportional visceral adiposity (visceral vs subcutaneous fat area ratio) was independently associated with poor disease-free survival (HR = 1.98; 95% CI, 1.02–3.87).¹⁴ Within the Melbourne Collaborative Cohort Study, prediagnostic BMI, waist circumference, percent body fat, and weight were evaluated as prognostic factors for overall and disease-specific colorectal cancer survival. BMI evaluated as a continuous variable was not associated with overall or disease-specific survival; however, other measures of adiposity were prognostic. Specifically, percent body fat, weight, and waist circumference were associated with increased disease-specific mortality (HR = 1.33; 95% CI, 1.04–1.71; HR = 1.15; 95% CI, 1.02–1.29; and HR = 1.20; 95% CI, 1.05–1.37, respectively).¹⁵

While there appears to be an association between body size and colorectal cancer recurrence and possibly overall survival, reports on this issue have been inconsistent. A majority of the findings come from retrospective studies or those nested within clinical trials, with only a few examining additional lifestyle factors such as physical activity or dietary intake. Furthermore, BMI may not be the best measure of adiposity and may need to be replaced by percent body fat or waist circumference.

Modulators of Obesity and Colorectal Cancer Outcomes

The inconsistency of findings between obesity and colorectal cancer outcomes may be due to the complex interaction between adiposity, physical inactivity, and dietary intake. Haydon et al¹⁶ reported that patients who were physically active after colorectal cancer diagnosis and during treatment had significantly reduced the risk of colorectal cancer recurrence or death compared with patients who reported no physical activity. An ongoing study testing an intervention focused on symptom management, lifestyle, and psychosocial support will provide support for improvements in lifestyle factors (physical activity, healthy diet, weight management, and smoking cessation) and colorectal cancer outcomes.¹⁷ In addition, dietary factors, which are closely linked to obesity, might modify the relationship between obesity and colorectal cancer recurrence or survival. Meyerhardt et al¹⁸ reported the association between dietary patterns (Western diet high in fat, sugar, and red meat or a prudent diet high in fruits, vegetables, and fish) before and during treatment and outcomes. Independent of BMI and physical activity, patients with the highest intake of the Western diet had elevated risk of disease-free mortality (HR = 3.25; 95% CI, 2.04–5.19) and overall mortality (HR = 2.32; 95% CI, 1.36–3.96). When restricted to those with a BMI of 25 kg/m² or higher, the negative impact of a Western diet was evident among patients with moderate to high intake (60% of the patient population), suggesting that it takes less of a Western-style diet among overweight patients to see an increased risk of recurrence.¹⁸

In addition to physical activity and diet, obesity has an impact of psychosocial functioning, which if depressed

has been shown to negatively impact cancer survival, especially on patients with advanced disease. Thus, there may be an interaction between obesity, quality of life, and colorectal cancer outcomes. In a clinical trial treating metastatic colorectal cancer patients, higher BMI before initiation of the chemotherapy regimen was predictive of improved perceptions of appearance, bowel function, and appetite.¹⁹ However, the interaction between BMI level, quality of life parameters, and colorectal cancer outcomes was not evaluated. Within another cohort, colorectal cancer patients who were physically active reported better overall quality of life than patients who were inactive.²⁰ Furthermore, evidence suggested that the impact of physical activity on quality of life may be stronger among patients with more advanced disease as opposed to less advanced disease.²⁰ Based on these findings, there may be an interaction between body size, physical activity, and quality of life, but the impact on colorectal cancer outcomes is unknown.

Obesity, Inflammation, and Colorectal Cancer Outcomes

Obesity is associated with chronic low-level systemic inflammation,^{21–24} and the evidence linking chronic inflammatory processes to colorectal carcinogenesis is quite convincing.²⁵ Obesity-induced inflammation is caused by the production of proinflammatory adipocytokines (eg, leptin, resistin) and cytokines (eg, tumor necrosis factor- α , interleukin-6, interleukin-1, and monocyte chemoattractant protein-1) and a reduction of anti-inflammatory adipocytokine (eg, adiponectin) and cytokines by the adipose tissue.^{23,24,26} Progress has been made in understanding the interrelationship between obesity, systemic inflammation, and colorectal cancer outcomes (recurrence, disease-free survival, and overall survival). The evidence supporting an association between systemic inflammation and colorectal cancer prognosis has been extensively investigated. However, the depth of the literature varies by tumor marker. This review focuses on systemic inflammatory markers as they best represent the interrelationship between obesity, inflammation, and colorectal cancer outcomes.

McMillan et al²⁷ reported in 2003 that preoperative C-reactive protein (CRP) above 10 mg/L was significantly associated with overall mortality (HR = 2.63; 95% CI, 1.42–4.88) and disease-specific mortality (HR = 3.47; 95% CI, 1.59–7.60). These results have been replicated in several independent studies and consistently demonstrate that CRP is an independent predictor of colorectal cancer survival.^{4,28–32} Interestingly, in a study of patients undergoing curative resection for colorectal cancer with or without adjuvant chemotherapy, CRP was independently associated with poorer overall survival. CRP was a stronger negative predictor of survival among patients who received adjuvant chemotherapy compared with those who underwent surgery alone (HR = 5.57; 95% CI, 1.32–23.5 vs HR =

2.10; 95% CI, 1.04–4.25).²⁹ The Glasgow Prognostic Score (GPS) is a combined score of elevated CRP (> 10 mg/L) and low albumin (< 35 g/L) and has been demonstrated as a predictive test for poor outcomes in a variety of cancers.^{33–36} McMillan et al³⁷ reported significant univariate associations between a modified GPS (hypoalbuminemia considered only with elevated CRP) and poorer overall and cancer-specific survival. Of note, the independent prognostic value of GPS was not reported. Leitch et al³⁸ reported that this modified GPS was independently predictive of colorectal cancer-specific survival among patients undergoing curative resection. Ishizuka et al³⁰ reviewed the medical records of 315 colorectal cancer patients to obtain routine laboratory test results for CRP and albumin to generate the GPS. Increased GPS was significantly associated with reduced survival time in univariate Kaplan-Meier analyses.³⁰ However, GPS was not significantly associated with survival in multivariate Cox regression models.³⁹ Among colorectal cancer patients with advanced disease (eg, liver metastases), CRP, not GPS, was independently associated with cancer-specific survival.³² However, Leitch et al³⁸ found a significant independent association with modified GPS (HR = 1.44; 95% CI, 1.01–2.04) and cancer-specific mortality among patients with advanced disease. The use of a cumulative prognostic score, such as GPS, has the potential to simultaneously incorporate several biomarkers into one measure; it remains to be seen if the GPS is the best tool for colorectal cancer prognosis.

A discussion of inflammation and cancer outcomes is incomplete without mentioning the importance of anti-inflammatory drugs. In contrast to prognostic tumor markers, the epidemiologic data on reduction of inflammation via the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin and colorectal cancer survival are limited. In a recent study by Chan et al,⁴⁰ regular aspirin use after diagnosis independently reduced overall mortality (HR = 0.79; 95% CI, 0.65–0.97) and colorectal cancer-specific mortality (HR = 0.71; 95% CI, 0.53–0.95). These data are supported by evidence of reduced mortality and recurrence of other cancers, such as breast cancer and skin cancer, with increasing NSAID use. In the Iowa Women's Health Study, the use of aspirin, but not other NSAIDs, was associated with reduced risks of cancer incidence and mortality.⁴¹ Regular use of ibuprofen, but not aspirin, was associated with a decreased risk of breast cancer recurrence.^{42,43} However, elevated concentrations of the proinflammatory biomarkers CRP and serum amyloid A (SAA) measured 24 months following a breast cancer diagnosis have been recently associated with 3-fold higher mortality.⁴⁴ Weak protective associations between NSAIDs and the recurrence of nonmelanoma skin cancer have also been reported.⁴⁵ Therefore, recent evidence from a large clinical trial and similar findings for other cancers support the use of aspirin or NSAIDs to delay recurrence of colorectal cancer and improve survival.

Metabolic Alterations Linking Obesity and Inflammation to Colorectal Cancer Outcomes

Obese individuals are generally not afflicted by obesity alone, but it is one of multiple chronic conditions, including diabetes, cardiovascular disease, and/or high blood pressure, that can develop simultaneously. Insulin-resistance or metabolic syndrome is defined by the clustering of these chronic conditions with increased BMI or waist circumference.⁴⁶ The presence of one or more of these comorbid conditions elevates risk for having a detrimental colorectal cancer outcome. Diabetes, which is the result of altered glucose and insulin homeostasis, may be a particularly important metabolic alteration linking obesity to colorectal cancer outcomes. Diabetic patients have been shown to be more likely to have a cancer recurrence and shorter disease-free survival compared to cancer patients without diabetes.^{47,48} Among over 1,100 colorectal cancer patients in Norway, no significant difference in 5-year cancer-specific survival was observed between diabetic and nondiabetic patients, however, there was a significantly lower overall survival rate among diabetic patients (46% vs 65%, $P = .001$), presumably due to cardiac disease.⁴⁹ A cumulative increased risk of colorectal cancer recurrence has been demonstrated with an increasing number of metabolic syndrome conditions such as diabetes, elevated BMI or high percentage of visceral fat, and elevated serum triglycerides.^{13,14} Among rectal cancer patients, treatment with neoadjuvant chemoradiation was less effective among diabetic patients compared with nondiabetics, including an increased progression rate (24% vs 5%, $P = .046$).⁴⁸ It appears that diabetic patients are at increased risk of colorectal cancer recurrence and death. However, mortality might not be directly linked to colorectal cancer. Based on the literature, it is unclear if there is a difference in colorectal cancer outcomes among patients with prediabetes, controlled diabetes, or uncontrolled diabetes. Direct measure of fasting insulin and glucose may be a better measure of the metabolic alterations in diabetes than self-reported medical history of diabetes, which may or may not be controlled by medications.

Metabolic biomarkers in circulation have been considered as prognostic biomarkers of colorectal cancer. It is hypothesized that alterations in circulating insulin-like growth hormones (IGFs), insulin, and/or glucose reflect an underlying biological link between obesity and colorectal carcinogenesis.^{15,16} Insulin and IGF-1 are key physiological regulators of energy metabolism and growth. The IGF axis includes circulating IGF-1 and -2 ligands, seven ligand-binding proteins (IGFBP1–7), and two classes of cellular receptors: insulin receptors and IGF receptors (IGFRs). At the cellular level, free IGF and insulin bind insulin receptors and IGFRs, which activate cell growth and proliferation and also inhibit apoptosis.^{17,18} IGFBP-3 has been shown to induce apoptosis, suppress angiogenesis, and inhibit cell growth in IGF-independent mechanisms.^{50,51}

Surprisingly, there are few observational studies and, consequently, a lack of clinical trials that have fully inves-

tigated relationships between obesity-related metabolic biomarkers (insulin and the IGF axis) and colorectal cancer prognosis.^{18,20} Haydon et al¹⁶ observed a significant reduction in the number of colorectal cancer deaths with increasing serum IGFBP-3, but not IGF-1, among physically active colorectal cancer survivors but no significant reduction with either IGFBP-3 or IGF-1 levels among those patients who were physically inactive. Wolpin et al⁵² reported that prediagnostic C-peptide levels (a reliable marker of insulin levels) were positively associated with increased overall mortality, and IGFBP-1 levels were inversely associated with both colorectal cancer-specific and overall mortality in two large cohort studies. However, prediagnostic IGF-1 and IGFBP-3 levels, which were associated with increased risk of colorectal cancer in these cohorts, were not associated with survival. Fuchs et al⁵³ reported that elevated pretreatment IGF-1, IGF-2, and IGFBP-3 levels were significantly associated with delayed cancer progression and increased overall survival rates among metastatic colon cancer patients. Elevated IGFBP-3 levels were also significantly associated with improved response to chemotherapy. These initial studies suggest a relationship between markers of insulin and the IGF axis and colorectal cancer prognosis. However, limitations such as timing of blood collections for biomarker assessment and use of clinical trial patients make these findings difficult to interpret and difficult to apply to general populations. Overall, metabolic biomarkers have been shown to be associated with cancer mortality among metastatic and nonmetastatic colorectal cancer patients.

Conclusions

The number of colorectal cancer survivors in the United States is large and increases steadily. However, prognosis is varied, with recurrence affecting nearly one-third of colorectal cancer patients.³ There has been a significant advancement over the past 10 years in the investigation of colorectal cancer-specific prognostic markers.⁴ These efforts have identified mutations in KRAS,⁵⁴ epidermal growth factor receptor (EGFR), and microsatellite instability (MSI) as predictors of treatment response. These advancements in the field of prognostic markers are facilitating individualized cancer treatment but leave patients with few options for taking action to improve their outcomes. This review focused on alternative prognostic factors that are modifiable, including obesity, inflammation, and metabolic conditions.

There is epidemiological and biological evidence suggesting a role for adiposity, hyperinsulinemia, altered glucose homeostasis, and elevated IGF axis members in the prognosis of colorectal cancer.^{11,52,53} Increasing adiposity appears to be associated with increased colon cancer-specific mortality, worse disease-free colon cancer survival among women, and decreased disease-free rectal cancer survival among men. Physical activity following diagnosis is beneficial and may modify these associations.⁵⁵ However, randomized intervention studies among colorectal cancer patients are still needed before defining recommendations specific for colorectal

cancer patients. Motivational intervention trials are underway to evaluate health coaches as a mechanism for improved behavior and thus improved health outcomes.^{17,56} Additional physical activity or dietary intervention studies, comparable to those conducted to improve breast cancer outcomes,⁵⁷ are needed for colorectal cancer patients. In addition, metabolic prognostic biomarkers need to be studied further in comparison to current standards of surveillance biomarkers such as carcinoembryonic antigen (CEA). Obesity-related biomarker levels measured just prior to surgery and during recovery appear to be the most feasible in predicting prognosis. Further data are needed on the predictability of metabolic biomarkers following diagnosis. Clearly, with the advent of promising new targeted agents (IGF-1R inhibitors and metformin),^{58,59} greater understanding of the IGF signaling axis in colorectal cancer will be crucial to allow for optimal patient selection and prediction of treatment outcome.

The benefits of anti-inflammatory medications, specifically aspirin, have recently been extended to improved colorectal cancer survival.⁴⁰ However, additional reports are needed to rectify the paucity of epidemiologic research on the use of NSAIDs and health outcomes among cancer patients. A recent publication reported no change in CRP level following a year-long physical activity intervention among healthy individuals.⁶⁰ These findings dampen the enthusiasm for this type of an intervention for reduction of systemic inflammation,⁶⁰ leaving the use of NSAIDs or aspirin as the only known option at this time. The emerging interrelationship between adiposity, systemic inflammation, and colorectal cancer prognosis will be an important area for future investigations.

Addressing survivorship issues in the colorectal cancer patient requires cooperation among multiple caregiver disciplines including oncologists, primary care physicians, and rehabilitation specialists. To meet the needs of survivors and caregivers, transdisciplinary research approaches are recommended that cover a wide spectrum of disciplines. Emerging modifiable predictors of colorectal cancer prognosis will empower patients to be directly involved in improving their recovery and ultimately their survival. The literature suggests that obesity and obesity-related inflammation and metabolic conditions contribute to the prognosis of colorectal cancer. Interventions to reduce weight and control inflammation and metabolic conditions such as diabetes need to be evaluated. Solidifying prognostic markers and health behaviors that predict a favorable outcome (increased disease-free survival and overall survival) should lead to the rapid translation into cancer survivor recommendations and long-term improved outcomes.

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