Energetics in Colorectal and Prostate Cancer

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ABSTRACT

For decades, extensive research has explored the association between factors related to energy balance and the development of both colorectal cancer and prostate cancer. Physical inactivity, obesity, higher red meat consumption or Western pattern diet, insulin and insulin-like growth factors (IGFs) appear to increase the risk of colorectal cancer while obesity, high animal fat intake, insulin and IGs have been associated with increasing prostate cancer risk and/or aggressiveness. Recently, there are growing observational data on the relationship between energetic host factors and progression of these cancers. While there are no large randomized trials in either colorectal or prostate cancer assessing these factors on disease progression or disease-related mortality, the data supporting associations between some of these factors and colorectal or prostate cancer survivorship are getting more compelling. This article will evaluate the emerging data on energy balance in patients with colorectal or prostate cancer.

INTRODUCTION

The American Cancer Society has convened three expert panels in the past decade to critically examine the data on nutrition and physical activity in cancer survivors.1-3 In 2001, the panel reported: "For many of the most important nutrition and physical activity questions faced by cancer survivors, the scientific evidence comes only from in vitro and laboratory animal data or anecdotal reports from poorly designed clinical studies.1” Moreover, the findings from these studies are often contradictory. Very few controlled clinical trials have been done to test the impact of diet, nutritional supplements, or nutritional complementary methods on cancer outcomes among cancer survivors. Only a few observational epidemiologic studies have examined the relationship between nutritional factors and cancer outcomes.

While randomized trials are still few in number, increasing data from observational studies have allowed the panel to provide more guidance in the last two reports in 2003 and 2006.2,3 Three cancers that have gained appreciably more data are breast, colorectal, and prostate cancer; breast cancer will be discussed in a separate review in this issue, and we have been asked to review the literature related to colorectal and prostate cancer. Colorectal cancer is estimated to affect 146,970 people in the United States4 and 1,023,152 people worldwide5 each year. Prostate cancer is diagnosed in 192,280 men in the United States4 and 679,000 men globally6 annually. In both diseases, greater than 50% of those diagnosed will be long-term survivors from their cancer. Further, both diseases have seen continued improvements in median overall survival in patients with metastatic disease.6,7 Cancer patients and survivors continually seek information on ways to improve their outcomes after diagnosis. Factors that influence energy balance may impact on the outcomes of patients with colorectal and prostate cancer. For this review, we will consider data on energy balance in colorectal cancer and prostate cancer, including physical activity, body mass, change in weight, and dietary factors, as related to disease outcomes. While there are important data on the impact of these factors on quality of life, physical functioning, and tolerance to chemotherapy, this review will be primarily limited to human data on associations between these factors and disease recurrence or progression and mortality.

COLORECTAL CANCER

Epidemiologic and scientific research indicates that diet and other lifestyle factors have a significant influence on the risk of developing colorectal cancer.8 Host factors that influence energy balance, including obesity, certain diets, and physical inactivity, increase one’s risk of developing colorectal cancer. Until recently, it was largely unknown if any of these modifiable factors influence the outcomes of patients already diagnosed with colorectal cancer.
However, data are emerging that these factors indeed may impact on disease outcomes and mortality in colorectal cancer survivors.

**Physical Activity**

Extensive research has examined the association between physical activity and the primary risk of colon and/or colorectal cancer. In a recent meta-analysis of 52 studies, Wolin et al. reported an inverse association between physical activity and primary colon cancer with an overall relative risk of 0.76 (95% CI, 0.72 to 0.81), comparing the most to least active individuals across studies. No association has been observed between physical activity and the primary risk of rectal cancer.

In contrast, there are only limited data on the impact of exercise on cancer recurrences/progression and mortality in survivors of colorectal cancer. In a study of prediagnosis physical activity and disease outcomes, 526 survivors of colorectal cancer were identified from a cohort of 41,528 Australians that had a previous assessment of physical activity. Analyses adjusted for some prognostic factors showed that activity levels were associated with improved disease-specific survival in the entire cohort (hazard ratio [HR], 0.73; 95% CI, 0.54 to 1.00) although the association was largely restricted to stage II and III tumors (HR, 0.49; 95% CI, 0.30 to 0.79). In an ancillary study from the same cohort, survivors of colorectal cancer who were physically active before diagnosis were found to have higher insulin-like growth factor binding protein-3, which was associated with a significant reduction in disease-specific death (HR, 0.52; 95% CI, 0.33 to 0.83). The authors suggest that a possible mechanism for the association between physical activity and disease-specific survival in survivors of colorectal cancer may be through the insulin-like growth factor axis, particularly insulin-like growth factor binding protein-3.

Three studies have examined the association between postdiagnosis physical activity and disease outcomes in survivors of colorectal cancer. The first is the Cancer and Leukemia Group B (CALGB) observational study of 832 patients with stage III colon cancer enrolled in a randomized adjuvant chemotherapy trial (CALGB 89803) and observed for a median of 3.8 years. Higher levels of self-reported physical activity approximately 6 months after completion of chemotherapy (18+ metabolic equivalent task [MET] hours/wk) were associated with disease-free, recurrence-free, and overall survival, compared with men who engaged in 3 or fewer MET hours per week.

The second postdiagnosis observational exercise study utilized the Nurses’ Health Study and included 573 women diagnosed with stages I to III colorectal cancer who self-reported leisure-time physical activity before diagnosis and 1 to 4 years after diagnosis. Significant 40% to approximately 60% lower risk of both colorectal cancer-specific mortality (Fig 1B) and overall mortality were observed among patients with increasing postdiagnosis physical activity, adjusted for other prognostic factors. In that study, level of physical activity before diagnosis was not associated with mortality. Finally, a study recently published that demonstrated comparable benefit of exercise in colorectal cancer survivors from the Health Professionals Follow-Up Study. Among 668 men with stage I to III colorectal cancer, more than 27 MET hours per week of exercise had an adjusted hazard ratio for colorectal cancer-specific mortality of 0.47 (95% CI, 0.24 to 0.92) compared with men who engaged in 3 or fewer MET hours per week.

Based on these data, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial was developed as a multinational collaboration between Canada and Australia to determine the effects of a 3-year structured physical activity intervention on disease outcomes in 962 high-risk stage II and III colon cancer survivors who have completed adjuvant chemotherapy within the previous 2 to 6 months (Fig 2). The primary end point was disease-free survival and secondary end points included patient-reported outcomes, health-related fitness, biologic correlative markers, and an economic analysis. The trial is currently open to accrual.

Several observational studies have shown that higher physical activity levels or meeting physical activity guidelines is associated with better patient-reported quality of life, physical functioning, and fatigue. Only one randomized trial has investigated the effects of an exercise intervention in colorectal cancer survivors. That study suffered from contamination in the comparison group that undermined the intention-to-treat analyses. In a secondary
Body Mass and Change in Weight

Despite the relatively consistent evidence that increasing body mass index influences the risk of developing colorectal cancer, prospective observational cohort studies regarding the impact of obesity on clinical outcomes in nonmetastatic colorectal cancer has been less certain (Table 1). In a large randomized trial of adjuvant chemotherapy for stage II and III colon cancer (INT 0089), obese women (BMI ≥ 30 kg/m²) experienced a 24% nonstatistically significant worse disease-free survival compared with normal weight women (BMI, 21 to 24.9 kg/m²); in contrast, BMI was not related significantly to long-term outcomes among male patients in that cohort. Among patients enrolled in two different adjuvant chemotherapy trials for colon cancer, very obese patients (BMI ≥ 35 kg/m²) experienced a 27% statistically significant increase in cancer recurrence or death compared with normal weight participants; no sex interaction was detected. In a third study using CALGB 89803, patients with BMI ≥ 35 kg/m² experienced a multivariate hazard ratio for disease-free survival of 1.24 (95% CI, 0.84 to 1.83), compared with normal weight individuals.

Only one small study has utilized a measure of adiposity besides BMI. Among 161 patients with resected colorectal cancer, Moon et al found that high visceral fat area to subcutaneous fat area ratio as measured from the digital images of patients’ computed tomography

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<table>
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<tr>
<th>First Author</th>
<th>Year of Diagnosis</th>
<th>No. of Patients and Stage of Disease</th>
<th>Outcome Measure</th>
<th>Hazard Ratio or $P$ (compared with normal weight)</th>
<th>Variables Controlled in Multivariate Analysis</th>
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<tbody>
<tr>
<td>Tartter⁵⁵ 1976-1979 279 colon cancer Duke B2, C1, C2</td>
<td>Recurrence rate</td>
<td>$P = .003$ for above median weight</td>
<td>Age, sex, race, performance status, clinical bowel obstruction or perforation at presentation, stage of disease, presence of peritoneal implants, and whether the patient completed adjuvant therapy</td>
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<tr>
<td>Meyerhardt⁵⁶ 1988-1992 3,759 colon cancer Duke B2, B3, C</td>
<td>Disease-free survival</td>
<td>1.11 (95% CI, 0.94 to 1.30); BMI ≥ 30 kg/m²</td>
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<td></td>
<td>Overall survival</td>
<td>1.11 (95% CI, 0.96 to 1.29); BMI ≥ 30 kg/m²</td>
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<tr>
<td>Meyerhardt⁵⁷ 1990-1992 1,792 rectal cancer, stage II and III</td>
<td>Disease-free survival</td>
<td>1.10 (95% CI, 0.91 to 1.32); BMI ≥ 30 kg/m²</td>
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<td></td>
<td>Overall survival</td>
<td>1.09 (95% CI, 0.90 to 1.33); BMI ≥ 30 kg/m²</td>
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<td></td>
<td>Local recurrences</td>
<td>1.31 (95% CI, 0.91 to 1.88); BMI ≥ 30 kg/m²</td>
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<tr>
<td>Dignam⁵⁸ 1989-1994 4,288 colon cancer Duke B and C</td>
<td>Disease-free survival</td>
<td>1.06 (95% CI, 0.93 to 1.21); BMI 30-34.9 kg/m²</td>
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<td>Colon cancer events</td>
<td>1.04 (95% CI, 0.88 to 1.24); BMI 30-34.9 kg/m²</td>
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<tr>
<td></td>
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<td>1.38 (95% CI, 1.10 to 1.73); BMI ≥ 35 kg/m²</td>
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<tr>
<td>Meyerhardt⁵⁹ 1999-2001 1,053 colon cancer stage III</td>
<td>Disease-free survival</td>
<td>1.00 (95% CI, 0.72 to 1.40); BMI 30-34.9 kg/m²</td>
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<td></td>
<td>Recurrence-free survival</td>
<td>1.24 (95% CI, 0.84 to 1.83); BMI ≥ 35 kg/m²</td>
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<tr>
<td></td>
<td>Overall survival</td>
<td>0.90 (95% CI, 0.61 to 1.34); BMI 30-34.9 kg/m²</td>
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<td></td>
<td></td>
<td>0.87 (95% CI, 0.54 to 1.42); BMI ≥ 35 kg/m²</td>
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Abbreviation: BMI, body mass index.
taken before the surgery resulted in significantly worse disease-free survival ($P = .008$).

One study has addressed the impact of weight change on recurrence in colorectal cancer survivors. In the CALGB 89803 cohort, increasing weight after diagnosis (between time on adjuvant therapy and 6 months after completion of adjuvant therapy) was not associated with disease-free or overall survival.29

Diet

While various dietary factors have been associated with colorectal cancer development, few studies have assessed the influence of diet on colon cancer recurrence and survival.31-33 Using data from 411 patients with colon cancer from two population-based case-control studies, Slattery et al31 observed an improved survival with increasing consumption of calories, fat, and protein. Among 148 patients with colorectal cancer, Dray et al33 reported improved survival with increasing consumption of calories based on dietary information before diagnosis. Both of these two studies were limited by their small sample size, heterogeneous patient population that included all stages of disease, inability to adjust for cancer treatment, and limited capacity to adjust for other prognostic factors.

The largest prospective observational study on diet in colon cancer survivors utilized the cohort from CALGB 89803 in which participants completed a food frequency questionnaire during adjuvant therapy and 6 months after the completion of adjuvant therapy.32 Two major dietary patterns were identified, prudent and Western pattern, by factor analysis. The prudent pattern was characterized by high fruit and vegetable, poultry and fish intakes; the Western pattern was characterized by high meat, fat, refined grains, and dessert intakes. All patients were assigned a relative value along the spectrum of both dietary patterns and the two patterns were not correlated with each other. Compared with patients in the lowest quintile of Western pattern diet, those in the highest quintile experienced worse disease-free survival, with an adjusted HR of 3.25 (95% CI, 2.04 to 5.19; $P$ for trend < .001). In contrast, the prudent pattern diet was not significantly associated to cancer recurrence or mortality.

PROSTATE CANCER

Prostate cancer is the most frequent and second most lethal malignancy in men.4 Survival after prostate cancer diagnosis can often exceed a decade and fewer than 5% of men without metastatic disease at diagnosis will die from prostate cancer within the first 5 to 10 years after diagnosis.34,35 While early cancer detection by prostate-serum antigen (PSA) identifies many patients at early curable stage, overtreatment may also occur among men with indolent cancer that may never progress. There is an urgent need to identify factors (including diet and lifestyle) that may influence the aggressiveness of the tumor.

Adiposity and Clinical Significant Prostate Cancer

More than 20 prospective studies have consistently demonstrated an increased prostate cancer mortality rate among men with higher BMI.36-40 but most did not distinguish whether this association is due to an increased risk of having an aggressive disease at diagnosis or worse outcomes after initial diagnosis. This distinction is especially important because heavy men are less likely to receive PSA or digital rectal exam screening.40 Further, obesity-related hemodilution reduces the sensitivity of PSA testing.41,42 The National Institutes of Health-AARP Diet and Health Study and Health Professionals Follow-Up Study considered PSA screening and reported obese men (≥ 30 kg/m²) had a significant approximately two-fold increase in prostate cancer mortality after controlling for screening.36,46 In a series of men treated with radical prostatectomy by a single surgeon, more than half of the obese men had preoperative PSA velocity ≥ 2 ng/mL per year compared with one third or fewer of men with lower BMI.43 These observations strongly suggest that prostate cancer in obese men may behave more biologically aggressive, independent of screening behavior.

Most,44-51 but not all,52,53 clinical studies among patients undergoing prostatectomy or radiotherapy suggest that obesity at the time of prostate cancer diagnosis is associated with higher risk of post-treatment PSA failure (Table 2).54-58 Among eight studies that have examined the association of BMI with prostate cancer–specific mortality,34,35,46,54-57 five reported a positive association.46,54-58 In Gong et al,56 for example, men with a BMI greater than 30 kg/m² were 2.6 times more likely to die of prostate cancer after controlling for age at diagnosis, race, smoking status, Gleason grade and clinical stage, and primary treatment.

In contrast, three large, prospective cohort studies have not shown an association between BMI and prostate cancer outcomes.34,35,56 For example, in a multi-institutional cohort of 7,274 men with localized prostate cancer treated with definitive therapy, there were no significant associations between BMI and biochemical progression or the need for secondary treatment, prostate cancer survival, or overall survival.35 Many clinical studies suffer from their inability to account for reverse causality and residual confounding, patient selection biases and competing risks. To better control for the above mentioned issues, Ma et al58 recently assessed the association of prediagnostic BMI collected at baseline and 8 years follow-up in a cohort of 2,546 male participants. Compared with those with baseline BMI under 25 kg/m², men with BMI 25 to 29.9 kg/m² and BMI ≥ 30 kg/m² had 1.4-fold (95% CI, 1.1 to 1.8) and 2.6-fold (95% CI, 1.6 to 4.3) higher risk of prostate cancer mortality, respectively, controlling for age at diagnosis, smoking status, and competing cause of deaths ($P$ trend = .0008).

Despite its effectiveness in the treatment of locally advanced and high-grade localized prostate cancer, long-term androgen deprivation therapy (ADT) causes a number of metabolic consequences including increased fat mass and decreased lean body mass,59,60 and increased fasting glucose and hyperinsulinemia.61 Men undergoing long-term ADT (≥ 12 months) have higher prevalence of diabetes and higher cardiovascular mortality.7,62-66 Use of ADT has nearly doubled over the past two decades.67,68 If obesity and related metabolic changes are considered part of the driving force for aggressive tumor behavior, these findings raise the speculative possibility that ADT-related weight gain and hyperinsulinemia may favor aggressive androgen-independent disease progression. It also underscores the need to develop strategies to prevent these metabolic changes, which may help to prevent not only prostate cancer progression but also ADT treatment-related diabetes and cardiovascular disease.

Physical Activity

A significant amount of research has examined the association between physical activity and the primary risk of prostate cancer,
but there are no meta-analyses quantifying this association. In one recent summary of only cohort studies, Johnsen et al\textsuperscript{74} noted that nine of 22 studies found an inverse association between physical activity and prostate cancer risk, 12 reported no association, and one reported a significant positive association. Based on these inconsistent results, the World Cancer Research Fund and American Institute for Cancer Research concluded that the evidence for an association between physical activity and prostate cancer risk is inconclusive.\textsuperscript{75}

No studies have examined the association between postdiagnosis physical activity and disease outcomes in prostate cancer survivors. Several observational and intervention studies have examined physical activity and health-related fitness or patient-reported outcomes in prostate cancer survivors.\textsuperscript{71} These studies have consistently demonstrated that physical activity is positively associated with, or has positive effects on, muscular strength, lean body mass, patient-reported quality of life, physical functioning, and fatigue. In a recent trial, Segal et al\textsuperscript{72} examined the effects of 24 weeks of resistance or aerobic training versus usual care on fatigue, quality of life, physical fitness, body composition, PSA, testosterone, hemoglobin, and lipid levels in 121 patients with prostate cancer receiving radiotherapy. Results showed that both resistance and aerobic exercise improved fatigue over the short-term, however, only resistance exercise improved fatigue over the longer term and provided additional improvements in quality of life, muscular strength, body fat, and triglycerides.

### Dietary Factors and Prostate Cancer Progression

Most reviews of diet and prostate cancer progression have suggested that dietary saturated fat is detrimental whereas plant-based diet could be beneficial for prostate cancer progression.\textsuperscript{73-77} This notion is supported by data from two prospective observational studies, which found that patients with prostate cancer with higher intake of saturated fat had worse disease-specific survival\textsuperscript{78} or PSA failure after prostatectomy.\textsuperscript{79} In the later study, higher BMI and intake of saturated fat had worse disease-specific survival\textsuperscript{78} or PSA failure after prostatectomy.\textsuperscript{79} In the Prostate Cancer Lifestyle Trial,\textsuperscript{80} investigators randomized patients with prostate cancer under watchful waiting to 24 weeks of either a low-calorie, low-fat diet \textsuperscript{2.23 (95% CI, 1.07 to 4.64) BMI 25-30 kg/m\textsuperscript{2} (compared with normal weight) Age, smoking, Gleason, stage, treatment|

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<tr>
<th>First Author</th>
<th>Year of Diagnosis</th>
<th>No. of Patient and Prior Treatment</th>
<th>Type and No. of Outcomes</th>
<th>Hazard Ratio or P (compared with normal weight)</th>
<th>Variables Controlled in Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqui\textsuperscript{74}</td>
<td>1990-1999</td>
<td>5,135 (prostatectomy)</td>
<td>290 progression; 151 fatal prostate cancer</td>
<td>BMI was not associated with prostate cancer mortality or total mortality</td>
<td>Gleason score, PSA, surgical margin, seminal vesicle invasion, adjuvant treatment</td>
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<tr>
<td>Gong\textsuperscript{74}</td>
<td>1993-2004</td>
<td>752 (any prior therapy)</td>
<td>50 fatal prostate cancer</td>
<td>2.64 (95% CI, 1.18 to 2.92); BMI $\geq 30$ kg/m\textsuperscript{2}</td>
<td>Age, race, smoking, treatment; Gleason score, stage</td>
</tr>
<tr>
<td>Palma\textsuperscript{75}</td>
<td>1993-2001</td>
<td>706 (radiation)</td>
<td>292 biochemical progression</td>
<td>Overall survival (No. of deaths NR) P = .02 BMI $\geq 30$ kg/m\textsuperscript{2}</td>
<td>Age, PSA, Gleason, tumor stage, risk group, treatment</td>
</tr>
<tr>
<td>Efstathiou\textsuperscript{76}</td>
<td>1987-1992</td>
<td>788 (RTOG 85-31)</td>
<td>169 fatal prostate cancer</td>
<td>1.52 (95% CI, 1.02 to 2.28); BMI 25-30 kg/m\textsuperscript{2}</td>
<td>Age, race, Gleason, stage, treatment</td>
</tr>
<tr>
<td>Merrick\textsuperscript{76}</td>
<td>1995-2003</td>
<td>1,093 (brachytherapy)</td>
<td>12 fatal prostate cancer</td>
<td>NS for BMI $\geq 30$ kg/m\textsuperscript{2}</td>
<td>Age and smoking relate to low overall survival</td>
</tr>
<tr>
<td>Smith\textsuperscript{77}</td>
<td>1992-2002</td>
<td>1,554 (radiation and ADT)</td>
<td>210 fatal prostate cancer</td>
<td>1.77 (95% CI, 1.22 to 2.55); highest v lowest tertile of weight</td>
<td>Age, race, Gleason, stage, PSA, treatment, diabetes</td>
</tr>
<tr>
<td>Ma\textsuperscript{78}</td>
<td>1982-2007</td>
<td>2,546 (any prior therapy)</td>
<td>281 fatal prostate cancer</td>
<td>1.57 (95% CI, 1.11 to 2.24); BMI 25-30 kg/m\textsuperscript{2}</td>
<td>Age, smoking, Gleason, stage</td>
</tr>
<tr>
<td>Davies\textsuperscript{75}</td>
<td>1995-2007</td>
<td>7,274 (any prior therapy)</td>
<td>220 fatal prostate cancer</td>
<td>NS for BMI 30-34.9 and BMI $\geq 35$ kg/m\textsuperscript{2}</td>
<td>Age, clinical risk category, diabetes, surgery v no surgery</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; PSA, prostate serum antigen; NR, not reported; RTOG, Radiation Therapy Oncology Group; NS, not significant; ADT, androgen deprivation therapy.
Energetics in Colorectal and Prostate Cancer

Increasing evidence supports the hypothesis that energy balance-related host factors influence colorectal and prostate cancer prognosis. For both cancers, one potential mechanism is related to hyperinsulinemia. Insulin and the insulin-like growth factor family have been associated with enhanced tumor growth and antiapoptosis. Cancer recurrences are believed to be growth of micrometastases. Thus, an environment that allows such microscopic tumors to proliferate could be detrimental. Cohort studies in colorectal and prostate cancer demonstrating that prediagnostic measurements of C-peptide, IGFBP1, and adiponectin are associated with cancer-related mortality support the notion that aggressive neoplastic behavior may be manipulated by systemic metabolic factors. Further considerations of potential mechanisms are found in other reviews in this issue of the Journal of Clinical Oncology dedicated to host factors and cancer.

To date, studies in colorectal and prostate cancer on energy balance as a host factor in tumor progression are primarily limited to preclinical and observational studies. Although efforts are made in these studies to account for reverse causality, biases, and residual confounding, ultimately randomized controlled trials are needed to provide definitive evidence on the causal effects of energy balance on disease outcomes in these patient populations. A limited number of these studies are developing. We hope that others will achieve funding and reach their accrual goal to further define the role of energetics in colorectal and prostate cancer. Nonetheless, colorectal and prostate cancers are typically diagnosed in older individuals for whom cardiovascular disease, type II diabetes, and hypertension are common comorbidities. Maintaining a healthy body weight, exercising, and controlling obesity-related metabolic risk factors may reduce not only cancer-specific mortality but also total mortality in cancer survivors.

**POTENTIAL MECHANISMS FOR THE ASSOCIATIONS BETWEEN ENERGY BALANCE AND COLORECTAL AND PROSTATE CANCER OUTCOMES**


**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.

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