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Diet and Lifestyle in Colorectal Cancer Survivors

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Synopsis

Much research supports the association between diet and lifestyle in the development of colorectal cancer. Recent studies have demonstrated an association between various energy balance host factors, including obesity, physical inactivity and certain dietary factors, and outcomes. In this review, we will summarize the impact of modifiable lifestyle factors including pre- and post-diagnosis adiposity, physical activity, and diet on prognosis of colorectal cancer patients. We will focus on associations of these factors in stage I–III colorectal cancer survivors and also summarizes the possible mechanisms for the association between modifiable lifestyle factors and prognosis of colorectal cancer patients.

Introduction

The American Cancer Society estimates that there are more than 1.1 million colorectal cancer survivors in United States.[1] Colorectal cancer survivors constitute 10 percent of the entire number of cancer survivors and the number is increasing.[2] Both genetic and lifestyle factors contribute to cancer development and prognosis of colorectal cancer. Since lifestyle factors such as obesity, physical inactivity, diet, smoking, and alcohol consumption could be modifiable[3,4] while genetic factors are not, much attention have been paid to the impact of lifestyle factors on incidence and prognosis of colorectal cancer.

Changing these modifiable factors toward healthy lifestyle may be crucial components of cancer treatment in addition to standard treatments to prevent recurrence and improve survival of colorectal cancer patients. While an increasing number of studies have examined the association of diet and lifestyle factors with cancer recurrence and survival outcome in locally advanced colorectal cancer patients[5–9], it is important to distinguish whether these exposures were measured before or after cancer diagnosis. For example, adiposity before diagnosis and after diagnosis may have different impact on survival outcomes of colorectal cancer patients. Exposures after diagnosis associated with prognosis of cancer may provide

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important implications on directing recommendations to cancer survivors. However, if an association exists only between pre-diagnosis adiposity and prognosis of colorectal cancer, it is less certain how to guide a patient but such data may be important towards understanding the biology of colorectal cancer.

In this review, we will summarize the associations of modifiable lifestyle factors including pre- and post-diagnosis adiposity, physical activity, and diet on prognosis of colorectal cancer patients. Given that most published data to date is from patients without metastatic disease, we will focus on associations of these factors in stage I–III colorectal cancer survivors. This review also summarizes the possible mechanisms for the association between modifiable lifestyle factors and prognosis of colorectal cancer patients.

I. Association between the pre-diagnosis lifestyle factors and risk of mortality in colorectal cancer survivors

Adiposity

Several studies have examined the association between pre-diagnosis adiposity and colorectal cancer prognosis (Table 1).[6,10–13] Those studies used a variety of metric for adiposity, including body mass index (BMI), waist-hip ratio (WHR), and waist circumference (WC). Campbell et al[6] examined 2,303 men and women with stage I–III colorectal cancer and reported that those with BMI higher than 25 kg/m^2 had worse colorectal cancer-specific mortality and all-cause mortality. Similarly, Doria-Rose et al[10] studied 633 postmenopausal women with colorectal cancer and reported that obese patients (BMI ≥ 30 kg/m^2) had a 2.1-fold higher risk of colorectal cancer specific-mortality and all-cause mortality compared to normal weight patients.

Other studies have reported similar findings when employing alternative measurements for adiposity such as percent body fat, WC, and WHR. Heydon et al[14] reported that colorectal cancer patients with increasing WC per 10 cm had a 1.33 times higher risk of disease-specific death. The authors concluded that pre-diagnosis abdominal obesity might be a critical risk factor for mortality in patients with all-cause mortality, and made the recommendation for maintaining a normal weight and WC. In a study that compared BMI, weight, WHR and WC, Prizment et al[11] reported that while higher BMI (≥25 kg/m^2) and weight (≥140 pounds) were not significantly associated with colon cancer mortality, higher WHR (≥ 0.81) and WC (≥32.5 inch) were significantly associated with mortality. This study suggested that WHR and WC, which reflect abdominal adiposity, might be better predictors of colon cancer mortality, compared to BMI and weight.

Physical activity

Reports on association between the level of physical activity before cancer diagnosis and the risk of mortality in colorectal cancer patients have been mixed (Table 2).[12,14–17] Some studies found significant associations between level of pre-diagnosis physical activity levels[12,14] and the risk of mortality while others have found no association.[15] Meyerhardt et al[15] studied stage I–III female colorectal cancer patients and did not find any association between the level of pre-diagnosis physical activity and the risk of mortality. On the other

hand, Haydon et al[14] found that pre-diagnosis physical activity level was significantly associated with increased disease-specific survival. We have recently performed a meta-analysis of the association between pre-diagnosis physical activity and the risk of mortality in stage I–III colorectal cancer patients.[7] The meta-analysis demonstrated that colorectal cancer patients who participated in any amount of physical activity exhibited 25% and 24% risk reduction in colorectal cancer-specific death and death from all cause, respectively, compared with patients who did not participate in any physical activity. The study also found a dose dependent risk reduction in colorectal cancer-specific death and all-cause death, suggesting that those who participated in more physical activity before diagnosis have a lower risk of recurrence and death after the completion of standard therapy.

Diet

While there are diverse dietary factors related to the development of colorectal cancer,[18] few studies have focused on diet before diagnosis and mortality for colorectal cancer patients (Table 3).[8,19,20] Among the diverse dietary factors, there is relatively consistent evidence that red and processed meat is related to an increased risk of colorectal cancer.[21] Recently, McCullough et al[8] have collected diet information from 2,315 participants diagnosed with colorectal cancer in 1992–1993, 1999, and 2003 and followed their mortality through December 31st, 2010. They reported that those with higher red and processed meat intake (4th quartile) before cancer diagnosis had 29% and 63% increase in all-cause and cardiovascular disease mortality, respectively, compared with those with low red and processed meat intake (1st quartile). They did not observe association between amount of red and processed meat intake and colorectal cancer specific mortality. Furthermore, Zell et al[19] studied 511 colorectal cancer patient (144 Familial and 376 Sporadic colorectal cancer) and found that those who had high meat intake had reduced 10 year overall survival (4th quartile 42% vs. 1–3rd quartile 65%) and 2.24 times increased risk of death in an adjusted analysis compared with those who had low meat intake among familiar colorectal cancer patients. No association was observed between amount of meat intake and overall survival in sporadic colorectal cancer patients. Additionally, Zhu et al[20] performed a one-year recall of meat intake in 529 colorectal cancer survivors and reported that the highest quartile of processed meat intake was significantly associated with poorer disease-free survival (hazard ratio (HR): 1.82,95% CI: 1.07–3.09) and overall survivor (HR:2.13, 95% CI:1.03–4.43) in colon cancer patients. However, they did not observe any significant association between amount of processed meat intake and survivor outcomes in rectal cancer patients. Furthermore, they found no associations between prudent vegetable or the high-sugar pattern and disease-free and overall survivor in colon and rectal cancer patients.

Mechanism for Pre-diagnosis Energy Balance Factors and Outcomes

Several hypotheses on why energy balance-associated host factors before diagnosis may negatively impact on the prognosis of colorectal cancer have been proposed. First, many patients who with unfavorable energy balance (ie. obese or physically inactive) prior to diagnosis will have similar situation after diagnosis. Obesity and physical inactivity are associated with insulin resistance and subsequent hyperinsulinemia, which is linked to increased cancer risk and mortality due to its inducing insulin-like growth factors (IGFs) that promote cancer growth.[22] Colorectal cancer patients with higher levels of C-peptide (a

breakdown product of insulin production at the time of diagnosis) have shown higher mortality compared with those patients who had lower levels of C-peptide.[23] Also, these host factors induce an increasing level of tumor necrosis factor (TNF)-α, interleukin (IL)-6, or leptin that promotes cancer growth, along with a decreasing level of adiponectin that also promotes cancer growth.[24–29] Given that the primary risk for patients with stage I–III colorectal cancer is growth of occult micrometastases, such growth factors can stimulate micrometastases to lead to recurrent disease.

Pre-diagnosis obesity or physical inactivity may impact the molecular nature of the colorectal cancer that develops, leading to more aggressive histology. For example, obesity and physical inactivity are associated with the development of CTNNB1 (β-Catenin) negative colorectal cancer.[30] CTNNB1 tumors have a trend towards worse colorectal cancer-specific survival.[31] In obese patients, nuclear CTNNB1 negativity was associated with significantly worse cancer-specific and overall survival. Similarly, among nuclear CTNNB1-negative stage I–III patients, post-diagnosis physical activity was associated with significantly better cancer-specific survival while physical activity was not associated with survival among nuclear CTNNB1-positive stage I–III patients.

In terms of red and processed meat and survival, prior research has indicated that several factors may be instrumental in cancer development. Such factors include the: 1) production of heterocyclic amines when meat is cooked at high temperature,[32] 2) involvement of N-nitroso compounds from the heme in the gastrointestinal tract, [33,34] and 3) use of nitrosamines, N-nitroso compounds and their precursors, due to nitrite or nitrate use in the preservation of meat.[35] However, it is unclear if increased exposure to these factors will lead to more aggressive cancers.

II. Association between post-diagnosis lifestyle factors and the risk of mortality

Adiposity

Reports on post-diagnosis BMI and outcomes in colorectal cancer have been mixed (Table 4).[5,6,12,36–41] Some studies showed that being obese may have negative impact on survival of colorectal cancer[6,36,37,41] while other studies showed that there is no association between post-diagnosis obesity and prognosis of colorectal cancer.[38] In one early report, Meyerhardt et al[36] examined the association between obesity and prognosis of stage II and III colon cancer patients and found that female patients with a BMI of 30 kg/m^2 or greater were associated with a 34% significant increase in mortality and a 24% non-statistically significant increase in disease recurrence, while there was no such association between obesity and disease recurrence in men. Dignam et al[37] reported on a similar population of colon cancer patients and found a statistically significant 38% increase in the risk of recurrence and 28% increase in the risk of mortality among patients with a BMI greater than or equal to 35 kg/m^2, and did not find an interaction by gender. One study, limited to rectal cancer patients, did not show any significant association between body mass index and disease-free or overall survival,[38] though subgroup analyses by Campbell and colleagues did suggest obesity was associated with worse outcomes in rectal cancer patients.[6]

In studying the impact of being obese after colorectal cancer diagnosis on prognosis of colorectal cancer, it is very important to consider reverse causality: meaning that less obese patients may have worse prognosis if the reason for lower body weight could be well related with disease progression.[42] Some people have lower body mass as a result of healthy lifestyle including exercise and diet, while some people lose weight as a result of cancer recurrence. This may be one of the reasons why post-diagnosis obesity seems to associate less with prognosis of colorectal cancer than pre-diagnosis obesity does. This is the limitation of observational epidemiological studies. In addition, nearly all studies to date have focused on BMI due to the availability of height and weight in these cohort studies. However, other measures of adiposity may be more appropriate and should be considered in future studies. Finally, even if a certain level of adiposity is associated with worse outcomes, it is unclear if changing weight would influence this association. Only one study to date has reported the impact of weight change after diagnosis on prognosis of colon cancer patients. Meyerhardt and colleagues studied weight gain or weight loss from approximately 3 months after surgery to approximately 15 months after surgery in stage III colon cancer patients and found no significant associations with either gain or loss for cancer recurrences or mortality.[38] Ultimately, randomized controlled trials of weight control and reduction would be needed to further understand such a relationship.

Physical activity

Studies of the association between post-diagnosis physical activity and the risk of recurrence and mortality in colorectal cancer patients have led to fairly consistent conclusions (Table 5).[5,12,15–17,43] Increasing level of physical activity significantly improved overall mortality in colorectal cancer patients and either significantly or non-significantly trended to improved disease-free survival or colorectal cancer-specific mortality. In a recent meta-analysis of prospective cohort studies[7], we found that patients with any physical activity after diagnosis had reduced risk of colorectal cancer-specific mortality (relative risk 0.74 [95% CI 0.58–0.95]), compared to patients with no physical activity. Those who participated in high levels of physical activity after diagnosis (vs. low levels) had a RR of 0.65 (95% CI: 0.47–0.92). While efforts in these studies are made to account for potential for reverse causality, one cannot fully eliminate the potential that ability to be more active may be reflective of a healthier colorectal cancer survivor. Further, whether increasing level of physical activity after diagnosis will improve outcomes is unknown at this time.

Diet

As was found with pre-diagnosis diet and colorectal mortality, few studies have examined the association between post-diagnosis diet and mortality for colorectal cancer patients (Table 6).[8,9,44] In contrast to their prior study of pre-diagnosis patients, McCullough et al[8] reported that red and processed meat intake after diagnosis was not independently associated with survival outcomes. On the other hand, Meyerhardt et al[9] reported an association between Western dietary pattern, which consisted of red and processed meat, refined grains, and sugar desserts, and the risk of recurrence and mortality in colon cancer patients. Meyerhardt et al[9] studied 1009 colon cancer patients and collected dietary information within 3 months of surgery (while on adjuvant therapy) and 6 months after completing adjuvant chemotherapy. Using cumulative averaging of these 2 dietary time points and

factor analysis to determine dietary patterns, investigators found that the highest quintile in the Western dietary pattern group had a 3.25 times worse disease-free survival compared to the lowest quintile. In a second study of the same cohort of colon cancer patients, patients with the highest quintile of glycemic load had a 1.79 times higher risk of recurrence and morality compared to the lowest quintile.[44] Interestingly, the association between glycemic load and outcomes was influenced by BMI ($P_{\text{interaction}}$ =.01). Whereas glycemic load was not associated with disease-free survival in patients with BMI < 25kg/m^2, higher glycemic load was statistically significant associated with worse disease-free survival among overweight or obese participants (BMI ≥ 25kg/m^2; HR = 2.26; 95% CI = 1.53 to 3.32). This interaction further supports the potential relationship between energy balance and outcomes in colorectal cancer patients.

Mechanism for Post-diagnosis Energy Balance Factors and Outcomes

For patients with nonmetastatic colorectal cancer at time of diagnosis, the primary risk within the first several years is recurrence of disease. Recurrences are presumed to be micrometastases in primarily distant organs that over time growth to detectable metastases. The presumed role of adjuvant therapy is to impact on these micrometastases, whether through direct cell death or other mechanisms. It is not known if all micrometastases will grow to manifest as frank recurrences. However, several factors are presumed to help stimulate cell growth, including insulin and insulin-related growth factors. Obesity, lack of physical activity, Western pattern diet and high glycemic load are known to increase insulin resistance, which increases the level of insulin. In that insulin is one of the most potent apoptosis inhibitors and an insulin-reducing agent metformin inhibits cancer cell proliferation[45,46], these factors leading to unfavorable energy balance can induce hyperinsulinemia and increase the risk of recurrence by stimulating growth of micrometastases. Further, hyperinsulimia increases the production of IGF-1, which is another cell growth factor. These negative energy balance factors can increase adipocytokines (leptin and adiponectin), as discussed earlier.[28] An exercise intervention was found to reduce leptin, TNF-α, and IL-6, while increasing adiponectin levels, for colorectal cancer patients.[47]

Independent of risk of colorectal cancer recurrences, hyperinsulinemia patients may be more vulnerable to other diseases such as type 2 diabetes and cardiovascular disease which are one of most known causes of mortality in colorectal cancer patients.[6] Furthermore, during cancer treatment, various clinical and molecular factors including chemotherapy, other treatments, and drugs could alter vulnerability and lead to inflammation and pathogenesis for the colorectal cancer patients with obesity, thereby reducing survivorship.[48]

Recent molecular epidemiology studies have further strengthened the potential mechanism for energy balance and outcomes. For colon cancer patients who had CDKN1B (p27) expression (a potent cyclin dependent kinase inhibitor), at least 18 MET-hours/week physical activity was associated with 67 percent in colon cancer-specific mortality, compared to less than 18 MET-hours/week.[16] For patients CDKN1B loss, there are no association between physical activity and mortality outcome. This finding suggests that post-diagnosis physical activity might restrict available energy, thereby inhibiting the

growth of CDKN1B expressing tumors. Second, post-diagnosis physical activity might lead to a beneficial effect that reduces PTGS2 (COX2). PTGS2 is a crucial inflammatory response and is related to colorectal carcinogenesis. Yamauchi and colleagues reported that physically active patients with PTCG2 expressing tumors had better survival than physically activity patients without a PTCG2 expressing tumor.[49] Finally, WNT-CTNNB1 signaling could be a key regulator of energy metabolism and carcinogenesis. When colon cancer patients had a negative status for nuclear CTNNB1, it was found that post-diagnosis physical activity had a favorable association with colorectal cancer-specific survival.[31] Further studies are required to find other related molecular mechanisms.

III. Energy balance intervention studies in colorectal cancer survivors

All reported intervention studies to date in colorectal cancer survivors have examined quality of life related endpoints.[50–52] Currently, there is one ongoing intervention study to specifically study disease-free survival in stage II and III colorectal cancer survivors.[50] Courneya et al [50] endeavor to study the effect of physical activity intervention over a 3-year period, and how that intervention affected recurrences, mortality, physical functioning, quality of life, and biologic correlative markers for colon cancer patients. The study is sponsored by the National Cancer Institute of Canada and has ongoing accrual in Canada and Australia. Additional research opportunities exist that need to address other approaches to extending the mortality of colorectal cancer, which include developing diverse tailored intervention programs, such as home-based and web-based programs that change the patient's modifiable lifestyle factors.

Conclusion

Lifestyle factors that include obesity, physical activity, and diet are emerging as potential critical elements in improving colorectal cancer survival outcomes. The association between colorectal cancer mortality and modifiable lifestyle factors is growing in evidence. Changes in individual health behaviors both before and after a diagnosis of colorectal cancer may improve outcomes of survivors. Several studies have indicated that maintaining a normal weight, participating in regular physical activity, and eating a healthy diet may be important preventative steps leading to improve survival outcomes. Also, several epigenetic studies have demonstrated, at the cellular level, the possible mechanisms of colorectal cancer that can be positively influenced by changing lifestyle. However, extended lifestyle intervention studies, along with additional randomized trials and epigenetic studies are needed in order to provide firm evidence about the effect of lifestyle factors (including obesity, physical activity and diet) on colorectal cancer survival outcomes.

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Key points section

- Lifestyle factors that include obesity, physical activity, and diet are emerging as potential critical elements in improving colorectal cancer survival outcomes.
- Changes in individual health behaviors both before and after a diagnosis of colorectal cancer may improve outcomes of survivors
- Studies have indicated that maintaining a normal weight, participating in regular physical activity, and eating a healthy diet may be important preventative steps leading to improve survival outcomes.
- Epigenetic studies have demonstrated, at the cellular level, the possible mechanisms of colorectal cancer that can be positively influenced by changing lifestyle.

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Table 1

Prospective cohort studies of pre-diagnosis BMI, kg/m^2 and survival outcomes in colorectal cancer patients

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
Doria-Rose, (2006),[10] Wisconsin Cancer Reporting System, U.S.A	633 Female Colon and rectal	9.4 years	**CRC specific-mortality**		Age, stage, postmenopausal hormone use, and smoking
			<20.0	1.6 (0.9–3.1)	
			20.0–24.9	Referent	
			25.0–29.9	1.3 (0.9–1.9)	
			≥30	1.5 (0.9–2.6)	
			All-cause mortality		
			<20.0	1.5 (1.0–2.4)	
			20.0–24.9	Referent	
			25.0–29.9	1.2 (0.9–1.6)	
			≥30	1.5 (1.0–2.2)	
Prizment (2010),[11] Iowa Women's Health Study, U.S.A.	1,096 Female Colon	20 years	**CRC specific mortality**		Stage, age, education, and smoking
			<18.5	1.84 (0.84–4.03)	
			18.5.0–24.9	Referent	
			25.0–29.9	1.18 (0.87–1.52)	
			≥30	1.35 (1.00–1.82)	
			All-cause mortality		
			<18.5	1.89 (1.01–3.53)	
			18.5–24.9	Referent	
			25.0–29.9	1.12 (0.89–1.41)	
			≥30	1.45 (1.14–1.85)	
Kuiper (2012),[12] Women's Health Initiative, U.S.A.	1339 Female Colon and Rectal	11.9 years	**CRC specific mortality**		Age, study arm, BMI, tumor stage, ethnicity, education, alcohol, smoking, hormone therapy use
			18.5–24.9	Referent	
			25.0–29.9	0.77(0.52–1.13)	
			≥30	1.17 (0.80–1.72)	
			All-cause mortality		
			18.5–24.9	Referent	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			25.0–29.9	0.90(0.66–1.23)	
			≥30	1.19 (0.88–1.62)	
Campbell (2012),[6] Cancer Prevention Study-II Nutrition Cohort, U.S.A.	2,303 Both Genders Colon and Rectal	16 years	**CRC specific mortality**		Age, sex, smoking status, BMI, red meat intake, tumor stage, leisure-time spent sitting, education
			Female		
			<18.5	0.83 (0.25–2.76)	
			18.5.0–24.9	Referent	
			25.0–29.9	1.19 (0.80–1.78)	
			≥30	1.52 (0.96–2.41)	
			Male		
			<18.5	Not reported	
			18.5.0–24.9	Referent	
			25.0–29.9	1.06 (0.77–1.48)	
			≥30	1.31 (0.88–1.95)	
			Both		
			<18.5	0.67 (0.21–2.12)	
			18.5.0–24.9	Referent	
			25.0–29.9	1.09 (0.85–1.40)	
			≥30	1.35 (1.01–1.80)	
			All-cause mortality		
			Female		
			<18.5	1.74 (0.85–3.58)	
			18.5.0–24.9	Referent	
			25.0–29.9	1.22 (0.95–1.63)	
			≥30	1.42 (1.01–2.00)	
			Male		
			<18.5	1.40 (0.55–3.56)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.97 (0.79–1.19)	
			≥30	1.21 (0.94–1.57)	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			Both		
			<18.5	1.53 (0.88–2.66)	
			18.5.0–24.9	Referent	
			25.0–29.9	1.06 (0.90–1.25)	
			≥30	1.30 (1.06–1.58)	
Pelser (2014),[13] NIH-AARP Diet and Health Study, U.S.A.	4,213 Colon 1,514 Rectal Both Genders	5 years	**CRC specific mortality among colon cancer cases**		lag time, sex, education, family history of colon cancer, cancer stage, first course of treatment (surgery, radiation, chemotherapy), and also mutually adjusted for quintiles of HEI-2005 scores, BMI, physical activity, alcohol, and smoking history.
			18.5–24.9	Referent	
			25.0–29.9	0.97 (0.82–1.15)	
			≥30	1.15 (0.96–1.39)	
			All-cause mortality		
			18.5–24.9	Referent	
			25.0–29.9	1.02 (0.88–1.17)	
			≥30	1.19 (1.02–1.39)	
			CRC specific mortality among rectal cancer cases		
			18.5–24.9	Referent	
			25.0–29.9	0.92 (0.70–1.22)	
			≥30	1.04 (0.75–1.44)	
			All-cause mortality		
			18.5–24.9	Referent	
			25.0–29.9	0.85 (0.68–1.07)	
			≥30	1.00 (0.77–1.30)	

Table 2

Prospective cohort studies of pre-diagnosis physical activity and survival outcomes in colorectal cancer patients

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)	Adjustment factors
Heydon (2006),[14] Melbourne Collaborative Cohort Study, Australia	526 Both Genders Colon and Rectal	5.5 years	**CRC specific-mortality** Exerciser versus non-exerciser 0.73 (0.54–1.00) **All-cause mortality** Exerciser versus non-exerciser 0.77 (0.58–1.03)	Age, sex, stage, BMI
Meyerhardt (2006),[15] Nurses' Health Study, USA	573 Female Colon and Rectal	9.6 years	**CRC specific mortality** <3 MET-hrs/week: Referent 3–8.9: 0.83 (0.45–1.53) 9–17.9: 1.05 (0.56–1.99) ≥ 18: 0.86 (0.44–1.67) **All-cause mortality** <3 MET-hrs/week: Referent 3–8.9: 0.85 (0.52–1.37) 9–17.9: 1.14 (0.69–1.87) ≥ 18: 0.95 (0.57–1.59)	Age, stage, tumor differentiation, year of diagnosis, time between study entry to questionnaire, BMI, smoking
Meyerhardt (2009),[16] Health Professionals Follow-up Study, USA	599 Male Colon and Rectal	8.6 years	**CRC specific mortality** <3 MET-hrs/week: Referent 3.1–9.0: 0.56 (0.28–1.13) 9.1–18: 0.64 (0.33–1.24) 18.1–27: 0.53 (0.26–1.10) ≥ 27: 0.52 (0.29–0.94) **All-cause mortality** <3 MET-hrs/week: Referent 3.1–9.0: 0.55 (0.36–0.85) 9.1–18: 0.60 (0.41–0.89)	Age, stage, year of diagnosis, tumor differentiation, tumor location, BMI, smoking

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			18.1–27	0.51 (0.34–0.79)	
			≥ 27	0.48 (0.34–0.69)	
Kuiper (2012),[12] Women's Health Initiative, U.S.A.	1339 Female, Colon and Rectal	11.9 years	**CRC specific mortality**		Age, study arm, BMI, tumor stage, ethnicity, education, alcohol, smoking, hormone therapy use
			0 MET-hrs/week	Referent	
			>0–2.9	0.98 (0.58–1.66)	
			3.0–8.9	1.01 (0.65–1.57)	
			9.0–17.9	0.74 (0.46–1.20)	
			≥18.0	0.68 (0.41–1.13)	
			All-cause mortality		
			0 MET-hrs/week	Referent	
			>0–2.9	0.93 (0.61–1.43)	
			3.0–8.9	1.01 (0.71–1.43)	
			9.0–17.9	0.77 (0.52–1.12)	
			≥18.0	0.63 (0.42–0.96)	
Campbell (2013),[17] Cancer Prevention Study-II, U.S.A.	2262 Both Genders Colon and Rectal	6.8 years	**CRC specific mortality**		Age, sex, smoking status, BMI, red meat intake, tumor stage, leisure-time spent sitting, education
			<3.5 MET-hrs/week	Referent	
			3.5-<8.75	0.68 (0.49–0.95)	
			≥8.75	0.78 (0.57–1.08)	
			All-cause mortality		
			<3.5 MET-hrs/week	Referent	
			3.5-<8.75	0.69 (0.55–0.85)	
			≥8.75	0.72 (0.58–0.89)	

MET-hrs/week= metabolic equivalent tasks-hours per week

Table 3

Prospective cohort studies of pre-diagnosis diet and survival outcomes in colorectal cancer patients

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Dietary Measure	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
Zell (2006),[19] USA,	511 Both Genders Colon and Rectal	7.9 years	Red and processed meat	**All-cause mortality**		Age, stage, and sex
				Quartiles 1–3 vs. Quartiles 4	Familial CRC; 2.24 (1.25–4.03) Sporadic CRC; 1.02 (0.67–1.15)	
Zhu (2013),[1] Newfoundland Familial Colorectal Cancer Registry, Canada.	529 Both Genders Colon and Rectal	6.4 years	Processed meat dietary pattern	**Disease-free survival**		Total energy intake, sex, age at diagnosis, stage at diagnosis, marital status, family history, reported screening procedure, reported chemoradiother apy and microsatellite instability status, where appropriate.
				Highest vs. lowest quartile	1.82 (1.07–3.09)	
McCullough (2013),[8] Cancer Prevention Study II Nutrition Cohort, U.S.A.	2,315 Both Genders Colon and Rectal	7.5 years	Red and processed meat	**All-cause mortality**		Age at diagnosis, sex, tumor stage at diagnosis, 1992 energy intake
				Top vs. bottom quartile	1.29 (1.05–1.59)	

CRC= colorectal

Table 4

Prospective cohort studies of post-diagnosis BMI, kg/m^2 and survival outcomes in colorectal cancer patients

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
Meyerhardt (2003),[36] National Cancer Institute INT-0089, U.S.A.	3,759 Both Genders Colon	9.4 years	All-cause mortality		Age, race, baseline, performance status, bowel obstruction, bowel perforation, Duke stage, presence of peritoneal implants, predominant macroscopic pathologic feature, and completion chemotherapy
			Female		
			<21	1.08 (0.87–1.35)	
			21–24.9	Referent	
			25.0–27.49	1.18 (0.94–1.49)	
			27.5–29.9	1.23 (0.95–1.60)	
			≥30	1.34 (1.07–1.67)	
			Male		
			<21	1.33 (1.05–1.67)	
			21–24.9	Referent	
			25.0–27.49	1.03 (0.87–1.22)	
			27.5–29.9	0.96 (0.78–1.17)	
			≥30	0.94 (0.77–1.15)	
			Both		
			<21	1.15 (0.98–1.35)	
			21–24.9	Referent	
			25.0–27.49	1.10 (0.95–1.26)	
			27.5–29.9	1.05 (0.90–1.24)	
			≥30	1.11 (0.96–1.29)	
Meyerhardt (2004),[53] National Cancer Institute INT-0114, U.S.A.	1,688 Both genders Rectal	9.9 years	**All-cause mortality**		Age, race, nodal status, extent of tumor invasion, clinical bowel obstruction, and distance from anal verge
			Female		
			<21	1.29 (0.87–1.91)	
			21–24.9	Referent	
			25.0–27.49	0.75 (0.49–1.16)	
			27.5–29.9	0.89 (0.61–1.33)	
			≥30	0.94 (0.66–1.33)	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			Male		
			<21	1.62 (1.08–2.43)	
			21–24.9	Referent	
			25.0–27.49	1.07 (0.86–1.33)	
			27.5–29.9	0.99 (0.79–1.25)	
			≥30	1.19 (0.94–1.52)	
			Both		
			<21	1.43 (1.08–1.89)	
			21–24.9	Referent	
			25.0–27.49	0.97 (0.80–1.17)	
			27.5–29.9	0.95 (0.78–1.15)	
			≥30	1.09 (0.9–1.33)	
Dignam (2006),[37] National Surgical Adjuvant Breast and Bowel Project Randomized Trials, U.S.A.	4288 Female Colon	11.2 years	**All-cause mortality**		Age, sex, race, performance status, number of positive lymph nodes, presence of bowel obstruction, and treatment
			<21.0	1.49 (1.17–1.91)	
			21.0–24.9	Referent	
			25.0–29.9	1.02 (0.91–1.14)	
			30–34.9	1.11 (0.96–1.28)	
			≥30	1.28 (1.04–1.57)	
Meyerhardt (2008),[38] National Cancer Institute CALGB 89803, U.S.A.	1,053 Both Genders Colon	5.3 years	**All-cause mortality**		Sex, age, depth of invasion through bowel wall, number of positive lymph node, presence of clinical perforation at time of surgery, presence of bowel obstruction, baseline CEA, grade of tumor differentiation, baseline performance status, treatment arm, weight change between first and second questionnaire, BMI at the time or second questionnaire, and time between study entry and completion of second questionnaire
			<21.0	1.07 (0.61–1.87)	
			21.0–24.9	Referent	
			25.0–29.9	0.72 (0.50–1.03)	
			30–34.9	0.90 (0.61–1.34)	
			≥30	0.87 (0.54–1.42)	
Sinicrope (2010),[39] ACCENT Group database, U.S.A.	4,381 Both Genders Colon	8 years	**All-cause mortality**		age, stage, treatment, and sex
			Female		
			<20.0	1.32 (1.05–1.67)	
			20.0–24.9	Referent	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			25.0–29.9	1.18 (0.94–1.49)	
			30–34.9	1.24 (1.01–1.53)	
			≥30	1.11 (0.84–1.45)	
			Male		
			<20.0	1.14 (0.81–1.61)	
			20.0–24.9	Referent	
			25.0–29.9	0.82 (0.71–0.95)	
			30–34.9	0.94 (0.78–1.15)	
			≥30	1.35 (1.02–1.79)	
			Both		
			<20.0	1.24 (1.03–1.5)	
			20.0–24.9	Referent	
			25.0–29.9	0.90 (0.80–1.00)	
			30–34.9	1.07 (0.93–1.23)	
			≥30	1.19 (0.98–1.45)	
Baade (2011),[5] Queensland, Australia	2,561 Both Genders Colon and Rectal	4.9 years	**CRC specific mortality**		Age, sex, stage at diagnosis, smoking, site of tumor, treatment (surgery only vs. surgery and adjuvant therapy)
			<18.5	1.74 (0.85, 3.58)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.75 (0.59–0.97)	
			≥30	1.34 (0.70–2.58)	
			Unknown	1.34 (0.70–2.58)	
			All-cause mortality		
			<18.5	2.29 (1.47–3.59)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.75 (0.61–0.94)	
			≥30	0.78 (0.59–1.03)	
			Unknown	0.94 (0.51–1.74)	
Chin (2012),[40] China	2,765 Both Genders Colon and Rectal	5 years	**CRC specific mortality**		Tumor, nodes, metastasis stage, age, gender, comorbidities, carcinoembryonic antigen, hemoglobin, albumin, operative timing,
			Female		

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			<18.5	1.16 (0.75–1.82)	postoperative morbidity, tumor location, histologic type, and histologic grade
			18.5.0–24.9	Referent	
			25.0–29.9	0.96 (0.60–1.43)	
			≥30	1.11 (0.84–1.43)	
			Male		
			<18.5	1.46 (0.84–2.52)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.96(0.69–1.32)	
			≥30	1.21(0.83–1.77)	
			Both		
			<18.5	1.33 (0.94–1.87)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.96 (0.76–1.2)	
			≥30	1.06 (0.80–1.41)	
			All-cause mortality		
			Female		
			<18.5	1.55 (1.11–2.16)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.95 (0.71–1.27)	
			≥30	0.99 (0.69–1.41)	
			Male		
			<18.5	1.55 (1.03–2.35)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.77 (0.58–1.01)	
			≥30	0.91 (0.66–1.25)	
			Both		
			<18.5	1.58 (1.23–2.05)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.83 (0.68–1.01)	
			≥30	0.94 (0.68–1.01)	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)	Adjustment factors
Kuiper (2012),[10] Women's Health Initiative, U.S.A.	676 Female Colon and Rectal	11.9 years	**CRC specific mortality** 18.5.0–24.9: Referent 25.0–29.9: 0.45 (0.22–0.92) ≥30: 0.95 (0.49–1.85) **All-cause mortality** 18.5.0–24.9: Referent 25.0–29.9: 0.78 (0.47–1.27) ≥30: 1.09 (0.65–1.83)	Age, study arm, time from diagnosis to measurement, pre-diagnostic BMI, tumor stage, ethnicity, education, alcohol, smoking, hormone therapy use
Campbell (2013),[17] Cancer Prevention Study-II Nutrition Cohort, U.S.A.	2,303 Both Genders Colon and Rectal	6.8 years	**CRC specific mortality** Female <18.5: 0.39 (0.12–1.32) 18.5.0–24.9: Referent 25.0–29.9: 0.81 (0.50, 1.31) ≥30: 1.09 (0.60, 2.01) Male <18.5: 2.48 (0.55–11.3) 18.5.0–24.9: Referent 25.0–29.9: 0.91 (0.61–1.34) ≥30: 1.29 (0.82–2.01) Both <18.5: 0.64 (0.25–1.60) 18.5.0–24.9: Referent 25.0–29.9: 0.87 (0.65–1.17) ≥30: 1.14 (0.81–1.60) **All-cause mortality vs. BMI, kg/m^2** Female <18.5: 1.19 (0.65–2.18) 18.5.0–24.9: Referent 25.0–29.9: 0.84 (0.60–1.16)	Age, sex, smoking status, BMI, red meat intake, tumor stage, leisure-time spent sitting, education

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			≥30	1.19 (0.79–1.78)	
			Male		
			<18.5	2.78 (1.29–5.96)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.82 (0.66–1.03)	
			≥30	0.89 (0.67–1.18)	
			Both		
			<18.5	1.30 (0.82–2.06)	
			18.5.0–24.9	Referent	
			25.0–29.9	0.83 (0.70–1.00)	
			≥30	0.93 (0.75–1.17)	
Sincrope (2013),[41] National Cancer Institute and conducted by Mayo Clinic/North Central Cancer Treatment Group and the Southwest Oncology group, U.S.A.	25.291 Both Genders Colon	7.8 years	**All-cause mortality**		age, stage, treatment, and sex
			Female		
			<20.0	1.12 (1.00–1.25)	
			20.0–24.9	Referent	
			25.0–29.9	1.05 (0.97–1.14)	
			30–34.9	1.10 (0.99–1.23)	
			≥35	1.07 (0.93–1.24)	
			Male		
			<20.0	1.39 (1.21–1.60)	
			20.0–24.9	Referent	
			25.0–29.9	0.95 (0.87–1.02)	
			30–34.9	1.10 (1.99–1.2)	
			≥35	1.16 (1.0–1.35)	
			Both		
			<20.0	1.21 (1.11–1.32)	
			20.0–24.9	Referent	
			25.0–29.9	1.10 (1.04–1.17)	
			30–34.9	1.10 (1.02–1.18)	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)	Adjustment factors
		≥35	1.11 (1.00–1.23)	

Table 5

Prospective cohort studies of post-diagnosis physical activity and survival outcomes in colorectal cancer patients

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
Meyerhardt (2006),[15] Nurses' Health Study, USA	554 Female, Colon and Rectal	9.6 years	**CRC specific mortality**		Age of diagnosis, stage, tumor differentiation, year of diagnosis, time between study entry to questionnaire, BMI, smoking, receipt of chemotherapy, time from diagnosis to physical activity measurement
			<3 MET-hrs/week	Referent	
			3–8.9	0.92 (0.50–1.69)	
			9–17.9	0.57 (0.27–1.20)	
			≥ 18	0.39 (0.18–0.82)	
			All-cause mortality		
			<3 MET-hrs/week	Referent	
			3–8.9	0.77 (0.48–1.23)	
			9–17.9	0.50 (0.28–0.90)	
			≥ 18	0.43 (0.25–0.74)	
Meyerhardt (2006),[43] CALGB 89803, U.S.A.	832 Both Genders Colon	3.8 years	**Disease free survival**		Sex, age, depth of invasion through bowel wall, number of positive lymph node, presence of clinical perforation at time of surgery, presence of bowel obstruction, baseline CEA, grade of tumor differentiation, baseline performance status, treatment arm, weight change between first and second questionnaire, BMI at the time or second questionnaire, and time between study entry and completion of second questionnaire
			<3 MET-hrs/week	Referent	
			3–8.9	0.87 (0.58–1.29)	
			9–17	0.90 (0.57–1.40)	
			18–26.9	0.51 (0.26–0.97)	
			≥ 27	0.55 (0.33–0.91)	
			Recurrence free survival		
			<3 MET-hrs/week	Referent	
			3–8.9	0.86 (0.57–1.30)	
			9–17	0.89 (0.55–1.42)	
			18–26.9	0.51 (0.26–1.01)	
			≥ 27	0.60 (0.36–1.01)	
			All-cause mortality		
			<3 MET-hrs/week	Referent	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			3–8.9	0.85 (0.49–1.49)	
			9–17	0.71 (0.36–1.41)	
			18–26.9	0.71 (0.32–1.59)	
			≥ 27	0.37 (0.16–0.82)	
Meyerhardt (2009),[16] Health Professionals Follow-up Study, U.S.A	661 Male Colon and Rectal	8.6 years	**CRC specific mortality**		Age, stage, year of diagnosis, disease stage, tumor differentiation, tumor location, BMI, smoking
			<3 MET-hrs/week	Referent	
			3.1–9	1.06 (0.55–2.08)	
			9.1–18	1.30 (0.65–2.59)	
			18.1–27	0.76 (0.33–1.77)	
			≥ 27	0.47 (0.24–0.92)	
			All-cause mortality		
			<3 MET-hrs/week	Referent	
			3.1–9	1.00 (0.68–1.48)	
			9.1–18	1.12 (0.74–1.70)	
			18.1–27	0.74 (0.46–1.20)	
			≥ 27	0.59 (0.41–0.86)	
Baade (2011),[5] Queensland, Australia	1,825 Both Genders Colon and Rectal	4.9 years	**CRC specific mortality**		Age, sex, stage at diagnosis, smoking, site of tumor, treatment (surgery only vs. surgery and adjuvant therapy)
			Sedentary	Referent	
			Insufficiently active	0.90 (0.69–1.17)	
			Sufficiently active	0.88 (0.68–1.15)	
			All-cause mortality		
			Sedentary	Referent	
			Insufficiently active	0.72 (0.57–0.90)	
			Sufficiently active	0.75 (0.60–0.94)	
Kuiper (2012),[12] Women's Health Initiative, U.S.A.	676 Female Colon and Rectal	11.9 years	**CRC specific mortality**		Age, study arm, time from diagnosis to measurement, pre-diagnostic BMI, tumor stage, ethnicity, education, alcohol, smoking, hormone therapy use
			0 MET-hrs/week	Referent	

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Relative risk/Hazard Ratio (95% Confidence Interval)		Adjustment factors
			>0–2.9	0.49 (0.21–1.14)	
			3.0–8.9	0.30 (0.12–0.73)	
			9.0–17.9	0.53 (0.22–1.25)	
			≥ 27	0.29 (0.11–0.77)	
			All-cause mortality		
			0 MET-hrs/week	Referent	
			>0–2.9	0.71 (0.40–1.30)	
			3.0–8.9	0.42 (0.23–0.77)	
			9.0–17.9	0.57 (0.31–1.07)	
			≥ 27	0.41 (0.21–0.81)	
Campbell (2013),[17] Cancer Prevention Study-II, U.S.A.	1800 Both Genders Colon and Rectal	6.8 year	**CRC specific mortality**		Age, sex, smoking status, BMI, red meat intake, tumor stage, leisure-time spent sitting, education
			<3.5 MET-hrs/week	Referent	
			3.5-<8.75	1.00 (0.64–1.56)	
			≥8.75	0.87 (0.61–1.24)	
			All-cause mortality		
			<3.5 MET-hrs/week	Referent	
			3.5-<8.75	0.78 (0.60–1.00)	
			≥8.75	0.58 (0.47–0.71)	

MET-hrs/week= metabolic equivalent tasks-hours per week

Table 6

Prospective cohort studies of post-diagnosis diet and survival outcomes in colorectal cancer patients

First author (year), name of cohort, country	Study participants	Median Years of Follow-up	Dietary Measure	Relative risk/Hazard Ratio (95% Confidence Interval)	Adjustment factors
Meyerhardt (2007),[9] National Cancer Institute-sponsored Cancer and Leukemia Group B (CALGB) 89803, U.S.A.	1,009 Both Genders Colon	5.3 years	Western pattern diet	**Disease-free survival** Highest vs. lowest quintile: 3.25 (2.04–5.19) **Recurrence-free survival** Highest vs. lowest quintile: 2.85 (1.75–4.63) **Overall survival** Highest vs. lowest quintile: 2.32 (1.36–3.96)	Stage, age, nodal stage, BMI, physical activity, baseline performance status, or treatment group.
Meyerhardt (2012),[44] National Cancer Institute-sponsored Cancer and Leukemia Group B (CALGB) 89803, U.S.A.	1,011 Both Genders Colon	7.3 years	Glycemic load	**Disease-free survival** Highest vs. lowest quintile: 1.79 (1.29–2.48) **Recurrence-free survival** Highest vs. lowest quintile: 1.98 (1.39–2.80) **Overall survival** Highest vs. lowest quintile: 1.76 (1.22–2.54)	Sex, age, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, body mass index, physical activity level, and cereal fiber intake
McCullough (2013),[8] Cancer Prevention Study II Nutrition Cohort, U.S.A.	1,186 Both Genders Colon and Rectal	7.6 years	Red and processed meat	**Colorectal cancer-specific mortality** Highest vs. lowest quartile: 1.34 (0.77–2.33) **Overall mortality** Highest vs. lowest quintile: 1.09 (0.81–1.48)	Age at diagnosis, sex, tumor stage at diagnosis, energy intake. weight change