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Beyond Standard Adjuvant Therapy for Colon Cancer: Role of Nonstandard Interventions

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Abstract

Epidemiologic and scientific research indicates that diet and other lifestyle factors have a significant influence on the risk of developing colorectal cancer. Obesity, consumption of red meat, a Western pattern diet, alcohol, and smoking influence one's risk of developing colorectal cancer while physical activity, vitamin D, post-menopausal estrogen use, aspirin and NSAIDs decrease one's risk. 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 of factors that may influence disease recurrences and mortality for colorectal cancer survivors. Prospective observational studies have shown that increased exercise after diagnosis and avoidance of a Western pattern diet are associated with reduced risk of cancer recurrence and improved overall survival in early- stage colorectal cancer after standard therapy. Patients with class II and III obesity (BMI ≥ 35 kg/m^2) have a modestly increased risk of recurrence. Regular use of aspirin or cyclooxygenase-2 inhibitors decrease recurrence rates as well as increased serum vitamin D levels. In contrast, change of weight after diagnosis or smoking status (never, past or current) are not associated with outcomes after diagnosis. The data supporting these observations will be reviewed, potential mechanisms of actions will be discussed and next steps forward will be proposed.

In 2010, an estimated 142,570 individuals will be diagnosed with colorectal cancer and 51,370 will die from the disease in the United States.[1] Eighty percent will be diagnosed without clinical or radiographic evidence of metastatic disease. Depending on the stage of disease and pathological features of the tumor, recurrence rates between 10–60% have been demonstrated. Greater than 50% of patients with 4 or more lymph nodes will recur or die at 5 years after diagnosis despite standard treatment with surgery and adjuvant chemotherapy. There is a clear need to further optimize the outcomes for patients with colorectal cancer.

Epidemiologic and scientific research indicates that diet and other lifestyle factors have a significant influence on the risk of developing colorectal cancer.[2] Obesity, consumption of red meat or a Western pattern diet, alcohol, and smoking increase one's risk of developing colorectal cancer while physical activity, calcium, vitamin D, post-menopausal estrogen use, aspirin or non steroidal anti-inflammatory usage decrease one's risk. 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 of host factors that

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may impact disease recurrences and mortality for colorectal cancer survivors. The sources of these data remain limited to observational studies, though interventional trials are now underway.

Physical activity in colorectal cancer survivors

Lack of physical activity has been the most consistently demonstrated lifestyle factor increasing the risk of developing colorectal cancer, particularly colon cancer.[3] The International Agency for Research on Cancer concluded that the evidence supports a causal relation between inactivity and colorectal cancer risk.[4] In a recent meta-analysis of 52 studies, Wolin and colleagues reported an inverse association between physical activity and primary colon cancer with an overall relative risk (RR) of 0.76 (95% confidence interval [CI]: 0.72–0.81), comparing the most to least active individuals across studies.[5] No association has been observed between physical activity and the primary risk of rectal cancer.[3]

In the past five years, data have emerged for the potential influence of exercise in colorectal cancer survivors with stage I to III disease. In a study of physical activity and disease outcomes, 526 colorectal cancer survivors were identified from a cohort of 41,528 Australians that had a pre-diagnosis assessment of physical activity.[6] Increased exercise was associated with improved disease-specific survival (adjusted hazard ratio [HR] = 0.73; 95% CI: 0.54 –1.00). In subgroup analyses, the association seemed restricted to stage II and III tumors (HR=0.49; 95% CI: 0.30–0.79). In efforts to correlate these findings with molecular markers, the investigators reported that physically active colorectal cancer survivors had higher insulin-like growth factor binding protein-3 (IGFBP-3), which was associated with a significant reduction in disease-specific death (HR=0.52; 95% CI: 0.33–0.83).[7] These data suggest that the association between physical activity and disease-specific survival in colorectal cancer survivors may be through the insulin-like growth factor (IGF) axis, particularly IGFBP-3.

Three studies have examined the association between post-diagnosis physical activity and disease outcomes in colorectal cancer survivors (Table 1).[8–10] A prospective, observational study of 832 patients who participated in an adjuvant study comparing 5-fluorouracil (5-FU) and leucovorin to irinotecan, 5-FU and leucovorin (IFL) for stage III colon cancer (CALGB 89803) found that higher levels of self-reported physical activity approximately 6 months after completion of chemotherapy (at least 18 metabolic equivalent task [MET]-hours/week) were associated with superior disease-free, recurrence-free, and overall survival, adjusted for known prognostic factors, including body mass index (BMI). [10] For reference, 3 MET-hours is equivalent to one hour average pace walking.

In a second study, a cohort of 573 women diagnosed with stages I – III colorectal cancer who participate in the Nurses' Health Study and self-reported leisure-time physical activity before diagnosis and 1–4 years after diagnosis was utilized to test the association between exercise before diagnosis and after diagnosis and survival outcomes.[8] Women who were most physically active experienced 61% reduced colorectal cancer–specific mortality and 57% reduced overall mortality compared to inactive women, adjusted for other prognostic factors. Level of physical activity prior to diagnosis was not associated with mortality.

A similar study to that of the Nurse's Health Study was recently reported utilizing male colorectal cancer survivors from the Health Professionals Follow-up Study.[9] Amongst 668 men with stage I–III colorectal cancer, more than 27 MET-hours per week of exercise had an adjusted HR for colorectal cancer-specific mortality of 0.47 (95% CI: 0.24–0.92) compared with men who engaged in 3 or less MET hours per week.

Based on these data, a multinational trial in Canada and Australia, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial, was developed to determine the effects of a 3 year structured and supervised 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 2–6 months (Figure 1).[11] The primary end point is disease-free survival and secondary endpoints include 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.[12–17] To date, only one randomized trial of an exercise intervention in colorectal cancer survivors has been published.[18] There was appreciable contamination in the comparison group, impacting the intention-to-treat analyses. In a secondary analysis, participants whose fitness increased over the course of the intervention, regardless of group assignment, reported significantly improved quality of life, physical functioning, and psychosocial distress compared to participants whose fitness decreased.

Adiposity in colorectal cancer survivors

The impact of adiposity on outcomes in non-metastatic colorectal cancer has been less certain.[19–24] There are relatively consistent data that obese subjects have an increased risk of developing colorectal cancer.[25] However, prospective observational cohort studies in colon or rectal cancer survivors have only shown a modest association with outcomes.[20,22] When detected, the association has primarily been restricted to those with BMI ≥ 35 mg/m^2 (class II and III obesity), with approximately 25% worsening of disease-free survival.

Only one study has observed the influence of change in weight after diagnosis on cancer recurrences and survival.[20] In breast cancer survivors, gain in weight has been associated with increased risk of cancer in some,[26,27] but not all studies.[28,29] Increasing weight after diagnosis (between time on adjuvant therapy and 6 months after completion of adjuvant therapy) was not associated with disease-free survival or overall survival in the CALGB 89803 cohort.

Diet and Colon Cancer Outcomes

Diet has been extensively studied as a risk factor for the development of colorectal cancer.[25,30–33] In contrast, few studies have examined the association between diet and outcomes in colorectal cancer survivors.[34–36] Slattery and colleagues studied 411 colon cancer patients from two population-based case-control studies and observed an improved survival with increasing consumption of calories, fat, and protein.[34] Among 148 patients with colorectal cancer, Dray et al reported improved survival with increasing consumption of calories based on dietary information prior to diagnosis.[36] These two studies were limited by their heterogeneous patient population that included all stages of disease, small sample size, lack of data on cancer treatment, and limited capacity to adjust for other prognostic factors.

To address these concerns, a prospective observational study on diet in 1,009 colon cancer survivors from CALGB 89803 was reported in which participants completed a food frequency questionnaire during adjuvant therapy and 6 months after the completion of adjuvant therapy.[35] Using factor analysis, two major dietary patterns were identified, prudent and Western pattern. 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. The two patterns were not correlated with each other (Spearman correlation coefficient = 0.02). Western pattern diet was associated with disease-free and overall survival (Figure 2). 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: 2.04–5.19; P for trend <0.0001). In that patient cohort, patients in the highest quintile of Western pattern diet consumed a mean intake of 6 servings of red meat per week, 5.6 servings of processed meat per week, 5.8 servings of refined grains daily and 2.5 servings of sugary desserts daily.[37] In comparison, those in the lowest quintile of Western pattern diet reported a mean intake of 2.3 servings of red meat and 1.8 servings of processed meats per week and 2.0 servings of refined grains and less than 1 serving of sugary desserts daily. In contrast, the prudent pattern diet was not significantly associated to cancer recurrence or mortality. Since these patterns are mutually exclusive, based on the data, the data would suggest an avoidance or reduction of foods associated with a Western pattern diet but not necessarily an increase in foods associated with the prudent pattern diet.

Potential Mechanisms of Energy Balance Factors and Outcomes in Colorectal Cancer Survivors

Physical activity, adiposity and diet influence energy balance within individuals. Molecular pathways associated with alterations in energy balance are a leading potential mechanism for the association between these host factors and outcomes in colorectal cancer survivors. Shifts in energy balance may lead to changes in insulin and insulin-like growth factors (IGF) levels as well as sensitivity to insulin.[38–40] In observational studies, colon cancer risk is elevated in individuals with higher circulating levels of insulin or C-peptide (a marker of insulin secretion)[41–43] and IGF-1 or IGF-1/IGF binding protein (IGFBP)-3 ratio.[44–48] Preclinically, insulin stimulates pathways that increase levels of free IGF-1, and both insulin and IGF-1 promote cell proliferation and inhibit apoptosis in colon cancer cells.[49–53] In one study, obesity and physical inactivity influenced colon cancer risk primarily through the insulin axis, but non-hyperinsulinemic (ie. non-overweight, physically active) men were still at elevated risk if they had high IGF-1 levels, suggesting that high circulating IGF-1 (or IGF-1/IGFBP-3 ratio) and hyperinsulinemia may represent two different axes that influence colorectal neoplasia risk.[54]

The presumed cause of disease recurrence and colorectal cancer-specific mortality in patients initially diagnosed with non-metastatic colorectal cancer is the growth of micrometastatic cells in distant organs. Physical activity, obesity and a Western pattern diet may influence insulin and insulin-like growth factors, which subsequently stimulate growth and inhibit apotosis of micrometastases. Among 373 patients diagnosed with nonmetastatic colorectal cancer in two prospective observational cohort studies, those in the top quartile of plasma C-peptide had an age-adjusted HR for death of 1.87 (95% CI: 1.04 to 3.36; P = 0.03 for trend), whereas those in the top quartile of circulating IGFBP-1 had a significant reduction in mortality (HR = 0.48; 95% CI: 0.28 to 0.84; P = 0.02 for trend), both compared to patients in respective bottom quartiles.

Other potential mechanisms for the influence of physical activity, adiposity and diet are alterations in vitamin D (as these host factors influence vitamin D levels), changes in hormones (particularly estrogen), inflammation and immune modulation.

Aspirin and Nonsteroidal Anti-inflammatory Agents (NSAIDs)

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) have long been studied as agents that may influence cancer development and progression.[55] Data from observational

studies and intervention trials consistently demonstrate that usage of these agents reduces the risk of colorectal adenomas and/or cancer.[55–60] Hypotheses for the mechanism of action of these agents include inhibition of the cyclooxygenase (COX) family of enzymes (increasing arachidonic acid which stimulates the conversion of sphingomyelin to ceramide that mediates apoptosis as well as altering prostaglandin production which will decrease angiogenic factors), inhibition of the activation of nuclear factor- -B, interference of the binding of peroxisome-proliferator–activated receptor (PPAR) to DNA and other potential non-COX-mediated pathways.[61] Regardless of the precise mechanism, the data is so consistent that causality with colorectal cancer development is generally accepted.

In a randomized trial of 517 patients with prior stage I–III colorectal cancer, patients randomized to 325 mg daily aspirin experienced a reduction in number of subsequent polyps (adjusted relative risk 0.65 [95% CI: 0.46–0.91]) as well as time to detection of a first adenoma (HR = 0.64 [95% CI: 0.43 – 0.94]).[62] Recently, two prospective cohorts of colorectal cancer survivors have suggested an association between use of aspirin or cyclooxygenase 2 (COX-2) inhibitors and cancer recurrence and survival in non-metastatic colorectal cancer patients. Chan and colleagues reported that among 1,279 stage I – III colorectal cancer survivors, those who regularly used aspirin after diagnosis experienced an adjusted HR for colorectal cancer specific mortality of 0.71 (95% CI: 0.53–0.95) and for overall mortality of 0.79 (95% CI: 0.65–0.97), compared to nonusers.[63] When restricting the analyses to the 719 participants who did not use aspirin before diagnosis, aspirin use initiated after diagnosis was associated with an adjusted HR for colorectal cancer specific mortality of 0.53 (95% CI: 0.33–0.86).

In the CALGB 89803 cohort of stage III colon cancer patients, regular aspirin use (defined as consistent use while on adjuvant therapy and 6 months after the completion of adjuvant therapy) had a statistically significant 54% improvement in disease-free survival compared to non-regular users.[64] A similar impact was seen in patients who were on COX-2 inhibitors (celecoxib or rofecoxib).

The Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) trial was a randomized controlled trial in the United Kingdom evaluating the role of rofecoxib for stage II and III colon cancer who completed adjuvant therapy.[65] The trial activated in April 2002 but was terminated in September 2004 after withdrawal of rofecoxib from the market. Prior to study closure, 2,434 patients were randomized to placebo, 2 years of rofecoxib or 5 years of rofecoxib, with a median duration of time on trial of 7.4 months. The hazard ratio for disease-free survival with median follow-up of 3 years was 0.90 (95% CI, 0.77 – 1.06), favoring rofecoxib amongst stage II and III patients.

Given these data, the Cancer and Leukemia Group B and Southwestern Oncology Group recently activated a randomized trial to test celecoxib as an adjunctive to standard therapy in stage III colon cancer patients (Figure 3). The trial has a 2 × 2 randomization design, with the first randomization of 6 versus 12 treatments of 5-FU, leucovorin and oxaliplatin (FOLFOX) and the second randomization of celecoxib versus placebo initiated with FOLFOX and continuing for three years. Data testing duration of FOLFOX therapy will be pooled with at least 3 other trials in Europe to test for noninferiority. The trial will test for superiority in disease-free survival of celecoxib compared to placebo.

Vitamin D

Increasing evidence suggests an association between vitamin D and development of colorectal cancer.[66] A meta-analysis of five epidemiologic studies found a 51% decrease in the risk of colorectal cancer associated with plasma 25(OH)D levels in the highest quintile compared to those in the lowest quintile (P<0.0001).[67] The cellular effects of 1–25-

dihydroxycholecalciferol [1,25(OH)2D] are principally mediated through the vitamin D receptor (VDR), which regulates the transcription of genes involved in cellular differentiation and inhibition of proliferation.[68,69] Well differentiated human colon cancer cell lines have higher VDR expression [70] and the antiproliferative effects of vitamin D only occur in cell lines expressing high levels of VDR.[71]

The role of vitamin D in cancer survivors has recently generated much interest.[72] Ng and colleagues reported results of a cohort of 304 participants of the Nurse's Health Study and Health Professional Follow-up Study who were diagnosed with colorectal cancer and had a serum vitamin D level at least 2 years prior to diagnosis and found that those with the highest level of pre-diagnosis vitamin D had a statistically significant 55% improvement in overall mortality compared to those with the lowest level.[73] In an expanded effort using those cohorts, Ng and colleagues predicted serum 25 (OH) D levels in 1,107 subjects using race, geographic region, dietary vitamin D intake, BMI, and physical activity.[74] Compared with levels in the lowest quintile, participants with predicted 25 (OH) D levels in the highest quintile had an adjusted HR of 0.50 (95% CI, 0.26–0.95) for cancer-specific mortality and 0.62 (95% CI, 0.42–0.93) for overall mortality.

Cigarette smoking

Smoking has been associated with the development of colorectal cancer and may contribute up to 22% of cases.[75,76] Using data from CALGB 89803, Jackson and colleagues recently reported no association between smoking status (current, past and never smoker) or total tobacco usage and disease-free survival amongst patients with stage III colon cancer.[77] However, when limiting analyses to early years smoking intensity, the adjusted HR for disease-free survival for subjects with at least 12 pack-years of smoking prior to age 30 was 1.37 (95% CI 1.02–1.84) compared to never smoking (p trend 0.04). These results imply that smoking early in life may eventually lead to more aggressive colon cancers with higher risk of recurrence.

Summary

Cancer survivors often seek answers as to what additional steps they can take to increase the likelihood of "beating" their cancer. Patients frequently ask their oncologist what they should eat, does exercise matter, what supplements to take, and what else they can do. As with chemotherapy, no such modifiable diet or lifestyle intervention is likely to benefit all patients. However, it is becoming increasingly evident that certain factors may influence some patients' outcome. There are clear limitations to these data at this point. The data are observational at this point, albeit prospective with efforts to minimize bias and confounding. A randomized clinical trial is currently underway to test exercise and another to test celecoxib as adjunct to standard adjuvant therapy. The data is also principally limited to non-metastatic colorectal cancer. There are current efforts to collect similar prospective data of diet, lifestyle and supplements in patients undergoing chemotherapy with metastatic colorectal cancer. Further, there are studies underwent to test potential tumor and host biomarkers that may predict more or less likelihood of benefit or detriment from certain diet and lifestyle factors. These data are needed to better define a set of guidelines for colorectal cancer survivors.

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Figure 1.
Colon Health and Life-Long Exercise Change Trial (CHALLENGE) Schema

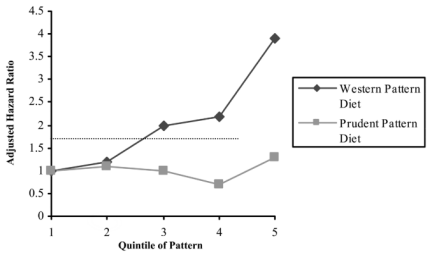

Figure 2.
Diet Patterns and Disease-Free Survival in Stage III Colon Cancer[35]

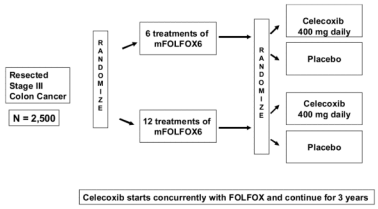

Figure 3.
Schema of CALGB/SWOG 80702 Phase III adjuvant therapy trial for stage III colon cancer patients

Table 1

Association between physical activity and outcome in colorectal cancer survivors

	CALGB 89803		Nurse's Health Study		Health Professionals Follow-up Study	
MET-hours/week	**Adjusted HR Disease-Free Survival (95% CI)**	**Adjusted HR Overall Survival (95% CI)**	**Adjusted HR for CRC-specific mortality (95% CI)**	**Adjusted HR for overall mortality (95% CI)**	**Adjusted HR for CRC-specific mortality (95% CI)**	**Adjusted HR for overall mortality (95% CI)**
< 3	Referent	Referent	Referent	Referent	Referent	Referent
3–8.9	0.87 (0.58–1.29)	0.85(0.49–1.49)	0.92 (0.50–1.69)	0.77 (0.48–1.23)	1.06 (0.55–2.08)	1.00 (0.68–1.48)
9–17.9	0.90 (0.57–1.40)	0.71 (0.36–1.41)	0.57 (0.27–1.20)	0.50 (0.28–0.90)	1.30 (0.65–2.59)	1.12 (0.74–1.70)
18–26.9	0.51 (0.26–0.97)	0.71 (0.32–1.59)	0.39 (0.18–0.82) for >18 MET-hrs/week	0.43 (0.25–0.74) for >18 MET-hrs/week	0.76 (0.33–1.77)	0.74 (0.46–1.20)
≥ 27	0.55 (0.33–0.91)	0.37 (0.16–0.82)			0.47 (0.24–0.92)	0.59 (0.41–0.86)
P trend	0.01	0.01	0.008	0.003	0.002	0.0003

CALGB = Cancer and Leukemia Group B; HR = hazard ratio; CRC = colorectal cancer

Table 2

Summary of studies of body mass index in colorectal cancer survivors

Author	Year of Diagnosis	Sample size	Stages of Disease	Outcome measure	Hazard Ratio (95% CI) or P value (compared to normal weight)
Tartter[78]	1976–1979	279	Duke B2, C1, C2 colon cancer	Recurrence rate	P = 0.003 for above median weight
Meyerhardt[19]	1988–1992	3759	Duke B2, B3, C colon cancer	Disease-free survival	1.11 (0.94–1.30) BMI ≥ 30 kg/m^2
				Overall survival	1.11 (0.96–1.29) BMI ≥ 30 kg/m
Meyerhardt [21]	1990–1992	1792	TNM Stage II and III rectal cancer	Disease-free survival	1.10 (0.91–1.32) BMI ≥ 30 kg/m^2
				Overall survival	1.09 (0.90–1.33) BMI ≥ 30 kg/m^2
				Local recurrences	1.31 (0.91–1.88) BMI ≥ 30 kg/m^2
Dignam [22]	1989–1994	4288	Duke B and C colon cancer	Disease-free survival	1.06 (0.93–1.21) BMI 30–34.9 kg/m^2 1.27 (1.05–1.53) BMI ≥ 35 kg/m^2
				Colon cancer events	1.04 (0.88–1.24) BMI 30–34.9 kg/m^2 1.38 (1.10–1.73) BMI ≥ 35 kg/m^2
Meyerhardt [20]	1999–2001	1053	TNM Stage III colon cancer	Disease-free survival	1.00 (0.72–1.40) BMI 30–34.9 kg/m^2 1.24 (0.84–1.83) BMI ≥ 35 kg/m^2
				Recurrence-free survival	0.97 (0.69–1.37) BMI 30–34.9 kg/m^2 1.27 (0.85–1.89) BMI ≥ 35 kg/m^2
				Overall survival	0.90 (0.61–1.34) BMI 30–34.9 kg/m^2 0.87 (0.54–1.42) BMI ≥ 35 kg/m^2
Hines [24]	1981–2001	496	TNM Stage I-IV colon cancer	Overall survival	0.77 (0.61–0.97) BMI ≥ 25 all stages 0.92 (0.65–1.30) stage I–II 0.92 (0.59–1.45) stage III 0.58 (0.37–0.90) stage IV

TNM = tumor, node, metastases staging; CI = confidence interval