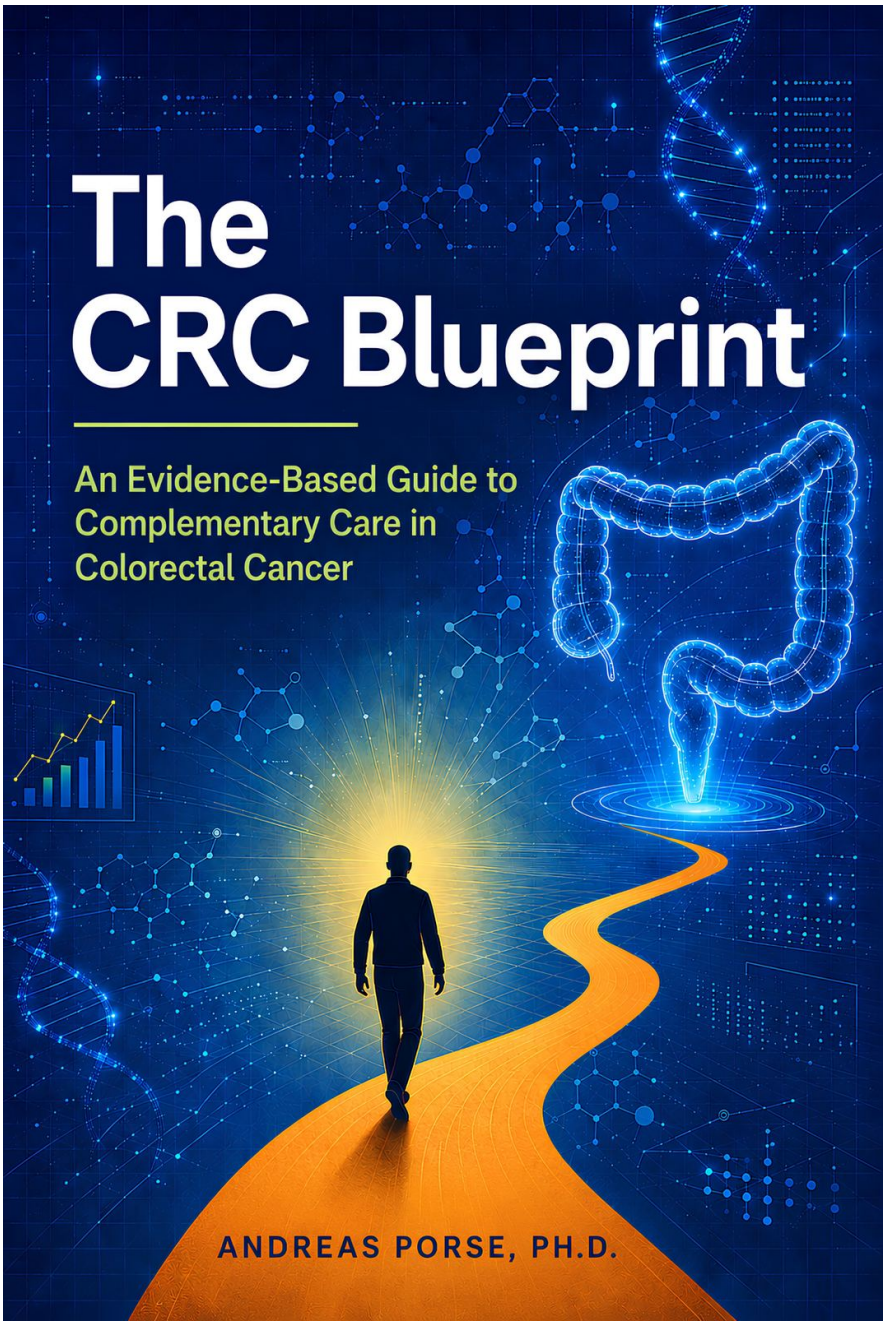
The
CRC Blueprint
An Evidence-Based Guide to Complementary Care in Colorectal Cancer
ANDREAS PORSE, PH.D.

The Colorectal Cancer Blueprint

An Evidence-Based Guide to Complementary Care in Colorectal Cancer

Andreas (Andy) Porse

Sample chapter

This is one complete chapter from *The Colorectal Cancer Blueprint*, reproduced exactly as it appears in the book. Every intervention in the full text is graded for evidence quality, effect size in colorectal cancer, and safety, using the colour-coded snapshot you will see at the top of the next page.

Chapter 6: Exercise and Colorectal Cancer

> **Chapter snapshot** · Evidence quality: **Very high** · Effect size in CRC: **High** · Safety: **Very high**

Regular moderate exercise reduces colon cancer recurrence by roughly 28% and death by 37%, making it one of the most powerful adjunctive interventions available to patients with colorectal cancer. The CHALLENGE trial, the first phase 3 RCT to demonstrate that a structured exercise programme improves survival in any cancer, reported a **6.4 percentage-point absolute improvement in 5-year disease-free survival** and a **7.1-point gain in 8-year overall survival** for stage III and high-risk stage II colon cancer patients randomised to exercise after chemotherapy. These effect sizes rival or exceed those of adding oxaliplatin to adjuvant fluoropyrimidine chemotherapy, yet exercise carries negligible toxicity. Before CHALLENGE, more than a dozen large observational studies and multiple meta-analyses had consistently linked post-diagnosis physical activity to 20–60% relative reductions in CRC-specific mortality, centred on the widely cited threshold of **≥18 MET-hours per week** (roughly five hours of brisk walking). With converging RCT, observational, and mechanistic evidence, exercise should now be regarded as a standard component of colon cancer survivorship care.

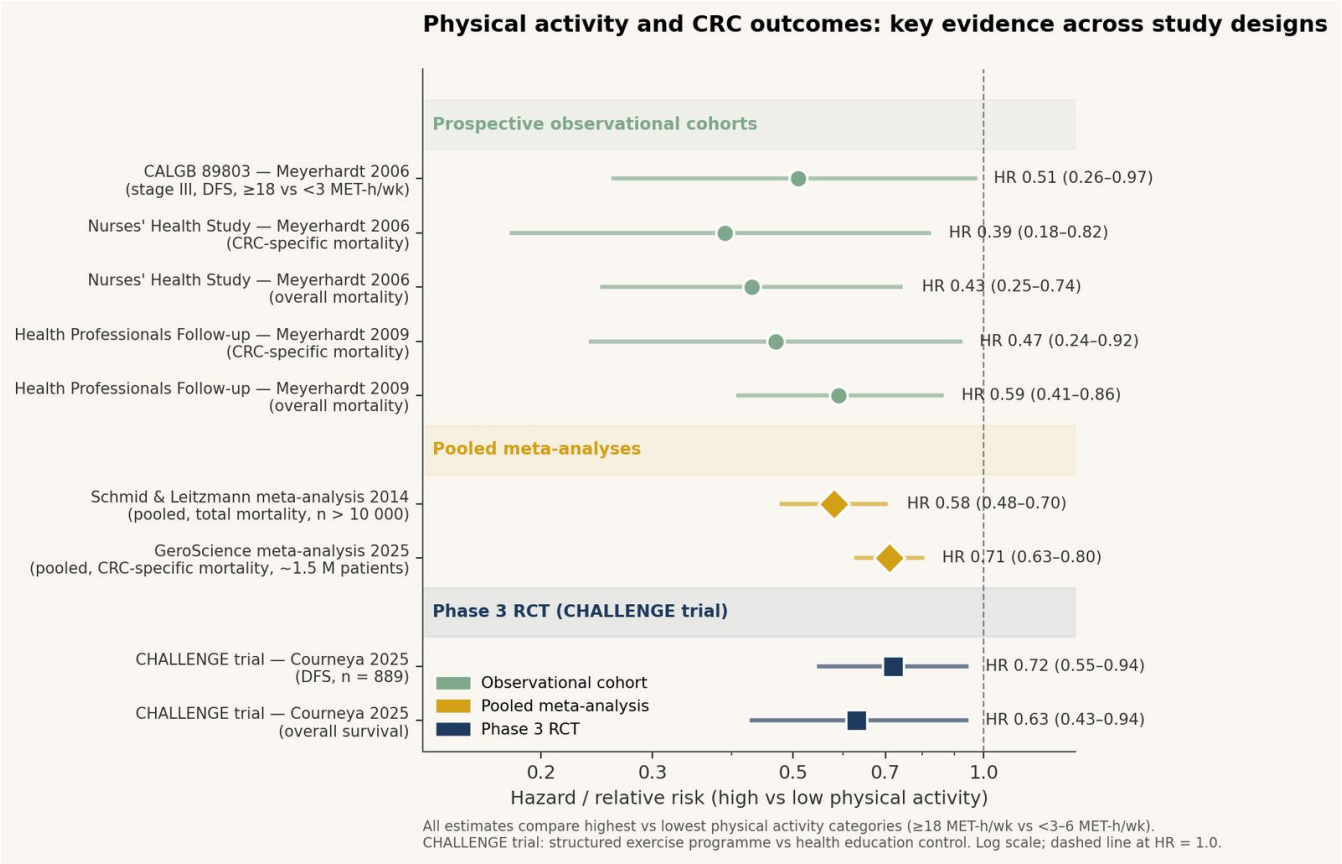

Figure 6.1. Hazard and relative risk estimates for physical activity and CRC outcomes across the major prospective observational cohorts, pooled meta-analyses, and the CHALLENGE phase 3 RCT. Every estimate lies to the left of HR = 1.0. The consistency of the signal across three decades, multiple countries, and three

independent levels of evidence is the defining feature of the exercise data in CRC.

The CHALLENGE trial changes the standard of care

The Colon Health and Life-Long Exercise Change (CHALLENGE) trial, published as Courneya et al. in the *New England Journal of Medicine* in July 2025 (Vol. 393, No. 1, pp. 13–25; DOI: 10.1056/NEJMoa2502760), is the landmark study in this field. Run by the Canadian Cancer Trials Group (CCTG CO.21) across **55 centres in six countries**, it randomised **889 patients** (445 exercise, 444 health education) with resected high-risk stage II or stage III colon adenocarcinoma who had completed adjuvant 5-fluorouracil–based chemotherapy 60–180 days earlier. Importantly, eligible patients had to be insufficiently active at baseline, exercising below 150 minutes per week of moderate activity.

The intervention was a **three-year structured aerobic exercise programme** delivered in phases. During Phase 1 (months 0–6), participants attended 12 biweekly face-to-face behavioural support sessions plus 12 supervised exercise sessions, gradually increasing recreational physical activity by at least **10 MET-hours per week**, equivalent to roughly 150 minutes of brisk walking. Phase 2 (months 6–12) individualised the target up to 20 MET-hours per week above baseline. Phase 3 (months 12–36) maintained monthly contact with a maximum of 27 MET-hours per week. Patients chose their own activities, walking, jogging, cycling, pickleball, guided by a personal Physical Activity Consultant using behavioural change techniques adapted from the Diabetes Prevention Program. The control group received standard health education materials but no structured programme, supervised sessions, or behavioural support.

At **median follow-up of 7.9 years**, the primary endpoint of disease-free survival (DFS) favoured the exercise group decisively. There were **93 DFS events in the exercise arm versus 131 in the control arm**, yielding a hazard ratio of **0.72 (95% CI 0.55–0.94; P = 0.02)**, a 28% relative reduction. Five-year DFS was **80.3% versus 73.9%** (absolute difference 6.4 percentage points; 95% CI 0.6–12.2). For overall survival, the results were even more striking: **41 deaths in the exercise group versus 66 in controls**, producing a hazard ratio of **0.63 (95% CI 0.43–0.94; P = 0.022)**, a 37% relative reduction. Eight-year overall survival reached **90.3% versus 83.2%**. Individual components showed fewer colon cancer recurrences (65 vs 81) and notably fewer new primary cancers (23 vs 42) in exercisers.

Safety was excellent. Musculoskeletal adverse events occurred in **19% of exercise versus 12% of control patients**, but only 10% of exercise-arm events were judged programme-related. No unexpected serious adverse events occurred. Quality of life improved significantly: SF-36 physical function scores showed a **mean change of 7.42 versus 1.10 at six months (P < 0.001)**. The exercise group also demonstrated sustained improvements in predicted VO_2max and six-minute walk distance across all three years. Body weight and waist circumference, however, did not differ between groups, suggesting the survival benefit operates through pathways beyond simple weight loss.

Critical appraisal should note that the trial enrolled 889 of a planned 962 patients over 15 years (2009–2024), and the event rate was lower than anticipated (224 of 380 planned events). The population was relatively young (median age 61), predominantly stage III (90%), and non-obese. Nearly half of exercise-arm patients did not complete treadmill testing at three years, raising adherence questions, though the intent-to-treat analysis

preserved the benefit. Detailed subgroup analyses by age, sex, BMI, MSI status, and chemotherapy regimen have not been publicly released but are expected in the supplementary appendix. Correlative biomarker analyses examining insulin, cytokines, and immune markers are ongoing.

From the CHALLENGE data, the **number needed to treat** to prevent one DFS event at five years is approximately **16** (1/0.064), and to prevent one death at eight years approximately **14** (1/0.071). These figures compare very favourably with most adjuvant oncology interventions.

Observational evidence consistently shows 30–50% risk reductions

The observational foundation supporting exercise in CRC survival is unusually robust, spanning multiple independent cohorts over two decades.

The sentinel study is **Meyerhardt et al. (JCO 2006; 24:3535–3541)**, a prospective analysis nested within the CALGB 89803 adjuvant chemotherapy trial. Among **832 patients with stage III colon cancer**, those engaging in **18.0–26.9 MET-hours per week** (roughly four hours of brisk walking weekly) had a disease-free survival hazard ratio of **0.51 (95% CI 0.26–0.97)** versus those below 3 MET-hours per week, a 49% relative risk reduction. Spline analysis showed measurable benefit beginning at **6–12 MET-hours per week**, with a plateau beyond approximately 30–35 MET-hours per week. These findings were consistent across subgroups defined by sex, BMI, nodal involvement, and chemotherapy regimen.

In the **Nurses' Health Study (Meyerhardt et al., JCO 2006; 24:3527–3534)**, 573 women with stage I–III CRC who achieved ≥18 MET-hours per week post-diagnosis had a CRC-specific mortality hazard ratio of **0.39 (95% CI 0.18–0.82; P for trend = 0.008)** and an overall mortality hazard ratio of **0.43 (95% CI 0.25–0.74; P for trend = 0.003)**. Women who increased activity from pre- to post-diagnosis showed a CRC-specific mortality HR of **0.48 (95% CI 0.24–0.97)**, while decreasers showed non-significant trends toward worse outcomes. Critically, pre-diagnosis activity alone was not predictive of survival after adjustment, it is post-diagnosis exercise that matters.

The complementary **Health Professionals Follow-up Study (Meyerhardt et al., Arch Intern Med 2009; 169:2102–2108)** examined **668 men** with stage I–III CRC. Those exercising above 27 MET-hours per week had a CRC-specific mortality HR of **0.47 (95% CI 0.24–0.92; P for trend = 0.002)** and an overall mortality HR of **0.59 (95% CI 0.41–0.86; P for trend = 0.0003)**. Ten-year CRC-specific survival was 88% at the highest activity level versus 79% at the lowest.

A critical confirmatory study is **Brown et al. (JCO 2023; 41:243–254)**, which replicated the CALGB 89803 findings in a contemporary cohort of **1,696 stage III patients** from the CALGB/SWOG 80702 trial who received modern FOLFOX-based chemotherapy. Three-year DFS was **87.1% for patients achieving ≥18 MET-hours per week versus 76.5% for those below 3 MET-hours per week**, an absolute difference of 10.6 percentage points (95% CI 4.7–19.4; P < 0.001). Both light-to-moderate and vigorous activity showed significant associations, and muscle-strengthening exercise independently predicted improved DFS (3-year DFS 88.8% vs 81.8%; P = 0.003). This study established that the exercise benefit persists in the oxaliplatin era.

Meta-analyses have pooled these data with high consistency. **Schmid and Leitzmann (Ann Oncol 2014; 25:1293–1311)** found that post-diagnosis physical activity in CRC survivors was associated with a total mortality relative risk of **0.58 (95% CI 0.48–0.70)** and CRC-specific mortality RR of **0.61 (95% CI 0.40–0.92)**, with each 10 MET-hours per week increase conferring a **28% decrease in total mortality** (95% CI 20–35%). **Je et al. (Int J Cancer 2013; 133:1905–1913)** pooled seven studies and found high post-diagnosis activity associated with a CRC-specific mortality RR of **0.65 (95% CI 0.47–0.92)**. The most recent large-scale analysis, a 2025 *GeroScience* meta-analysis of 151 cohorts and approximately 1.5 million cancer patients, found CRC-specific mortality HR of **0.71 (95% CI 0.63–0.80)** for the most versus least active patients. The World Cancer Research Fund's CUP Global 2024 review graded this evidence as "limited-suggestive," reflecting the inherent limitations of observational data, while acknowledging effect estimates of **0.69 (95% CI 0.62–0.77)** for all-cause mortality.

The dose-response relationship is non-linear. Initial benefits emerge at **6–12 MET-hours per week**, approximately equivalent to three hours of moderate walking. The most commonly cited inflection point is **18 MET-hours per week**, about five hours of brisk walking or 2.5 hours of jogging. Beyond **30–35 MET-hours per week**, additional benefit appears to plateau. This reassuring pattern means patients do not need to become marathon runners; consistent moderate activity delivers the vast majority of the survival benefit.

Eight interconnected mechanisms explain the exercise effect

Figure 6.2. The eight mechanisms by which structured exercise affects colorectal cancer biology. Exercise reduces insulin and IGF-1 signalling, lowers systemic inflammation (CRP, IL-6, TNF-α), enhances NK-cell and CD8 T-cell mediated tumour surveillance, modifies body composition and the pro-tumourigenic adipokine milieu, accelerates colonic transit, reshapes the gut microbiome toward butyrate producers, drives epigenetic changes through HDAC modulation, and reduces COX-2/PGE_2 signalling. The mechanisms are interlocking, not independent, which is why exercise's effect on outcomes is larger than any single pathway would predict.

The biological plausibility of exercise as an anti-cancer intervention rests on at least eight converging mechanisms, each supported by dedicated experimental and clinical evidence.

Insulin and IGF-1 axis modulation forms the theoretical cornerstone. McKeown-Eyssen (Cancer Epidemiol Biomarkers Prev, 1994) and Giovannucci (Cancer Causes Control, 1995) independently proposed that hyperinsulinemia, driven by obesity and sedentary behaviour, promotes colonocyte proliferation through insulin receptor and IGF-1 receptor signalling via the **PI3K/AKT/mTOR pathway**. Exercise reduces circulating insulin and increases IGF-binding protein-3 (IGFBP-3), decreasing bioavailable IGF-1. An RCT by Fairey et al. (Cancer Epidemiol Biomarkers Prev, 2003) demonstrated that 15 weeks of aerobic training reduced IGF-1 by 7.4 ng/mL and increased IGFBP-3 by 180.5 ng/mL. Among CRC patients in the Melbourne Collaborative Cohort, exercisers with high IGFBP-3 levels were approximately half as likely to die of CRC (HR 0.44; 95% CI 0.25–0.76).

Anti-inflammatory effects are robust and well-quantified. A 2025 meta-meta-analysis encompassing 30,017 participants found exercise significantly reduced CRP (pooled effect -0.380), IL-6 (-0.468), and TNF-α (-0.430). In the COURAGE trial of CRC survivors, low-dose exercise (150 min/week) reduced high-sensitivity CRP by **35.4%** and IL-6 by **29.6%**. The exercise-inflammation story is nuanced: acute muscle contraction releases IL-6 as a myokine, which paradoxically triggers anti-inflammatory cascades including IL-10 and IL-1 receptor antagonist, while suppressing TNF-α. Pedersen and Febbraio (Physiological Reviews, 2008) established skeletal muscle as an endocrine organ releasing anti-inflammatory myokines including SPARC, which has been shown to directly suppress colon tumorigenesis by increasing apoptosis, and irisin, which has independent anti-neoplastic properties.

Immune enhancement may be the most mechanistically compelling pathway. The seminal study by Rundqvist et al. (eLife, 2020) demonstrated that exercise-induced tumour control requires CD8+ T cells, their depletion completely abolished the anti-tumour effect. Acute exercise increases circulating NK cells by approximately **130%** and CD8+ T cells by **34%**, with exercise-induced epinephrine promoting immune cell recruitment into tumours through upregulated CXCL10 and CXCL12 chemokines. Exercise also normalises tumour vasculature, improving T cell infiltration. In Lynch syndrome patients, a 12-month aerobic programme sustained enrichment of cytotoxic CD8+ T cells in colonic epithelium. The traditional J-curve hypothesis holds that moderate exercise enhances immune function while overtraining may be immunosuppressive, though most evidence suggests the anti-tumour window is broad.

Body composition changes reduce the pro-tumorigenic adipokine milieu. Visceral adiposity independently increases CRC risk by approximately **7% per 2 kg/m² BMI gain**. Exercise reduces leptin (a pro-tumorigenic adipokine; meta-analysis showing reductions of approximately 5.66 ng/mL), increases adiponectin (anti-tumorigenic, promoting AMPK-mediated cell cycle arrest), and combats sarcopenia, which independently predicts shorter OS in CRC (HR 1.91; 95% CI 1.61–2.27). **Reduced colonic transit time** from physical activity decreases mucosal exposure to secondary bile acids and other luminal carcinogens. The Norwegian Nord-Trøndelag Health Study elegantly demonstrated that the exercise–colon cancer inverse association was strongest in the **transverse (HR 0.44) and sigmoid colon (HR 0.48)**, precisely the slowest-transit segments, lending strong support to this mechanism.

Microbiome modification is an emerging frontier. Allen et al. (Med Sci Sports Exerc, 2018) demonstrated that six weeks of endurance exercise increased butyrate-producing bacteria (*Faecalibacterium*, *Roseburia*, *Lachnospira*) and fecal butyrate concentrations, effects that reversed with return to sedentary behaviour. Butyrate functions as a natural HDAC inhibitor in colonocytes, re-expressing silenced tumour suppressor genes and inducing apoptosis in transformed cells while serving as the preferred energy source for healthy colonocytes, a metabolic selectivity that targets cancer cells preferentially. This connects directly to **epigenetic reprogramming**: exercise-induced changes in DNA methylation, histone acetylation (partly butyrate-mediated), and miRNA expression (including the oncomiR miR-21, tumour suppressors miR-143 and miR-145) collectively modulate CRC-relevant pathways. Finally, exercise may reduce **COX-2/PGE_2 signalling**, the same pathway targeted by aspirin and NSAIDs, decreasing immunosuppressive PGE_2 in colonic mucosa without the gastrointestinal toxicity of chronic NSAID use.

These mechanisms operate as an interconnected network. Visceral fat reduction (body composition) improves insulin sensitivity (insulin axis) and reduces chronic inflammation (inflammatory pathway). Exercise-driven microbiome changes increase butyrate (microbiome), which acts as an HDAC inhibitor (epigenetics). Reduced inflammation permits more effective immune surveillance (immune function). This overlapping, synergistic architecture likely explains the remarkably consistent epidemiological signal across diverse populations and study designs.

Exercise during chemotherapy is safe and may improve tolerance

A consistent concern among patients and oncologists is whether exercise is safe during adjuvant FOLFOX or CAPOX chemotherapy. The evidence is reassuring. In a study of **39 CRC patients undergoing FOLFOX** (Shim et al., Cancer Manag Res 2019), the exercise group had a **fivefold lower probability of chemotherapy dose adjustment** (OR 0.188; P = 0.023; 95% CI 0.044–0.793) and significantly fewer grade 3/4 nausea events (P = 0.018) and neurotoxicity events (P = 0.024). The ACT trial (van der Schoot et al., JACC: CardioOncology, 2022; N = 266) found exercise safely performed during chemotherapy with 75% adherence, and demonstrated that starting exercise during, rather than after, chemotherapy prevented **3.1 mL/kg/min more VO_2peak decline** than waiting. A small randomised crossover trial (Thomas et al., Support Care Cancer, 2020) even demonstrated that low-intensity cycling during chemotherapy infusion was safe with zero adverse events.

The effect on chemotherapy-induced fatigue represents one of the strongest evidence areas in exercise oncology. The definitive meta-analysis by **Mustian et al. (JAMA Oncology 2017)**, pooling 113 RCTs and 11,525 participants, found exercise produced a weighted effect size of **0.30 (95% CI 0.25–0.36; P < 0.001)** for fatigue reduction, significantly superior to pharmaceutical interventions, which achieved only 0.09 (P = 0.05, not significant). A 2023 network meta-analysis ranked combined aerobic plus resistance exercise first among all modalities (SUCRA 97.2%). Exercise is, put simply, the most effective treatment for cancer-related fatigue, more effective than any drug.

For oxaliplatin-induced peripheral neuropathy (CIPN), the evidence is promising but less mature. Kleckner et al. (Support Care Cancer, 2018) demonstrated that six weeks of home-based walking and resistance exercise reduced hot/coldness symptoms by 0.46 units on a 10-point scale (P = 0.045) in a 355-patient phase III trial. Zimmer et al. (Support Care Cancer, 2018) showed that an eight-week multimodal programme counteracted CIPN progression

in metastatic CRC patients. Combined sensorimotor, balance, and resistance training appears most beneficial, though dedicated large-scale CRC-specific trials are needed.

Practical exercise timing around infusions follows a straightforward pattern. Expert consensus suggests avoiding vigorous exercise on infusion days and keeping intensity low for 24–48 hours afterward. Most intervention studies schedule supervised sessions on non-infusion days, typically two to three times per week, with light walking encouraged on infusion days as tolerated. The key message is that chemotherapy is not a reason to stop moving, it is a reason to start.

Prehabilitation before surgery and the return to activity

Prehabilitation, structured exercise before colorectal surgery, improves postoperative outcomes measurably. A 2025 meta-analysis in the *Journal of the American Geriatrics Society* (14 articles, 2,314 patients) found prehabilitation reduced **length of hospital stay by 2.47 days** (95% CI 1.39–3.56), overall complication rates by **26%** (OR 0.74; 95% CI 0.59–0.94), and time to first flatus by 0.43 days. A separate meta-analysis of five RCTs (Cureus, 2025; 422 patients) confirmed a **40% reduction in overall postoperative complications** (OR 0.60; 95% CI 0.42–0.86; P = 0.02) and improved six-minute walk distance by **50.8 metres** at eight weeks post-surgery. Programmes typically span **four weeks**, combining moderate aerobic exercise, resistance training, inspiratory muscle training, and nutritional optimisation.

Returning to exercise after colorectal surgery follows a graded timeline. Mobilisation begins within 24 hours as part of Enhanced Recovery After Surgery (ERAS) pathways, gentle walking for 15–20 minutes two to three times daily. During weeks two through six, progressive walking continues with no lifting above 2–3 kg. At **six weeks**, most surgeons clear patients for non-impact aerobic exercise (cycling, elliptical) and light resistance training, avoiding direct core exercises. By **twelve weeks**, core strengthening and full activity progression are generally appropriate. Patients with stomas require particular attention: parastomal hernia risk necessitates avoiding heavy lifting for 12 weeks, using stoma support belts during exercise, and progressing core strengthening cautiously from pelvic tilts to more demanding exercises. Contact sports and swimming are generally not recommended for colostomy patients. After low anterior resection with anastomosis, excessive intra-abdominal pressure (heavy Valsalva manoeuvres) should be avoided in the early weeks, and pelvic floor rehabilitation is particularly important.

What to recommend: translating evidence into practice

The **2019 ACSM International Multidisciplinary Roundtable** (Campbell et al., Med Sci Sports Exerc 2019; 51:2375–2390), based on over 1,000 RCTs, provides the foundational framework. Cancer survivors should accumulate at least **150 minutes per week of moderate-intensity aerobic activity** (or 75 minutes vigorous), plus resistance training involving major muscle groups **at least twice weekly**. The American Cancer Society has suggested increasing toward **225 minutes per week** for appropriate patients. Every patient should, at minimum, "avoid inactivity."

For CRC patients specifically, the evidence favours **combined aerobic and resistance training** over either modality alone. Aerobic exercise carries the strongest epidemiological survival evidence, while resistance

training independently predicts improved DFS (Brown et al., 2023) and is essential for combating chemotherapy-induced sarcopenia. A practical prescription includes aerobic sessions of 20–30 minutes at moderate intensity (60–80% maximum heart rate) at least three times weekly, plus resistance training of 6–10 exercises at 1–4 sets of 8–15 repetitions at ≥50% of one-repetition maximum, two to three times weekly.

The MET concept deserves plain-language explanation for patients. One MET equals the energy cost of sitting quietly. Walking at a normal pace is roughly 3 METs; brisk walking reaches 3.5–4 METs; cycling at moderate effort is 4–6 METs; jogging hits 7–8 METs; and swimming laps approximately 8 METs. The survival-associated threshold of **18 MET-hours per week** translates to roughly five hours of brisk walking, or one hour of brisk walking five days per week. The CHALLENGE trial targeted an increase of 10 MET-hours per week, approximately 2.5 additional hours of moderate activity weekly, and this proved sufficient to generate significant survival benefits.

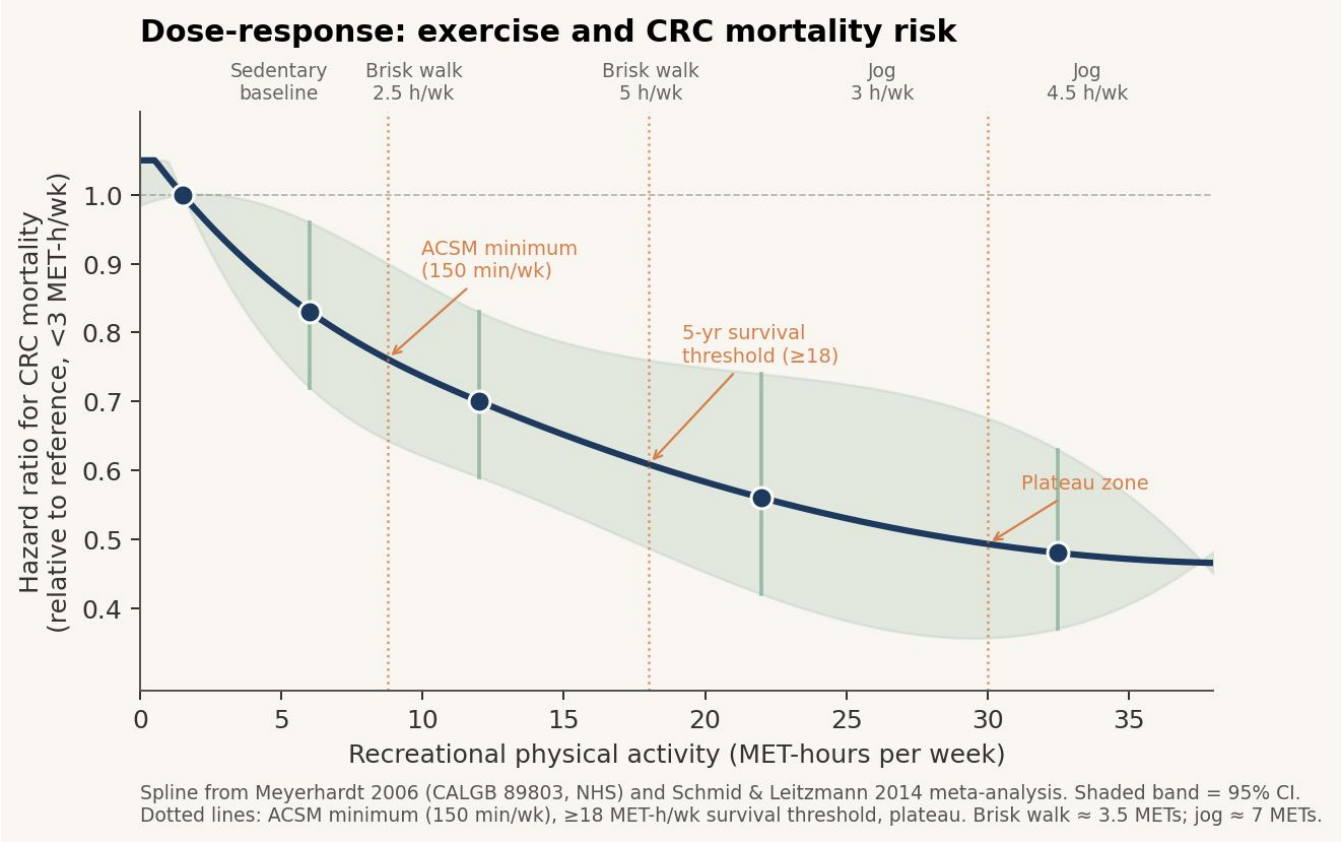

Figure 6.3. Dose-response between weekly physical activity (MET-hours per week) and CRC-specific mortality. The curve flattens after roughly 18 MET-hours per week. Three reference markers are shown: the ACSM minimum of 150 min/week, the survival inflection at ~18 MET-h/week, and the plateau zone above ~30 MET-h/week. For perspective: brisk walking ≈ 3.5 METs; jogging ≈ 7 METs. Most of the benefit is captured by reaching the 150-minute mark.

The recommended progression spans three treatment phases. During the post-surgical recovery phase (0–12 weeks), the focus is on gentle walking and early mobilisation. During chemotherapy, supervised exercise two to three times weekly for 60 minutes (combining endurance, resistance, and balance work) is feasible and safe, with

intensity modulated around infusion cycles. In the survivorship phase, the goal is reaching and sustaining ≥150 minutes per week of moderate aerobic activity plus twice-weekly resistance training. The CHALLENGE trial demonstrated that structured behavioural support, a dedicated exercise consultant, personalised prescription, regular check-ins, and progressive goal-setting, was critical to sustained adherence. As trial participant Terri Swain-Collins, a 62-year-old from Kingston, Ontario who remains cancer-free, noted: "That sense of accountability made all the difference. being told to exercise by a physician wouldn't have been enough; having someone walk alongside me, guide me and check in regularly was what made it possible."

Molecular subtypes and the frontier of precision exercise oncology

Whether exercise benefits differ by CRC molecular subtype is an emerging and largely unanswered question. The most informative study is **Hardikar et al. (Cancer Epidemiol Biomarkers Prev, 2015)**, which stratified the exercise–survival association by BRAF, KRAS, and MSI status in 1,309 patients from the Seattle Colon Cancer Family Registry. The finding was notable: **the beneficial association of physical activity with survival was not specific to any particular molecular subtype**. Higher pre-diagnostic recreational activity was associated with improved OS (HR 0.70; 95% CI 0.52–0.96) consistently across all molecular strata examined.

The most intriguing hypothesis concerns MSS (microsatellite-stable) tumours, the immunologically "cold" majority that respond poorly to checkpoint inhibitors. Exercise-induced NK cell mobilisation, CD8+ T cell activation, tumour vascular normalisation, and myokine release could theoretically convert cold tumours toward a more immunologically active phenotype. Preclinical support comes from Gouez et al. (Front Immunol, 2024), who showed that acute exercise before immuno-chemotherapy in the MC38 murine CRC model (an MSS-like model) significantly decreased early-phase tumour growth and increased T cell infiltration. Whether this translates to differential clinical benefit in MSS versus MSI-H patients remains untested in humans.

The PIK3CA mutation–aspirin interaction provides a tantalising parallel. The ALASCCA trial (NEJM, 2025) confirmed that low-dose aspirin reduced recurrence by **51%** (HR 0.49) specifically in PI3K-altered CRC, an effect mediated through COX-2/PGE_2 inhibition and PI3K pathway modulation. Exercise operates on overlapping pathways: reducing insulin/IGF-1 signalling through the same PI3K/AKT/mTOR cascade and suppressing COX-2-dependent inflammation. No clinical study has yet tested whether exercise benefit is greater in PIK3CA-mutant CRC, but this represents a compelling research hypothesis for the next generation of exercise oncology trials.

The CHALLENGE trial's planned correlative biomarker analyses, examining blood samples for insulin, IGF-1, cytokines, NK cell activity, and T cell function, should begin to illuminate which biological pathways mediate the observed survival benefit and may reveal subtype-specific effects.

Conclusion: the confidence interval for exercise

The totality of evidence supports a summary statement with high confidence: **regular moderate exercise is associated with an estimated 25–40% relative reduction in recurrence risk and a 6–7 percentage-point absolute improvement in 5-year disease-free survival for stage III colon cancer patients.** The CHALLENGE trial's HR of 0.72 for DFS and 0.63 for overall survival anchors the RCT evidence, while observational meta-analyses consistently cluster between HR 0.58 and 0.77 for post-diagnosis activity and cancer-specific mortality. The number needed to treat, approximately **16 patients exercising for five years to prevent one recurrence event**, and **14 to prevent one death over eight years**, is competitive with or superior to many approved pharmaceutical interventions. The 37% relative reduction in mortality reported in CHALLENGE may represent the upper bound of plausible effect, and critical appraisal rightly notes potential performance bias in an open-label trial. But even conservative estimates place exercise among the most impactful modifiable factors in CRC survivorship.

What distinguishes exercise from other complementary interventions is the convergence of evidence across multiple levels: a positive phase 3 RCT, more than a dozen concordant observational studies, consistent meta-analytic findings, plausible and well-characterised biological mechanisms operating through at least eight independent pathways, demonstrated safety during chemotherapy, and clear practical guidelines for implementation. No other lifestyle or complementary intervention in oncology can claim this breadth of supporting evidence. The remaining questions, whether benefit varies by molecular subtype, which biological mediators are most important, and how to achieve sustained adherence at scale, represent the next frontier. For the clinician advising a patient today, the evidence is clear: structured, moderate exercise should be prescribed alongside chemotherapy, surveillance, and supportive care as a standard component of colon cancer treatment.

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About the full book

The Colorectal Cancer Blueprint runs to 305 pages across 31 chapters, drawing on more than 360 peer-reviewed studies, meta-analyses, and clinical trials, with over 60 illustrations and graphs. It covers the biology and staging of the disease, the lifestyle levers with the strongest outcome data, an evidence-graded review of the supplement toolkit, repurposed drugs, an integrated chemotherapy cycle protocol, and ctDNA monitoring.

Written by a molecular biologist who is also a colorectal cancer patient.