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Role of Physical Activity and Diet After Colorectal Cancer Diagnosis

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A B S T R A C T

This review summarizes the evidence regarding physical activity and diet after colorectal cancer diagnosis in relation to quality of life, disease recurrence, and survival. There have been extensive reports on adiposity, inactivity, and certain diets, particularly those high in red and processed meats, and increased risk of colorectal cancer. Only in the past decade have data emerged on how such lifestyle factors are associated with outcomes in colorectal cancer survivors. Prospective observational studies have consistently reported that physical activity after colorectal cancer diagnosis reduces mortality. A meta-analysis estimated that each 15 metabolic equivalent task-hour per week increase in physical activity after colorectal cancer diagnosis was associated with a 38% lower risk of mortality. No randomized controlled trials have been completed to confirm that physical activity lowers risk of mortality among colorectal cancer survivors; however, trials have shown that physical activity, including structured exercise, is safe for colorectal cancer survivors (localized to metastatic stage, during and after treatment) and improves cardiorespiratory fitness and physical function. In addition, prospective observational studies have suggested that a Western dietary pattern, high carbohydrate intake, and consuming sugar-sweetened beverages after diagnosis may increase risk of colorectal cancer recurrence and mortality, but these data are limited to single analyses from one of two US cohorts. Additional data from prospective studies and randomized controlled trials are needed. Nonetheless, on the basis of the available evidence, it is reasonable to counsel colorectal cancer survivors to engage in regular physical activity and limit consumption of refined carbohydrates, red and processed meats, and sugar-sweetened beverages.

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INTRODUCTION

More than 1.2 million Americans are living with a diagnosis of colorectal cancer, and this number is expected to increase to 1.6 million by 2024.[1] Colorectal cancer survivors (defined as individuals who have ever been diagnosed with colorectal cancer) represent 8% of all cancer survivors, and the disease is the most prevalent cancer after prostate cancer among men and breast cancer among women.[1] The large number of colorectal cancer survivors reflects its high incidence rate (136,830 estimated new cases in 2014)[2] as well as improvements in diagnosis and treatment. Individuals diagnosed with localized colorectal cancer (approximately 40% of cases) have a 5-year survival of 90%, and individuals diagnosed with regional disease (approximately 36% of cases) have a 5-year survival of 70%.[2] In addition, although the long-term survival of individuals with metastatic colorectal cancer at diagnosis (approximately 20% of cases) remains poor, these patients are now living with their disease for more than 2 years on average.[3] Thus, there are a large number of individuals who have been or will be diagnosed with colorectal cancer, and there is time after diagnosis for these patients to make lifestyle changes that may lower their risk of disease recurrence and mortality.

Epidemiologic data suggest that certain modifiable lifestyle factors, including diet and physical activity, are more strongly associated with risk of colorectal cancer than any other cancer.[4] In 2011, the American Institute for Cancer Research and the World Cancer Research Fund released an updated report in which they concluded that there was convincing evidence that physical activity and foods containing fiber decreased risk of colorectal cancer, whereas body fat, height, and consumption of red and processed meats and alcohol increased risk.[5] These lifestyle-related factors also increase risk of cardiovascular and metabolic diseases,[6] and patients with colorectal cancer have a higher burden of comorbidities at diagnosis than individuals without cancer as well as individuals with breast or prostate cancer.[7] More than 40% of patients with colorectal cancer have comorbid conditions at diagnosis, in contrast to 32% of cancer-free Medicare beneficiaries, 32% of patients with breast cancer, and 31% of those with prostate cancer.[7] Among patients with colorectal cancer, the most common comorbidities at diagnosis are diabetes (17%), chronic obstructive pulmonary disease (13%), and congestive heart failure (12%).[7] In contrast, the prevalence of these conditions among cancer-free Medicare beneficiaries is 14%, 9%, and 7%, respectively. Diet and physical activity are well-established approaches to lowering risk of cardiovascular disease and diabetes and may improve outcomes after onset of these conditions.[8-13] Thus, improving diet quality and increasing physical activity among colorectal cancer survivors could have broad health benefits for these individuals.

In this review, we summarize the current data regarding the associations between physical activity and diet after colorectal cancer diagnosis and quality of life, disease progression, and survival. Although there have also been studies examining these lifestyle-related factors before diagnosis in relation to colorectal cancer prognosis, we chose to focus on studies that measured exposure after diagnosis, because this is the period during which colorectal cancer survivors can alter their behavior. This is a relatively new, evolving area of research, and we highlight common study limitations and suggest future research directions when appropriate. We conclude with recommendations for current best-management practices.

PHYSICAL ACTIVITY AFTER COLORECTAL CANCER DIAGNOSIS

Physical Activity and Colorectal Cancer–Specific and All-Cause Mortality: Data From Prospective Observational Studies

Evidence from prospective observational studies has consistently suggested that physical activity after colorectal cancer diagnosis reduces risk of colorectal cancer–specific and all-cause mortality. In a meta-analysis of six prospective cohort studies including 7,522 colorectal cancer survivors, high versus low physical activity after diagnosis was associated with a 42% lower risk of total mortality (hazard ratio [HR], 0.58; 95% CI, 0.48 to 0.70) and 39% lower risk of colorectal cancer–specific mortality (HR, 0.61; 95% CI, 0.40 to 0.92).[14] The authors estimated that each 15 metabolic equivalent task-hour per week (MET-h/wk) increase in physical activity after colorectal cancer diagnosis, equivalent to walking at a normal pace for 5 hours per week, was associated with a 38% lower risk of total mortality (HR, 0.62; 95% CI, 0.53 to 0.72) and a 35% lower risk of colorectal cancer–specific mortality (HR, 0.65; 95% CI, 0.53 to 0.79). However, data are limited regarding whether changing physical activity after colorectal cancer diagnosis is associated with improved outcomes. One exploratory analysis in a study of 573 women with stage I to III colorectal cancer reported that those who increased their activity after diagnosis relative to the amount they had performed before diagnosis had a 52% lower risk of colorectal cancer–specific mortality compared with women who did not change their activity level, independent of the amount of activity performed before diagnosis (HR, 0.48; 95% CI, 0.24 to 0.97; Fig 1).[15]

To better understand the biologic mechanisms, as well as support the potential for causality, recent observational studies have examined whether molecular features of colorectal tumors modify the relation between physical activity after colorectal cancer diagnosis and survival. For example, loss of p27 is a common occurrence in colorectal cancer and predicts worse prognosis. In animal models with chemically induced malignancies, energy restriction was associated with higher levels of p27 expression and subsequent cell-cycle arrest.[16] These preclinical data led to the hypothesis that individuals with colorectal tumors that express p27 may benefit more from physical activity after diagnosis than individuals with loss of p27. Indeed, one study demonstrated that among 251 patients with colorectal tumors that expressed p27, individuals who reported ≥ 18 MET-h/wk of physical activity after diagnosis had a 67% lower risk of colorectal cancer–specific mortality compared with less active individuals; there was no association among individuals with tumors with loss of p27 (interaction $P = .03$).[17] Similarly, the WNT-CTNNB1 signaling pathway plays a role both in colorectal cancer development and in adipogenesis, obesity, and metabolic diseases.[18] Activation of CTNNBI (with accumulation of nuclear signaling) leads to energy balance–independent cell growth. In one study, among patients whose colorectal cancer tumors were nuclear CTNNB1 negative, those who engaged in ≥ 18 MET-h/wk of physical activity after diagnosis had a 67% lower risk of colorectal cancer–specific mortality compared with those who did less, but postdiagnosis physical activity was not associated with risk of colorectal cancer–specific mortality among nuclear CTNNB1-positive patients (interaction $P = .05$).[19] Finally, physical activity may also influence inflammation-stimulated cell growth. Among 382 individuals with PTGS2-positive tumors (also known as COX-2), individuals in the highest quartile of physical activity had an 82% lower risk of colorectal cancer–specific mortality compared with the least-active individuals; there was no association between physical activity after diagnosis and survival among the 223 patients with PTGS2-negative

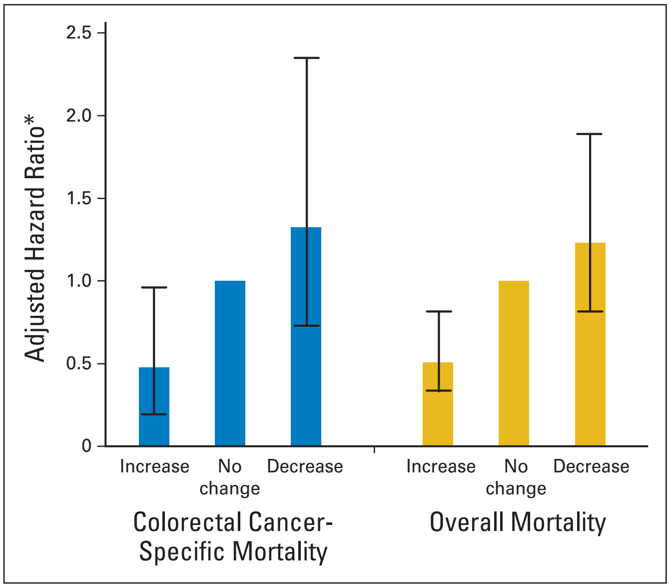

Fig 1. Change in physical activity reported before and after diagnosis of stage I to III colorectal cancer in relation to risk of colorectal cancer–specific and all-cause mortality among 523 women in Nurses' Health Study. Compared with women who reported same level of physical activity pre- and postdiagnosis (n = 203), those who reported more physical activity after diagnosis (n = 144) had approximately 50% lower risk of colorectal cancer–specific (hazard ratio [HR], 0.48; 95% CI, 0.24 to 0.97) and all-cause mortality (HR, 0.51; 95% CI, 0.30 to 0.85). (*) Compared with no change. Adjusted for body mass index, stage of disease (I, II, or III), grade of tumor differentiation, colon or rectal primary, age at diagnosis, year of diagnosis, receipt of chemotherapy (yes, no, or unknown), time from diagnosis to physical activity measurement, change in body mass index, and smoking status (current, past, or never). Data adapted.[15]

tumors (interaction $P = .02$).[20] Together, these data support the conclusion that physical activity after colorectal cancer diagnosis lowers risk of colorectal cancer progression and that this association may be mediated in part through modulation of energy metabolism and inflammatory pathways.

Physical Activity After Colorectal Cancer Diagnosis: Data From Randomized Controlled Trials

Although there is consistent evidence from observational studies of a beneficial association between physical activity after colorectal cancer diagnosis and survival, no randomized controlled trials have been completed to confirm that physical activity lowers risk of recurrence or mortality among colorectal cancer survivors. However, studies have examined the association between physical activity or exercise (ie, structured physical activity performed to improve physical fitness) and quality of life during and after colorectal cancer treatment.[21] From 2003 to 2014, six randomized controlled trials with interventions aimed specifically at increasing physical activity or exercise behavior included individuals with colorectal cancer (Table 1).[22-27] These studies included as few as 23 to as many as 102 patients with colon or rectal cancer at various stages of disease and times since diagnosis and treatment. The interventions for these trials all included recommendations to increase moderate to vigorous aerobic activity, but the target amount of activity varied across studies, and one study also included a resistance exercise program. In addition, each trial used a different approach to increase aerobic activity in the intervention arm, ranging from supervised exercise sessions to telephone counseling (Table 1 lists details).

The variations in study population, intervention, and outcomes across these studies limit the ability to make firm conclusions. However, the trials consistently reported that physical activity and/or structured exercise are safe and feasible for patients with colorectal cancer across the disease continuum (localized to metastatic stage, during and after treatment). Adherence to the interventions was high, ranging from 76% to 93%. In fact, drop-in among the control arm was a prominent issue. Courneya et al[27] reported that 52% of control patients achieved the targeted amount of moderate to vigorous aerobic activity during the study, limiting the investigators' ability to detect a difference between the intervention and control groups. Overall, although some studies did not report statistically significant differences in measured outcomes between groups, the evidence shows supportive that both telephone counseling to increase physical activity and supervised exercise are acceptable and can improve physical activity behavior, cardiorespiratory fitness, and physical function among colorectal cancer survivors.

Physical Activity in Colorectal Cancer Survivors: Next Steps

Multiple questions remain regarding the role of physical activity after colorectal cancer diagnosis. Most studies among colorectal cancer survivors have focused on total physical activity; however, data from other cancer sites suggest that intensity of physical activity may be important.[28,29] For example, among men initially diagnosed with localized prostate cancer, those who engaged in ≥ 3 hours per week of vigorous physical activity after diagnosis had a 61% lower risk of prostate cancer–specific mortality compared with men who engaged in < 1 hour per week, but there was no association between nonvigorous physical activity and risk of prostate cancer–specific mortality.[28] Vigorous activities in this study were defined as activities requiring ≥ 6 METs; nonvigorous activities required < 6 METs.[30] Studies in colorectal cancer survivors have examined total MET-h/wk after diagnosis, which combines intensity and duration of physical activity into one measure. For example, an individual can achieve 18 MET-h/wk by walking for 6 hours per week or running for 90 minutes per week. Different intensities and durations of activity elicit specific biologic responses,[31] and thus, in addition to studying total physical activity, future studies should examine vigorous and nonvigorous activities separately in relation to colorectal cancer survival.

In addition, all of the observational studies to date have relied on self-reported physical activity. Self-reported physical activity is a reasonable measure for ranking individual participation in structured physical activity (eg, exercise), but it does not provide an accurate absolute measure of duration or intensity of activity and is often a poor measure of unstructured forms of activity (eg, yard work).[32] Future studies examining the type, intensity, and duration of physical activity, as well as sedentary time, using a combination of self-reported and objective measures are needed to inform the design of interventions in randomized controlled trials and patient recommendations. In addition, few observational studies have reported on the association between postdiagnostic physical activity and colorectal cancer survival adjusting for prediagnostic levels; thus, it is unknown whether the observed associations between postdiagnostic physical activity and survival are independent of patients' activity levels before diagnosis. Randomized controlled trials are needed to definitively determine whether increasing physical activity after colorectal cancer diagnosis affects survival. Moreover, the effect of physical activity during different phases of the cancer continuum (eg, before, during, or after treatment; localized, regional, or metastatic stage) on risk of recurrence and survival is unknown. It is likely that the effects of physical activity, including the optimal type, duration, and intensity of activity, vary by time since diagnosis, disease stage, and treatment. Large prospective studies with multiple assessments of physical activity over time, detailed clinical data, and long follow-up are needed to examine this question. Lastly, the effect of physical activity after diagnosis on the incidence and progression of comorbidities among colorectal cancer survivors remains to be elucidated.

To address the question of whether aerobic exercise improves disease-free survival, the National Cancer Institute of Canada is conducting a randomized controlled trial of supervised exercise among 962 patients with stage II to III colon cancer who completed adjuvant treatment 2 to 6 months before enrollment.[33] The 3-year intervention includes supervised exercise and behavioral support delivered in person and via telephone. Patients will be assessed for disease-free survival every 6 months for 3 years and annually for up to 10 years. As of December 2013, the trial had randomly assigned 250 patients at 20 sites in Canada and 26 sites in Australia.[34]

DIET AFTER COLORECTAL CANCER DIAGNOSIS AND SURVIVAL

Although limited, emerging data have suggested certain aspects of diet after diagnosis may affect outcomes in colorectal cancer survivors (Table 2). The data for these studies have come from two prospective US cohorts. The CALGB (Cancer and Leukemia Group B) 89803 Diet

Table 1. Randomized Controlled Trials Including CRC Survivors With Interventions Specifically Aimed at Increasing Physical Activity (2003 to 2014)

Study	Year	Country	Study Population	Intervention and Comparison Details	Intervention Duration and Timing	Outcomes: Primary	Outcomes: Secondary	Follow-Up Schedule and Completion	Adherence to Intervention	Summary of Results
Backman et al[22]	2014	Sweden	71 stage I to IV BC (n = 54) and CRC survivors (n = 17)	Daily goal of 10,000 steps with weekly 1-hour supervised group walk (n = 35 [CRC, n = 8]) *v* control (n = 36 [CRC, n = 9])	10 weeks; during adjuvant chemotherapy	Feasibility and adherence (self-reported weekly pedometer step counts)	QOL, self-reported physical activity, anthropometry, blood pressure, pulse, fasting lipids, and C-peptide	0 and 10 weeks; 94%	93% among patients with CRC; 100% through week 7, declining to 63% at week 10	Intervention group maintained physical activity, whereas physical activity decreased in control group (*P* = .02); no effect on QOL, anthropometry, fasting lipids, or C-peptide
Lee et al[23]	2013	Korea	23 stage II to III CRC survivors	Group A (n = 12): goal to achieve 18 MET-h/wk of activity in first 6 weeks, increasing to 27 MET-h/wk depending on individual health conditions; supervised group sessions in weeks 1 to 4, 6, and 8; also received exercise log, pedometer, feedback, individualized goals, weekly counseling, and daily text messages; group B (n = 11): written information, pedometer, exercise log, supervised sessions in weeks 4 and 6	12 weeks; mean time since diagnosis, 19 months	Self-reported physical activity	Levels of insulin, HOMA-IR, IGF axis, and adipocytokines	0 and 12 weeks; 83%	NR	Both groups significantly increased vigorous physical activity, but no significant difference between groups for total, vigorous, or moderate physical activity; pooled analyses among all participants showed decrease in body weight, insulin, HOMA-IR, and TNF-α and increase in IGF-1, IGFBP-3, and adiponectin comparing baseline with 12 weeks
Cheville et al[24]	2013	United States	66 stage IV lung cancer (n = 34) or CRC survivors (n = 32)	Home-based REST and brisk walking program 4 days per week with one in-person visit and bimonthly telephone calls (n = 33 [CRC, n = 17]) *v* usual care (n = 33 [CRC, n = 15])	8 weeks; approximately 50% of participants were receiving treatment at enrollment	Self-reported mobility	Pain, QOL, fatigue, sleep quality, and ability to perform daily activities	0 and 8 weeks; 85%	77%	Self-reported mobility, fatigue, and sleep quality improved in intervention *v* control group
Pinto et al[25]	2013	United States	46 stage I to III CRC survivors	One in-person session covering how to exercise at moderate intensity followed by weekly telephone counseling, exercise logs, pedometers (n = 20) *v* contact control (n = 26); goal for intervention group was 30 minutes per day of moderate-intensity aerobic activity ≥ 5 days per week	12 weeks; mean time since diagnosis, 3 years	Self-reported physical activity	Objective physical activity, submaximal cardiorespiratory fitness test, motivational readiness for physical activity, fatigue, physical functioning, and QOL	0, 3, 6, and 12 months; 93% at 3 months and 91% at 12 months	Average No. of calls: intervention arm, n = 11 (92%); control arm, n = 12 (100%)	Intervention group reported more physical activity at 3 months than control group, but no difference in physical activity at 6 and 12 months; significant improvement in cardiorespiratory fitness in intervention *v* control group at all time points; no effect on fatigue, physical function, or QOL

(continued on following page)

Table 1. Randomized Controlled Trials Including CRC Survivors With Interventions Specifically Aimed at Increasing Physical Activity (2003 to 2014) (continued)

Study	Year	Country	Study Population	Intervention and Comparison Details	Intervention Duration and Timing	Outcomes		Follow-Up Schedule and Completion	Adherence to Intervention	Summary of Results
						Primary	Secondary			
Ligibel et al[26]	2012	United States	121 sedentary stage I to III BC (n = 100) and CRC survivors (n = 21)	Telephone-based intervention with 10 to 11 calls, workbook, and pedometer (n = 61 [CRC, n = 11]) *v* usual care (n = 60 [CRC, n = 10]); goal for intervention group was to perform ≥ 180 minutes per week of moderate-intensity activity	16 weeks; completed primary therapy 2 to 36 months before enrollment	Self-reported physical activity	Physical functioning, 6-minute walk test, anthropometry, QOL, and fatigue	16 weeks; 82%	Median No. of calls in intervention arm, n = 9 (82%)	No significant difference in self-reported physical activity; participants in intervention arm increased 6-minute walk test (P = .006) and physical functioning (P = .04) *v* control group; no significant differences in fatigue, QOL, or anthropometry
Courneya et al[27]	2003	Canada	102 stage I to IV CRC survivors	All participants underwent submaximal cardiorespiratory fitness test and received feedback on results and were then randomly assigned to home-based exercise prescription of 20 to 30 minutes of moderate to vigorous aerobic activity 3 to 5 days per week (n = 69) or usual care (n = 33); all participants were called weekly to inquire about activity levels	16 weeks; mean time since CRC surgery, 2 months	QOL	Satisfaction with life, depression, anxiety, fatigue, submaximal cardiorespiratory fitness test, body composition, and flexibility	16 weeks; 91%	76% of intervention arm reported > 60 minutes per week of moderate to vigorous aerobic activity	No significant effect on QOL, satisfaction with life, depression, anxiety, fatigue, cardiorespiratory fitness, body composition, or flexibility; 52% of control group reported engaging in > 60 minutes per week of moderate to vigorous aerobic activity during study

Abbreviations: BC, breast cancer; CRC, colorectal cancer; HOMA-IR, homeostasis model assessment of insulin resistance; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; MET, metabolic equivalent task; NR, not reported; QOL, quality of life; REST, rapid, easy, strength training; TNF-α, tumor necrosis factor alpha.

Table 2. Prospective Cohort Studies Among Individuals With Colon or Rectal Cancer Examining Postdiagnostic Diet in Relation to Cancer Recurrence, Cancer-Specific Mortality, and All-Cause Mortality

Study	Year	Study Population	Timing of Exposure Assessment	Outcomes Assessed	Follow-Up	Food/Nutrient	All-Cause Mortality (Q5 or Q4 *v* Q1)*			Cancer-Specific Mortality or Recurrence (Q5 or Q4 *v* Q1)†		
							HR	95% CI	Trend *P*	HR	95% CI	Trend *P*
Fuchs et al[35]	2014	1,011 stage III colon cancer survivors (CALGB 89803)	Median time after study entry (study entry was ≤ 8 weeks after CRC surgery), 3.5 months	Disease-free survival (n = 386); colon cancer recurrence (n = 343); all-cause mortality (n = 305)	Median, 7.3 years	Sugar-sweetened beverages (≥ two servings per day *v* < two servings per month)	2.32	1.36 to 3.96	< .001	2.85	1.75 to 4.63	< .001
Yang et al[36]	2014	1,111 stage I to III CRC survivors (CPS II)	Mean time after diagnosis, 2.6 years	All-cause mortality (n = 429); CRC-specific mortality (n = 143)	Mean, 7.6 years; SD, 3.4 years	Total calcium	0.72	0.53 to 0.98	.02	0.59	0.33 to 1.05	.01
						Dietary calcium	0.86	0.65 to 1.14	.21	1.00	0.61 to 1.63	.83
						Supplemental calcium	0.98	0.73 to 1.31	.88	0.65	0.38 to 1.11	.13
						Total vitamin D	0.88	0.57 to 1.35	.35	1.74	0.80 to 3.77	.52
						Dietary vitamin D	0.90	0.67 to 1.21	.33	1.28	0.77 to 2.10	.19
						Total dairy	0.75	0.56 to 1.01	.05	0.73	0.44 to 1.23	.32
						Milk	0.72	0.55 to 0.94	.02	0.93	0.59 to 1.49	.81
McCullough et al[37]	2013	1,186 stage I to III CRC survivors (CPS II)	NR	All-cause mortality (n = 472); CRC-specific mortality (n = 146); cardiovascular disease mortality (n = 110)	Mean, 7.6 years; SD, 3.4 years	Total red and processed meats	0.94	0.68 to 1.30	.36	1.10	0.61 to 1.98	.91
						Red meat	0.75	0.55 to 1.03	.09	1.13	0.62 to 2.06	.79
						Processed meat	1.11	0.82 to 1.49	.71	1.06	0.61 to 1.84	.84
Meyerhardt et al[38]	2012	1,011 patients with stage III colon cancer (CALGB 89803)	Median time after study entry (study entry was ≤ 8 weeks after CRC surgery), 3.5 months	Disease-free survival (n = 386); CRC recurrence (n = 343); all-cause mortality (n = 305)	Median, 7.3 years	Glycemic load	1.74	1.20 to 2.51	< .001	1.97	1.39 to 2.79	< .001
						Glycemic index	1.23	0.83 to 1.82	.22	1.24	0.85 to 1.81	.14
						Total fructose	1.11	0.79 to 1.58	.40	1.43	1.04 to 1.98	.01
						Total carbohydrate	1.80	1.25 to 2.60	< .001	2.06	1.45 to 2.91	< .001
Meyerhardt et al[39]	2007	1,009 patients with stage III colon cancer (CALGB 89803)	Median time after study entry (study entry was ≤ 8 weeks after CRC surgery), 3.5 months	Disease-free survival (n = 352); CRC recurrence (n = 324); all-cause mortality (n = 251)	Median, 5.3 years	Western dietary pattern	2.32	1.36 to 3.96	< .001	2.85	1.75 to 4.63	< .001
						Prudent dietary pattern	1.32	0.86 to 2.04	.54	1.13	0.77 to 1.67	.84

Abbreviations: CALGB, Cancer and Leukemia Group B; CPS, Cancer Prevention Study; CRC, colorectal cancer; HR, hazard ratio; NR, not reported; Q, quintile or quartile; SD, standard deviation.
*Multivariable results comparing highest versus lowest quintile or quartile, with exception of sugar-sweetened beverages (≥ two servings per day *v* < two servings per month).
†Results from CALGB 89803 are for colon cancer recurrence (Fuchs et al[35] and Meyerhardt et al[38,39]).

and Lifestyle Companion Study is embedded in a randomized phase III trial of adjuvant chemotherapy among 1,264 patients with stage III colon cancer who completed validated food frequency questionnaires (FFQs) at two time points (midway through chemotherapy and 6 months after completion of chemotherapy).[40] The second cohort is composed of 2,284 participants in the American CPS (Cancer Prevention Study) II Nutrition Cohort who completed a validated FFQ from 1992 to 1993 and were subsequently diagnosed with colorectal cancer during follow-up.[41] Participants in this cohort updated their dietary data in 1999 and 2003. In addition to these cohorts providing postdiagnostic diet data, seven studies have examined prediagnostic dietary factors with adjustment for energy intake in relation to survival among patients with colorectal cancer.[42-47] Our discussion focuses on studies of postdiagnostic diet, but we have included findings from case-only studies examining prediagnostic diet when relevant.

Dietary Patterns After Colorectal Cancer Diagnosis

Using data from CALGB 89803, Meyerhardt et al[39] reported that patients in the highest quintile of a Western dietary pattern score after diagnosis had a nearly three-fold increased risk of disease recurrence (quintile 5 *v* 1: HR, 2.85; 95% CI, 1.75 to 4.63; *P* trend < .001) and a 2.3-fold increased risk of all-cause mortality (quintile 5 *v* 1: HR, 2.32; 95% CI, 1.36 to 3.96; *P* trend < .001) compared with patients in the lowest quintile. The Western dietary pattern in this cohort was characterized by high- and low-fat dairy, refined grains, condiments, red and processed meats, desserts, and potatoes. No association was observed between adherence to a prudent dietary pattern, characterized by vegetable, legume, and fruit intake, after colon cancer diagnosis and risk of recurrence or all-cause mortality. Similar findings were reported in a cohort of 529 patients with stage I to III colorectal cancer in Newfoundland, Canada, although patients in that study were asked to report their usual diet in the year before diagnosis.[45] Patients in the fourth quartile of a processed-meat dietary pattern had an 82% increased risk of disease recurrence or death compared with patients in the lowest quartile (HR, 1.82; 95% CI, 1.07 to 3.09). No associations were observed between a prudent or high-sugar dietary pattern in the year before diagnosis and disease-free survival.

Red and Processed Meats After Colorectal Cancer Diagnosis

Postdiagnostic red and processed meat intake was not associated with colorectal cancer–specific or all-cause mortality in the CPS II Nutrition Cohort.[37] However, individuals who consumed more than the median amount of red and processed meats before and after colorectal cancer diagnosis had a 79% increased risk of colorectal cancer–specific mortality compared with individuals with intakes smaller than the median at both time points (HR, 1.79; 95% CI, 1.11 to 2.89).[37] The median pre- and postdiagnostic total red and processed meat intakes were 4.7 and 4.1 servings per week, respectively. Few individuals substantially increased or decreased their intake after diagnosis, so the authors had limited statistical power to examine the association between change in meat intake after colorectal cancer diagnosis and risk of mortality. In addition, high prediagnostic red and processed meat intake was associated with an increased risk of all-cause mortality (fourth *v* first quartile: HR, 1.29; 95% CI, 1.05 to 1.59; *P* trend = .03), but was not associated with risk of colorectal cancer–specific mortality, in this study population. Prediagnostic total meat and red meat intakes were also not associated with mortality among 704 women with colorectal cancer in the California Teachers Study.[46]

Milk and Calcium Intakes After Colorectal Cancer Diagnosis

Among participants with colorectal cancer in the CPS II Nutrition Cohort, milk intake after colorectal cancer diagnosis was inversely associated with all-cause mortality, but it was not associated with colorectal cancer–specific mortality.[36] Individuals who reported ≥ seven servings per week of milk after colorectal cancer diagnosis had a 28% lower risk of death than individuals who consumed < one serving per week (HR, 0.72; 95% CI, 0.55 to 0.94; *P* trend = .02). A similar magnitude of association was observed comparing the highest and lowest quartiles of total calcium intake after colorectal cancer diagnosis and all-cause mortality. No associations were observed between prediagnostic total dairy, milk, vitamin D, or calcium intake and all-cause or colorectal cancer–specific mortality in this cohort. Similarly, Dik et al[42] observed no association between total dairy, milk, yogurt, cheese, or dietary calcium intake before diagnosis and risk of all-cause or colorectal cancer–specific mortality among 3,859 colorectal cancer survivors.

Carbohydrates, Glycemic Load, and Sugar-Sweetened Beverages After Colorectal Cancer Diagnosis

The amount and source of carbohydrates consumed after diagnosis may be associated with colorectal cancer survival. High glycemic load and total carbohydrate intake, but not glycemic index, were positively associated with colon cancer recurrence and mortality in the CALGB 89803 cohort.[38] Individuals in the highest versus lowest quintile of glycemic load after colon cancer diagnosis had a 97% increased risk of disease recurrence (quintile 5 *v* 1: HR, 1.97; 95% CI, 1.39 to 2.79; *P* trend < .001) and a 74% increased risk of all-cause mortality (quintile 5 *v* 1: HR, 1.74; 95% CI, 1.20 to 2.51; *P* trend < .001). Glycemic load is a measure of the quantity and quality, or effect on glycemic response, of carbohydrates in the diet. The relation observed in CALGB 89803 seemed to be driven more by the quantity of carbohydrate consumed after colon cancer diagnosis than the quality. Individuals in the highest quintile of carbohydrate intake after colon cancer diagnosis had a two-fold increased risk of disease recurrence and all-cause mortality compared with individuals in the lowest quintile (quintile 5 *v* 1: recurrence HR, 2.06; 95% CI, 1.45 to 2.91; *P* < .001; all-cause mortality HR, 1.80; 95% CI, 1.25 to 2.60; *P* < .001). In addition, a detrimental association was observed for sugar-sweetened beverage consumption. Patients who consumed ≥ two sugar-sweetened beverages per day after colon cancer diagnosis had a 75% increased risk of recurrence compared with individuals who consumed < two per month (HR, 1.75; 95% CI, 1.04 to 2.94).[35]

Vitamin D After Colorectal Cancer Diagnosis

Vitamin D is endogenously synthesized in the skin when exposed to sunlight and obtained through supplements and some foods.[48] Food sources of vitamin D include fortified foods (eg, milk), fish, and eggs. In a meta-analysis of five prospective cohort studies including 2,330 patients with colorectal cancer, individuals in the highest versus lowest category of circulating 25(OH)D had a 29% lower risk of overall mortality (HR, 0.71; 95% CI, 0.55 to 0.91) and a 35% lower risk of colorectal cancer–specific mortality (HR, 0.65; 95% CI, 0.49 to 0.86).[49] Recently, Zgaga et al[50] reported similar results among 1,598 patients with stage I to III colorectal cancer. Individuals in the highest tertile of plasma 25(OH)D assessed postoperatively had a 30% lower risk of all-cause mortality (HR, 0.70; 95% CI, 0.55 to 0.89; $P = .003$) and a 32% lower risk of colorectal cancer–specific mortality (HR, 0.68; 95% CI, 0.50 to 0.90; $P = .008$) compared with individuals in the lowest tertile. Furthermore, variation in the vitamin D receptor gene significantly modified these associations, supporting a biologic effect of vitamin D after diagnosis on colorectal cancer progression. However, Yang et al[36] did not observe an association between vitamin D intake from foods or supplements and risk of colorectal cancer–specific or all-cause mortality. Additional studies are needed to determine whether increasing vitamin D intake after colorectal cancer diagnosis is associated with improved outcomes in colorectal cancer survivors.

Diet in Colorectal Cancer Survivors: Next Steps

Overall, emerging evidence suggests that diet after colorectal cancer diagnosis affects risk of disease recurrence and survival, but further research is needed to clarify what aspects of diet are most important, whether the effect of diet varies across stages of disease or treatment, and whether diet after diagnosis has an effect independent of prediagnostic diet. In addition, future studies should examine the effect of diet after colorectal cancer diagnosis on risk and progression of comorbidities, as well as quality of life, treatment tolerance, and survival among individuals with metastatic colorectal cancer. CALGB 80405, a phase III adjuvant chemotherapy trial among patients with stage IV metastatic colorectal cancer, will provide a rich resource to answer this latter question. More than 1,500 patients completed a validated FFQ within 1 month of first-line chemotherapy and are being observed over time for treatment toxicities, quality of life, and overall survival.[3] In addition, the COLON trial (Colorectal Cancer: Longitudinal Observational Study on Nutritional and Lifestyle Factors That May Influence Colorectal Tumour Recurrence, Survival, and Quality-of-Life) COLON trial is a prospective cohort study based in the Netherlands that is currently recruiting 1,000 patients with colorectal cancer at the time of diagnosis.[51] Participants in this study will complete a comprehensive questionnaire and FFQ, provide blood samples, and undergo imaging to evaluate muscle and fat distributions at baseline, 6 months, 2 years, and 5 years. Both of these cohorts will provide valuable resources for future analyses. Ultimately, however, randomized controlled trials testing the effect of diet on biologic and clinical outcomes in colorectal cancer survivors are needed.

COMPREHENSIVE LIFESTYLE INTERVENTIONS AMONG COLORECTAL CANCER SURVIVORS

Four randomized controlled trials with both dietary and physical activity components have included colorectal cancer survivors. All four studies assessed behavior change, quality of life, and measures of cardiovascular fitness and physical function as outcomes, but they did not test the impact of comprehensive lifestyle interventions on risk of colorectal cancer recurrence or survival.[52-55] The most informative of these for patients with colorectal cancer and their caregivers was the Australian CanChange trial. In this study, 410 individuals who had been diagnosed with colorectal cancer in the previous 12 months were randomly assigned to health coaching or usual care. The intervention was based on acceptance commitment theory and included 11 telephone sessions over 6 months, a workbook, postcard prompts, and pedometer.[55,56] Individuals randomly assigned to the control group received print materials. Patients in the intervention arm were counseled to exercise at least 150 minutes per week, consume at least two servings of fruit and five servings of vegetables per day, and achieve or maintain a healthy body weight. At 12 months, patients randomly assigned to the intervention reported a larger increase in total physical activity and had decreased their saturated fat intake and gained less weight compared with controls. Vegetable intake had increased more in the intervention group than in the control group at 6 months, but this change was not sustained at 12 months. The intervention had no effect on health-related quality of life or cancer-related fatigue.

The CanChange trial demonstrated that telephone-based health coaching can modify colorectal cancer survivors' diet and exercise behavior, but it is unknown if the intervention affected clinical outcomes, such as comorbidities, cancer recurrence, or mortality. In addition, a telephone-based intervention may not be feasible to implement in many settings. Future studies comparing diet and/or physical activity interventions delivered via mobile technology versus telephone would be of interest.[57,58] In addition, future studies should incorporate objective measures (eg, accelerometery; fasting lipids, glucose, and carotenoids; measured body weight) to support self-reported outcome data and examine whether the effect of an intervention varies across stage of disease, time since diagnosis, or sociodemographic factors.

DISCUSSION

In conclusion, observational data strongly support a beneficial effect of physical activity after colorectal cancer diagnosis on cancer-specific and overall survival, and the ongoing CHALLENGE (Colon Health and Life-Long Exercise Change) trial is designed to determine whether supervised exercise lengthens survival among patients with high-risk stage II or III colon cancer. Less is known regarding the role of dietary factors after diagnosis. No dietary pattern, food, or nutrient after colorectal cancer diagnosis has been studied in more than one large prospective US cohort study. Additional data from prospective studies and randomized controlled trials are urgently needed and, ultimately, will allow for more definitive guidance for colorectal cancer survivors.

Regarding recommendations, on the basis of the limited observational data available from cancer survivors as well as data on prevention of cancer and other chronic conditions, the American Cancer Society and the American Institute for Cancer Research have published guidelines for all cancer survivors regarding diet and physical activity after diagnosis.[59-61] We based the following recommendations specifically for colorectal cancer survivors on these guidelines, as well as on the available data on postdiagnostic lifestyle factors in colorectal cancer survivors.[14,35,38,39]

- Engage in regular physical activity.
    - Perform at least 150 minutes per week of aerobic activity, such as brisk walking. Every bout of activity lasting ≥ 10

minutes counts toward the weekly goal. More intense or longer durations of physical activity may have additional benefits (eg, 6 hours per week of walking, 90 minutes per week of running).
  - If 150 minutes of aerobic activity per week is not feasible, aim to be as physically active as possible.
  - Perform muscle-strengthening exercises ≥ 2 days per week.
- Minimize sedentary behavior, such as watching television. If you must sit for extended periods of time, take frequent short breaks to stand up, stretch, and walk around.
- Limit consumption of refined carbohydrates and foods with a high glycemic index, such as bread, pasta, white rice, potatoes, cold cereals, crackers, pretzels, cakes, cookies, and other sweets and desserts.
- Do not consume sugar-sweetened beverages, including sodas, sports drinks, and fruit or vegetable juices.
- Limit consumption of red and processed meats.
- Eat ≥ five servings per day of vegetables, including a variety of colors and types.

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Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Role of Physical Activity and Diet After Colorectal Cancer Diagnosis

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