REVIEW

MAYO CLINIC PROCEEDINGS:
INNOVATIONS, QUALITY & OUTCOMES

Lifestyle Factors and Cancer: A Narrative Review

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Abstract

Lifestyle factors and their impact on cancer prevention, prognosis, and survivorship are increasingly recognized in the medical literature. Lifestyle factors are primarily defined here as diet and physical activity. We conducted a narrative review of the primary published data, including randomized controlled trials and prospective studies, on the impact of primary lifestyle factors on oncogenesis and clinical outcomes in the preventative and survivorship setting. First, we discuss the oncogenic mechanisms behind primary lifestyle factors (diet, physical activity and, within these 2, obesity). Then, we discuss the impact of adherence to lifestyle guidelines and dietary patterns on cancer incidence based on primary data. Owing to the plethora of published literature, to summarize the data in a more efficient manner, we describe the role of physical activity on cancer incidence using summative systematic reviews. We end by synthesizing the primary data on lifestyle factors in the survivorship setting and conclude with potential future directions. In brief, the various large-scale studies investigating the role diet and physical activity have reported a beneficial effect on cancer prevention and survivorship. Although the impact of single lifestyle factors on cancer incidence risk reduction is generally supported, holistic approaches to address the potential synergistic impact of multiple lifestyle factors together in concert is limited. Future research to identify the potentially synergistic effects of lifestyle modifications on oncogenesis and clinical outcomes is needed, particularly in cancer subtypes beyond colorectal and breast cancers.

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The term lifestyle medicine is the study of how modifiable factors can impact health outcomes, including diet, physical activity, stress, social support, sleep, and mind-body connection, among others. Experts estimate at least 42% of newly diagnosed cancer cases in the United States are caused by modifiable lifestyle factors and are, therefore, potentially preventable.[1] Today, there is a large volume of data published on some modifiable risk factors, but there are still large gaps in our knowledge. Of these, primary lifestyle factors, specified here as dietary habits and physical activity, have the most evidence demonstrating an impact on cancer outcomes.[2,3] There are several measures/indices of the status of these 2 primary lifestyle factors, including weight, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), and obesity. Regardless of how diet and phsycial activity are measured, they have been associated with the risk of developing lung, prostate, colorectal, breast, mouth, throat, esophagus, pancreas, stomach, liver, and kidney cancers.[4-7] However, current research has focused mostly on breast and colorectal cancer subtypes.

Diet and physical activity significantly influence obesity, all have been linked with an increased risk in 13 cancers, many of which overlap the previous list.[8] Specifically, in the past 20 years, in the United States, excess weight (a surrogate for obesity) has been attributed to 14% and 20% of all cancer-related deaths in men and women, respectively.[9] Additionally, these primary lifestyle factors affect not only cancer incidence but also treatment outcomes, quality of life (QOL), and survivorship after the diagnosis. However, there is a paucity of larger randomized controlled trials (RCTs) investigating the effects of specific lifestyle interventions on the prevention, treatment, and recurrence of cancer.

In this narrative review, we first discuss the oncogenic mechanisms behind primary lifestyle factors (diet, physical activity, and, within these 2, obesity), followed by a discussion on the impact of adherance to lifestyle guidelines and dietary patterns on cancer incidence, based on primary data. Owing to the plethora of published literature, we describe the role of physical activity on cancer incidence using summative systematic reviews. Finally, we synthesize primary data on lifestyle factors in the survivorship setting and conclude with potential future directions.

ARTICLE HIGHLIGHTS

- Lifestyle modification has a beneficial impact on cancer outcomes.
- Specific diet and physical activity patterns and their clinical impact are highlighted in this narrative review.
- Mechanisms of oncogenesis in obesity and their modulation by lifestyle modification are described.
- Summary tables of the largest randomized controlled trials and prospective studies of lifestyle modification are provided, enabling quick clinician reference to inform future discussions with patients.

ONCOGENIC MECHANISMS BEHIND LIFESTYLE FACTORS

Carcinoigenesis is a complex process with multiple initiating events,which can be summarized by endogenous, exogenous, and environmental components (Figure). Lifestyle factors are part of the exogenous components, which include dietary patterns, physical activity, tobacco, and alcohol intake.[10,11] When combined with endogenous (genetic sequence variations, metabolic, and hormonal) and environmental (radiation, stress, infection, and toxins) factors, these insults induce sequence variations at the cellular level, leading to dysregulation of normal cellular process[12] and, ultimately, invasive cancer formation.

Obesity is a closely related measure of diet and physical activity (in addition to some endogenous components such as genetics, which are out of the scope of this review). Obesity has a significant role in cancer development, which may be modifiable by lifestyle factor changes. Obesity is characterized as a chronic inflammatory state, with elevated levels of proinflammatory cytokines and changes in adipokine secretion. This leads to oversecretion of insulin, culminating in increased release of insulin-like growth factor 1.[12] Both insulin and insulin-like growth factor 1 suppress apoptosis but promote cellular proliferation, angiogenesis, and lymphangiogenesis.[13] Many cancers express elevated levels of the insulin receptor, which are suspected to play a role in their oncogenesis.[14] Moreover, hyperinsulinemia stimulates metabolic pathways, resulting in elevated levels of reactive oxygen species that are known to induce DNA damage and may further contribute to carcinogenesis.[15] From a clinical standpoint, a higher dietary glycemic load/carbohydrate intake in individuals with BMI of $\geq$25kg/m^2 has been proposed to influence cancer growth by means of providing a constant supply of glucose for aerobic metabolism.[16]

In an obese state, excess adipose tissue causes higher levels of endogenous sex hormones, as fat cells are where the enzymatic conversion of steroid precursors to hormones occurs. A clincial example is as in endometrial and breast cancer, where higher levels of circulating sex hormones have been implicated with increased risk of endometrial cancer and breast cancer in postmenopausal women.[17,18] Normally, adipose tissue releases a balance of adipokines (both proinflammatory and anti-inflammatory hormones and cytokines). In visceral obesity, however, anti-inflammatory hormones are secreted in relatively lower levels, disrupting the balance of proinflammation and anti-inflammation and, therefore, suspected to promote more tumorigenesis.[19] In addition, chronically low levels of anti-inflammatory products in obesity also promotes angiogenesis, a well-known tumor-associated vascular factor, critical for cancer propogation and survival.[20,21]

Although obesity, which is related to more sedetary behavior, promotes carcinogenesis through the abovementioned mechanisms, physical activity has been found to promote adaptations in cells that might counter some oncogenesis aforementioned effects. Mechanistically, physical activity leads to short-term increases in the stress hormones norepinephrine

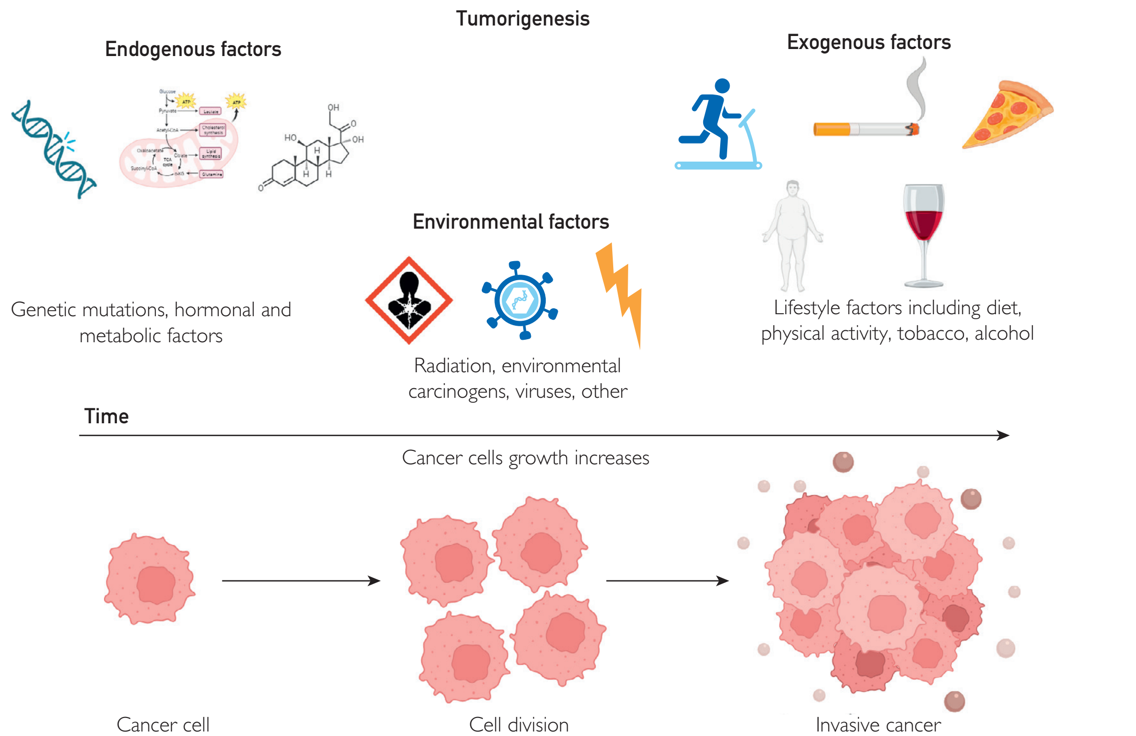

FIGURE. The impact of endogenous and exogenous factors on tumorigenesis. Tumorigenesis is a complex process with multiple initiating events, which is now widely recognized as being influenced by the relationship between both endogenous and exogenous components. Lifestyle factors make up the exogenous components and include dietary patterns, weight, physical activity, hormone therapy, and toxin exposure.[10] When combined with endogenous factors (genetic sequence variations, metabolic, and hormonal), these lifestyle insults induce sequence variations at the cellular level leading to dysregulation of normal cellular process.[11]

and epinephrine but, overall, attenuates the body's hormone responses to stress.[22] Physical activity also leads to the production of both proinflammatroy and anti-inflammatory cytokines but, specifically, interleukin-6, which leads to a cascade of overall anti-inflammatory cytokines and inhibits proinflammatory cytokines. Thereby, physcial activity may offer protection against chronic inflammation, such as that found in an obese state, which leads to oncogenesis.[23]

The mechanisms described support the link among diet, physical activity, measured here by obesity, and cancer. Subsequently, potential modulation with physical activity provides an opportunity where lifestyle modification may mitigate the occurance of cancer. In summary, lifstyle factor modification with diet and physical activity patterns that lead to a healthy/nonobese state may offer a safe and effect management strategy to impact multiple protumorigeneic mechanisms, such as decreasing inflammation, enhancing the immune response, optimizing DNA repair and stability, and modulating hormonal responses.

IMPACT OF LIFESTYLE PATTERN ADHERANCE ON CANCER INCIDENCE

Some authorities identify cancer as a chronic metabolic disease, with prevention strategies geared toward lifestyle factors that may influence other diseases related to cancer, including diabetes, obesity, hypertension, hyperlipidemia, and heart disease.[10,24] Interestingly, most of these comorbidities have a dysmetabolic state with overlaps with cancer mechanisms. In 2007, the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) promoted

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TABLE 1. Lifestyle Prevention

Author, year	Study type	N	Cancer	Summary
Thun et al, 2013	Prospective	518,982	Lung	For women who were current smokers, compared with women who had never smoked, the relative risks of death from lung cancer were 2.73, 12.65, and 25.66 in the 1960s, 1980s, and contemporary cohorts, respectively; corresponding relative risks for male current smokers, compared with men who had never smoked, were 12.22, 23.81, and 24.97, respectively.
Matthews et al, 2020	Prospective	755,459	15 cancer types	Engagement in recommended amounts of activity (7.5-15 MET-h/wk) was associated with a statistically significant lower risk of 7 of the 15 cancer types studied, including colon (8%-14% lower risk in men), breast (6%-10% lower risk), endometrial (10%-18% lower risk), kidney (11%-17% lower risk), myeloma (14%-19% lower risk), liver (18%-27% lower risk), and non-Hodgkin lymphoma (11%-18% lower risk in women).
Moore et al, 2016	Prospective	1.44 million	26 cancer types	Higher levels of leisure-time physical activity (90th percentile) versus lower levels (10th percentile) were associated with lower risks of 13 cancers.
Inoue et al, 2008	Prospective	79,771	Any	Compared with participants in the lowest quartile, increased daily physical activity was associated with a significantly decreased risk of cancer in both sexes.
Maruti et al, 2008	Prospective	64,777	Breast	Active women engaging in 39 or more metabolic equivalent hours per week (MET-h/wk) of total activity on average during their lifetime had a 23% lower risk of premenopausal breast cancer than women reporting less activity.
Patel et al, 2005	Prospective	72,174	Prostate	The incidence of aggressive prostate cancer was inversely associated with >35 metabolic equivalent-h/wk of recreational physical activity compared with that in men who reported no recreational physical activity.
Dallal et al, 2007	Prospective	110,599	Breast	When comparing long-term strenuous activity, defined as >5 h/wk per year), invasive breast cancer risk was inversely associated with long-term strenuous activity, as was in situ breast cancer risk. Strenuous and moderate long-term activities were associated with reduced risk of ER-negative but not ER-positive invasive breast cancer.
Martinez et al, 1997	Prospective	121,701	Colon	Women who expended more than 21 MET-h/wk on leisure-time physical activity had a relative risk of colon cancer of 0.54 in comparison with women who expended <2 MET-h/wk. Women who had a body mass index >29 kg/m^2 had a relative risk of colon cancer of 1.45 in comparison with women who had a body mass index <21 kg/m^2.
Rockhill et al, 1999	Prospective	121,701	Breast	Comparing those who reported engaging in moderate or vigorous physical activity for 7 or more hours per week with those who engaged in such physical activity for <1 hour per week, the relative risk was 0.82, using the cumulative average updating.
Eliassen et al, 2006	Prospective	87,143	Breast	Compared with those who maintained weight, women who gained 25.0 kg or more since age 18 y were at an increased risk of breast cancer, with a stronger association among women who have never taken postmenopausal hormones. Compared with those with weight maintenance, women who gained 10.0 kg or more since menopause were at an increased risk of breast cancer. Women who had never used postmenopausal hormones, lost 10.0 kg or more since menopause, and kept the weight off were at a lower risk than those who maintained weight.
Luo et al, 2017	Prospective	36,794	Endometrial	Women who had lost weight had a 29% lower risk of endometrial cancer.

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TABLE 1. Continued

Author, year	Study type	N	Cancer	Summary
Chlebowski et al, 2019	Prospective	61,335	Breast	Women with weight loss had a significantly lower risk (12%) of breast cancer compared with women whose weight remained stable (hazard ratio [HR], 0.88; 95% CI, 0.78-0.98; P=.02).
Tantamango-Bartley et al, 2013	Prospective	69,120	Any	Vegan diets showed protection for overall cancer incidence (HR, 0.84; 95% CI, 0.72-0.99). Lacto-ovo-vegetarians were associated with decreased risk of cancers of the gastrointestinal system (HR, 0.75; 95% CI, 0.60-0.92).
Kane-Diallo et al, 2018	Prospective	42,544	Lung, prostate, breast	A higher pro plant-based dietary score was associated with decreased risks of overall cancer and lung cancer.
Benetou et al, 2008	Prospective	25,623	Any	Higher degree of adherence to Mediterranean diet was associated with lower overall cancer incidence.
Couto et al, 2011	Prospective	142,605 men and 335,873 women	Any	A lower overall cancer risk was found among individuals with greater adherence to Mediterranean diet for a 2-point increment of the Mediterranean diet score.
Terry et al, 2001	Population-based prospective study	61,463	Colorectal	Individuals who consumed <1.5 servings of fruit and vegetables per day had a relative risk for developing colorectal cancer of 1.65 (95% CI, 1.23-2.20; P_{trend}=.001) compared with individuals who consumed more than 2.5 servings.
Orlich et al, 2015	Prospective	96,354	Colorectal	HRs for incident colorectal cancers in all vegetarians combined vs nonvegetarians were as follows: 0.78 (95% CI, 0.64-0.95) for all colorectal cancers; 0.81 (95% CI, 0.65-1.00) for colon cancer; and 0.71 (95% CI, 0.47-1.06) for rectal cancer. The adjusted HR for colorectal cancer in vegans was 0.84 (95% CI, 0.59-1.19); in lacto-ovo vegetarians, 0.82 (95% CI, 0.65-1.02); in pescovegetarians, 0.57 (95% CI, 0.40-0.82); and in semivegetarians, 0.92 (95% CI, 0.62-1.37), compared with nonvegetarians.
Bingham et al, 2003	Prospective	519,978	Colorectal	There was an inverse relationship between dietary fiber in foods and incidence of large bowel cancer (adjusted relative risk, 0.75; 95% CI, 0.59-0.95; for the highest versus lowest quintile of intake). The protective effect was greatest for the left-sided colorectal cancer and least for the rectum.
Larsson et al, 2005	Prospective	61,433	Colorectal	Higher intake of whole grains was associated with a lower risk of colon cancer but not of rectal cancer.
van Duijnhoven et al, 2009	Prospective	452,755	Colorectal	Consumption of fruit and vegetables was inversely associated with colorectal cancer in a comparison of the highest with the lowest EPIC-wide quintile of consumption (HR, 0.86; 95% CI, 0.75-1.00; P_{trend}=.04), particularly with colon cancer risk (HR, 0.76; 95% CI, 0.63-0.91; P_{trend}<.01).
Chlebowski et al, 2018	Secondary analysis of RCT	48,835	Breast	Postmenopausal women in the low-fat group had improved breast cancer—specific and overall survival
Peters et al, 2003	RCT	33,971	Colorectal adenoma	High intakes of dietary fiber were associated with a lower risk of colorectal adenoma, after adjustment for potential dietary and nondietary risk factors.

RCT, randomized controlled trial.

recommendations related to diet, nutrition, physical activity, and body composition in an effort to reduce incidence of cancer.[25]

Among many studies investigating the association between adherence to these recommendations and cancer incidence, the VITAL study followed a large prospective cohort of 30,000 postmenopausal women and reported that adherence to ≥5 recommendations led to a 60% reduction in incidence of breast cancer.[26] Similarly, 2 other studies investigating adherence to WCRF/AICR recommendations reported a 51% and 24% reduction in breast cancer risk in postmenopausal women adhering to ≥6 of these guidelines.[27,28]

In 2018, the Third Expert Report from the WCRF/AICR was published, highlighting the latest in cancer research and again emphasizing the interplay between diet and physical activity and the reduction in cancer rates.[29] Such findings suggest that the risk of many site-specific cancers can be reduced with implementation of WCRF/AICR recommendations. However, we note that there is a difference in quality of extrapobility between observational data included in the Third Expert Report and prospective studies such as the VITAL study, in which we can better assign a temporal relationship with adherance to recommendations and cancer outcomes.

IMPACT OF DIETARY PATTERNS ON CANCER INCIDENCE

Dietary interventions have reported a substantial impact on cancer development and prognosis. In this review, we focused on reviewing the largest prospective cohort studies (as RCTs have been limited), which heavily studied plant-based diets (Table 1). However, we discuss these studies briefly but first narrate our current understanding of different diets and their theorized effects on cancer incidence, to understand why and how certain diets were chosen to be the focus of these large prospective trials. Non—plant-based diet of interest, including ketogenic and fasting intervals, are currently being explored in preclinical settings and small-scale clinical studies[30] with interesting but immature results. Of note, other specific diets such as ketogenic and fasting intervals are much more restrictive, difficult to comply with, and most importantly, have complex interactions that are cancer site-specific and, therefore, should not be broadly recommended. For example, ketosis can slow glioblastoma tumor formation because gliomas are unable to effectively use ketones, and this induces a direct Warburg effect.[31] However, epithelial cancer cells of the head and neck metabolize ketones and lactate efficiently, and some research shows that a ketogenic state might propagate the growth of these cancers.[32] Ketone bodies may be usable by the actively growing and stem cell—like component of tumors such as breast cancer[33]; therefore, we need to better understand the long-term effects of a ketotic state in cancer.[34] A recent expert statement explained that most of the current published data support a plant-based diet over ketogenic diet as a safer and easier to maintain lifestyle to reduce cancer risk.[35]

An understanding of the link between nutrition and cancer has led to the development of diets for both cancer prevention and treatment, including the whole-food plant-based diet (WFPBD). This dietary pattern is high in fiber, carotenoids, and polyphenols, while minimizing processed foods and animal products. Although the mechanisms underlying diet and cancer are complex, the WFPBD is suspected to lead to reductions in cancer incidence and all-cause mortality through reduction in BMI and sufficient intake of fiber, phytonutrients, and antioxidants.[36] In addition, as seen in the Adventist Health Study-2 and EPIC Oxford and Oxford Vegetarian Cohort, plant-based diets are linked with a reduction in cancer incidence.[37,38]

In the Adventist Health Study-2, the association between various dietary patterns among 69,120 individuals was examined for overall incidence of any type of cancer except nonmelanoma skin cancer. When compared with nonvegetarian diet, plant-based diets were associated with a reduction in overall cancer risk with multivariate hazard ratio (HR) of 0.84 (95% CI, 0.72-0.99).[37] The WFPBD is highly rich in dietary fibers, which are associated with reductions in cancer-related mortality and all-cause mortality.

In addition high in fiber, the WFPBD is high in polyphenolic compounds, or flavonoids, which have been associated with health benefits. In a prospective study of 56,048 individuals, a moderate habitual intake of

TABLE 2. Impact of Lifestyle on Cancer Prevention and Prognosis: A Summary of the Literature

Author, year	Study type	N	Cancer	Findings
Applebaum et al, 2018	Prospective	168	Advanced cancer	Increased levels of optimism were associated with reduction in depressive symptoms and improved QOL. Increased perception of social support was also associated with improved QOL.
West-Wright et al, 2009	Prospective	3539	Breast	Women with intermediate (0.51-3.0 h/wk/y) or high (>3.0 h/wk/y) levels of long-term physical activity had a lower risk of death from breast cancer versus those with low activity levels.
Johnsson et al, 2019	Prospective	847	Breast	All-cause mortality was lower in the most active individuals, especially in women older than 55 y.
Jung et al, 2019	Prospective	3813	Breast	Women who increased their level of physical activity after diagnosis had decreased overall mortality, breast cancer—related mortality, and recurrence-free survival.
Mutrie et al, 2012	Prospective	148	Breast	Women who were more active throughout treatment to breast cancer had reported lower levels of depression and increased QOL compared with those who were less active.
Forsythe et al, 2013	Prospective	1183	Breast	Levels of pain in patients with breast cancer stage 0-IIIA who exercised regularly during treatment and maintained their body weight.
Kroenke et al, 2006	Prospective	2835	Breast	Socially isolated patients had a higher mortality risk after diagnosis.
Meyerhardt et al, 2012	Prospective	1011	Colon	In patients with stage III colon cancer reporting dietary intake during and 6 mo postadjuvant chemotherapy, higher dietary glycemic load and total carbohydrate intake was associated with an elevated risk of colon cancer recurrence and mortality.
Fung et al, 2014	Prospective	1201	Colorectal	Higher Alternative Healthy Eating Index 2010 score was significantly associated with lower overall mortality, as well as borderline significantly with lower risk of CRC mortality.
Appleby et al, 2016	Pooled analysis from 2 prospective studies	60,310	Any	Cancer (lower in fish eaters [HR, 0.82; 95% CI, 0.70-0.97]), including pancreatic cancer (lower in low meat eaters and vegetarians [HR, 0.55; 95% CI, 0.36-0.86, and HR, 0.48; 95% CI, 0.28-0.82, respectively]) and cancers of the lymphatic/hematopoietic tissue (lower in vegetarians [HR, 0.50; 95% CI, 0.32-0.79]).
Kenfield et al, 2014	Prospective	47,867	Prostate	There was a 22% lower risk of overall mortality among men with greater adherence to the Mediterranean diet after diagnosis.
Chan et al, 2006	Prospective	329	Prostate	There was an inverse relationship with increasing postdiagnosis consumption of tomato sauce and risk of progression of prostate cancer. Men in the highest quartile of consumption had a 40% reduce risk of progression versus lowest quartile.
Meyer et al, 1999	Prospective	384	Prostate	Saturated fat intake was significantly associated with disease-specific survival. Men in the upper tercile had 3 times higher risk of dying from prostate cancer compared with men in the lower tercile of saturated fat.
Yang et al, 2016	Prospective	926	Prostate	Western dietary pattern is related to higher risk of prostate cancer—specific and all-cause mortality. The Prudent dietary pattern (higher intake of fruits, vegetables, fish, legumes, and whole grains) was associated with a 36% lower risk of death.

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TABLE 2. Continued

Author, year	Study type	N	Cancer	Findings
Kenfield et al, 2011	Prospective	2705	Prostate	Physical activity for ≥3 hours a week improved prostate cancer—specific survival with a 61% decreased risk of prostate cancer—specific death.
Bruno et al, 2021	RCT	1344	Breast	Women who increased recommended food consumption or reduced discouraged food consumption reported an odds ratio (OR) of 1.37 (0.70-2.67) and 2.02 (1.03-3.98) to improve 3 or more metabolic syndrome parameters. Moreover, women in the higher category of dietary change reported 4 times higher OR of reducing body weight compared with those in the lower category.
Chlebowski et al, 2006, 2008	RCT	2437	Breast	Patients in the low-fat diet arm (intake <15%) experienced a 24% reduction in breast cancer relapse events, although this effect was reduced in long-term follow up.
Griffith et al, 2009	RCT	126	Breast, prostate, and other cancers	Physical activity throughout cancer treatment improved cardiorespiratory fitness and reduced pain.
Frattaroli et al, 2008	RCT	93	Prostate	For patients with prostate cancer on active surveillance, a whole-food plant-based diet (along with exercise, stress management, and support sessions) compared with control was associated with significantly reduced incidence of conventional prostate cancer treatment.
Cohen et al, 2011	RCT	159	Prostate	Stress management before prostate operation leads to reduced mood disturbance and elevated immune parameters after operation.

CRC, colorectal cancer; HR, hazard ratio; QOL, quality of life; RCT, randomized controlled trial.

flavonoids was associated with lower risk of all-cause mortality.[39] Although robust randomized studies incorporating WFPBD are limited, data suggest this dietary pattern may be beneficial to patient outcomes.

These findings support the integration of dietary changes to decrease the incidence of cancer. There are several studies on different aspects of diet modification in cancer subtypes, but the differences in intervention type and tumor subtypes confound the ability to make general dietary recommendations across cancer types in the primary prevention setting. Assumedly, a patient would be interested in general prevention of all subtypes of cancer put together in a cohesive guideline, which is an area for future endeavors.

ROLE OF PHYSICAL ACTIVITY IN CANCER INCIDENCE

There is a large body of literature revealing the impacts of physical activity and both cancer-related and all-cause mortality (Table 2). In this review, we describe the impact of exercise in cancer prevention based on select systematic reviews. In a comprehensive review by Friedenreich et al,[40] the impact of physical activity and breast cancer was examined by looking at 34 case-control and 28 cohort studies. This review found that 30 of 62 studies reported that compared with less physically active women within their study populations, there was a significant risk reduction in the development of breast cancer among more physically activity women, with average risk reduction of 25%-30%. Higher reduction rates were seen among women engaging in recreational activity, vigorous intensity activity, and those who had performed physical activity throughout their lifetime compared with distinct ages in life.

Similar findings were found in the meta-analysis by Wolin et al[41] evaluating the association between physical activity and prevention of colon cancer. In their analysis, 52 studies when looking at 26 distinct cancer types in a pooled analysis from 12 prospective studies involving 1.44 million individuals, the overall relative risk of colon cancer was reduced for both men and women at 0.76 (95% CI, 0.71-0.82) and 0.79 (95% CI, 0.71-0.88), respectively. Moore et al[42] found that when compared with lower levels of leisure-time physical activity (10th percentile), there was a reduced risk of 13 cancer types among those engaging in higher levels of leisure-time physical activity (90th percentile) with risk reductions of $\geq$20% for 7 cancers.

These findings support the concept that regular recreational exercise is associated with significant cancer risk reduction. Similar to dietary patterns, differences in intervention design and tumor types make general physical activity recommendations difficult in cancer care as a whole, but relatively more physical activity than less is supported as a modifiable risk factor.

IMPACT OF OBESITY ON CANCER OUTCOMES

As mentioned previously, obesity is closely related to diet and physical activity but does have some other endogenous/exogenous components. Because of this overlap, but of respect of the fact that obesity is a complex state not just equivalent to the sum of primary lifestyle factors, in this review, we mention some studies that looked at cancer outcomes stratified by obesity, not specifically diet or physical activity. Obesity has been attributed to an increased risk in both the development of and death from cancer.[9] Thus, it represents a modifiable risk factor that is commonly described in the literature. For example, obesity is implicated in studies evaluating weight loss (and, thus, reduced level of overweight/obesity) and BMI (which is a direct measure defining obesity) (Table 1). However, the specific mechanisms by which obesity impacts cancer development, disease progression, and cancer-associated outcomes is just now starting to be understood. One such example is found in multiple myeloma (MM), which is preceded by a premalignant state known as monoclonal gammopathy of undetermined significance (MGUS). This premalignant state is characterized by a spike in immunoglobulin in serum or urine without evidence of end-organ damage related to MM or other lymphoproliferative disorder.[43,44]

Obesity represents the only known modifiable risk factor for MM, and therefore, studies have examined if there is an association between obesity and transformation of MGUS with MM. Although several studies have not found a direct association between obesity and MGUS, there does appear to be an

TABLE 3. Impact of Lifestyle and Cancer Survivorship: A Summary of the Literature

Author, year	Study type	N	Cancer	Major findings
Kenfield et al, 2010	Prospective cohort	2686	Prostate	Men who were physically active had a 35% lower risk of death from any cause and a modest nonsignificant reduction in risk of prostate cancer—related death. More vigorous activity, and longer duration of activity, was associated with significant further reductions in risk for all-cause mortality.
Westoff et al, 2018	Prospective	595	Bladder	Patients in the highest tertile of adherence to the Western pattern experienced a 1.48 times higher risk of recurrence compared with patients in the lowest tertile.
Cannioto et al, 2023	Prospective cohort	1340	Breast	Strongest adherence to the American Cancer Society and American Institute of Cancer Research prevention recommendations was associated with a 37% reduced hazard of breast cancer recurrence and a 58% reduced hazard of mortality.
Boyapati et al, 2005	Prospective cohort	5042	Breast	Soy food intake was inversely associated with mortality and recurrence. The inverse association was evident among women with either estrogen receptor—positive or estrogen receptor—negative breast cancer and was present in both users and nonusers of tamoxifen.
Cho et al, 2003	Prospective	90,655	Breast	Women in the highest quintile of fat intake had a slight increased risk of breast cancer. The increase was associated with intake of animal fat but not vegetable fat. Among food groups contributing to animal fat, red meat and high-fat dairy foods were each associated with an increased risk of breast cancer.
Sun et al, 2018	Prospective cohort (2018)	2295	Breast	Poor diet quality was associated with higher risk of death. Increased diet quality was not associated with lower risk of death.
Chlebowski et al, 2006	Prospective cohort	2437	Breast	Dietary fat intake was lower in the intervention than that in the control group, corresponding to a statistically significant (P=.005), 6-pound lower mean body weight in the intervention group. Relapse events occurred in 9.8% women in the dietary group and 12.4% women in the control group.
Chelboweski et al, 2008	Prospective cohort	2437	Breast	There was no significant difference in deaths in intervention and control group. A significant overall survival benefit was seen for intervention group participants.
Dwyer et al, 2008	RCT	550	Breast	Neither total flavonoid intakes nor intakes of subclasses of flavonoids differed between those who had dramatically decreased their fat intakes and those who had not.
Pierce et al, 2007	RCT (WHEL subgroup)	3088	Breast	The intervention maintained a higher significant difference in servings of vegetables, fruit, fiber, and energy intake from fat. There was no difference in invasive breast cancer events between groups. No significant interactions were observed between diet group and baseline demographic characteristics, characteristics of the original tumor, baseline dietary pattern, or breast cancer treatment.
Caan et al, 2011	RCT (WHEL)	3088	Breast	As isoflavone intake increased, risk of death decreased. Women at the highest levels of isoflavone intake (>16.3 mg isoflavones) had a nonsignificant 54% reduction in risk of death.
Holmes et al, 2005	Prospective(Nurses' Health Study)	2987	Breast	Increased physical activity was associated with a decreased relative risk of death from breast cancer. The benefit of physical activity was particularly apparent among women with hormone-responsive tumors. Higher physical activity was associated with an absolute unadjusted mortality risk reduction.
Beasley et al, 2011	Prospective	4441	Breast	Women in the highest compared with lowest quintile of intake of saturated fat and transfat had a significantly higher risk of dying from any cause.
Holick et al, 2008	Prospective cohort	4482	Breast	Women who engaged in greater levels of activity had a significantly lower risk of dying from breast cancer.

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TABLE 3. Continued

Author, year	Study type	N	Cancer	Major findings
Irwin et al, 2008	Prospective (2008)	933	Breast	Decreased hazard ratio for death in more active women compared with inactive women if active before and after diagnosis. Women inactive before diagnosis had lower risk of death if they increased their physical activity after diagnosis. Women who decreased physical activity after diagnosis had a 4-fold increase in death.
Sternfield et al, 2009	Prospective (2009)	1970	Breast	The effect of reduced risk of recurrence and breast cancer–related mortality with physical activity was attenuated with adjustment for confounders. There was a positive association between physical activity and all-cause mortality.
Pierce et al, 2008	Prospective	1490	Breast	Reduced mortality was weakly associated with higher vegetable and fruit consumption, increased physical activity, and normal body mass index. The combination of consuming 5 or more servings of vegetables and fruits and equivalent of 30 minutes of walking was associated with a significant survival advantage. No apparent effect of obesity on survival.
Chen et al, 2011	Prospective	4826	Breast	Exercise after diagnosis was inversely associated with total mortality.
Anyene et al, 2021	Prospective cohort	3646	Breast	Healthful plant-based diet index was associated with reduced hazard ratio of all-cause mortality. Increased unhealthy plant-based diet index was associated with increased hazards.
de Glas et al, 2014	RCT	521	Breast	High levels of physical activity before and after the diagnosis were associated with better overall survival.
Demark-Wahnefried et al, 2015	RCT	692	Breast	Significant decreases in physical function and increases in symptoms were observed among controls from baseline to 6 mo but not in the intervention arm.
Goodwin et al, 2014	RCT	338	Breast	Mean weight loss was significantly greater in the intervention arm than that in the comparison arm.
McCullough et al, 2016	Prospective	4452	Breast	Postdiagnostic diet score was associated with neither breast cancer–specific mortality nor cardiovascular disease–related mortality.
Wang et al, 2021	Prospective	8482	Breast	Women with higher postdiagnostic diabetes risk reduction diet score had a lower risk of breast cancer–specific mortality and lower risk of all-cause mortality.
Zheng et al, 2018	Prospective	2150	Breast	Lower (more anti-inflammatory) scores were associated with a lower risk of cardiovascular disease–related mortality, but not with breast cancer–specific mortality.
Jang et al, 2018	Prospective	511	Breast	The dietary inflammatory index assessed after operation was significantly higher in patients with recurrence than those without recurrence, and it was positively associated with the risk for cancer recurrence.
Izano et al, 2014	Prospective	4103	Breast	Adherence to dietary approaches to stop hypertension, and Alternative Healthy Eating Index diets were associated with reduced risk of nonbreast cancer–related mortality. Diet scores were not significantly associated with breast cancer–related mortality.
Vrieling et al, 2013	Prospective	2522	Breast	Increasing consumption of an "unhealthy" dietary pattern was associated with an increased risk of nonbreast cancer–related mortality. No associations with breast cancer–specific mortality and breast cancer recurrence were found.
Wang et al, 2020	Prospective	3450	Breast	Participants in the highest quartiles of Chinese Food Pagoda and DASH diet score had lower risk of total mortality.

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TABLE 3. Continued

Author, year	Study type	N	Cancer	Major findings
George et al, 2014	Prospective	2317	Breast	Women consuming better-quality diets had a lower risk of death from any cause and from nonbreast cancer causes.
George et al, 2011	Prospective	670	Breast	Women consuming better-quality diets, as defined by higher Healthy Eating Index scores, had a reduced risk of death from any cause and an 88% reduced risk of death from breast cancer. Compared with inactive survivors consuming poor-quality diets, survivors engaging in any recreational physical activity and consuming better-quality diets had a reduced risk of death from any cause.
Kim et al, 2011	Prospective	2729	Breast	No association was found between diet quality indices and either total or nonbreast cancer—related deaths. However, a higher aMED (Mediterranean diet) score was associated with a lower risk of nonbreast cancer—related death in women with low physical activity.
Meyerhardt et al, 2006	Prospective cohort	832	Colon	Disease-free survival was better for high levels of physical activity (metabolic equivalent task hours per week). Postdiagnostic activity was associated with improvement in recurrence-free survival.
Meyerhardt et al, 2007	Prospective cohort	1009	Colon	More of a western dietary pattern after cancer diagnosis was associated with a significantly worse disease-free survival. The western dietary pattern was associated with a decrease in recurrence-free survival and overall survival.
Haydon et al, 2006	Prospective	526	Colorectal	Exercisers had improved disease-specific survival.
Meyerhardt et al, 2006	Prospective	573	Colorectal	Increasing levels of exercise after diagnosis reduced cancer-specific mortality and overall mortality.
Meyerhardt et al, 2009	Prospective	668	Colorectal	Increased physical activity was significantly associated with improved CRC-specific mortality and overall mortality.
Barot et al, 2023	Prospective	1098	Colorectal	Patients with the healthiest lifestyle had an improved recurrence-free survival and overall survival.
Van Blarigan et al, 2018	Prospective cohort	992	Colorectal	Patients with a higher American Cancer Society Nutrition score had a lower risk of death during the study period and improved disease-free survival.
Fadelu et al, 2018	Prospective	826	Colorectal	Increased nut consumption was associated with decreased hazard ratio of disease-free survival.
Tabung et al, 2020	Prospective	1718	Colorectal	Patients with CRC in the highest compared with those in the lowest empirical dietary index for hyperinsulinemia quintile had a greater risk of dying from CRC.
Zheng et al, 2020	Prospective	463	Colorectal	Lowest tertile (most anti-inflammatory diet) scores from diet plus supplements were associated with significantly lower all-cause mortality.
Ratjen et al, 2017	Prospective	1404	Colorectal	Higher adherence to the modified Mediterranean diet was significantly associated with lower all-cause mortality.
Fung et al, 2014	Prospective	1201	Colorectal	A higher Alternative Healthy Eating Index score was significantly associated with lower overall mortality and borderline significantly with lower risk of CRC-related mortality.
Sharma et al, 2018	Prospective	532	Colorectal	Processed meats, clusters characterized by meat and dairy products, and total grains, sugar, and soft drinks were associated with a higher risk of combined mortality, recurrence, or metastasis.
Zhu et al, 2013	Prospective	529	Colorectal	Disease-free survival was significantly worsened among patients with a high processed meat dietary pattern. No associations were observed with the prudent vegetable or the high-sugar patterns and disease-free survival.
Morey et al, 2009	RCT	641	Colorectal, breast, and prostate	Less decline in self-reported physical function in the intervention group compared with that in control.

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TABLE 3. Continued

Author, year	Study type	N	Cancer	Major findings
Guercio et al, 2015	RCT	953	Colorectal	Patients consuming 4 cups/d or more of total coffee had decreased hazard ratio for colon cancer recurrence or mortality compared with never drinkers.
Kanera et al, 2017	RCT	462	Multiple	A significant intervention effect after 12 mo was found for moderate physical activity. Age was the only significant moderator with the intervention being more effective with younger participants.
Mustian et al, 2013	RCT	410	Multiple cancer types	Yoga participants reported greater improvements in global sleep quality compared with standard care participants.
Thomson et al, 2023	RCT	1202	Ovarian	Baseline self-reported diet showed a mean daily intake of 6.6 servings of fruit and vegetables, 62.7 g of fats, and 21.7 g of fiber. Physical activity averaged 13.0 MET-h/wk of moderate to vigorous physical activity; 50.9 h/wk of sedentary time.
Hansen et al, 2020	Prospective	512	Ovarian	There association between a healthier lifestyle and better survival was stronger after diagnosis.
Thomson et al, 2014	Prospective	636	Ovarian	Higher diet quality was associated with lower all-cause mortality after ovarian cancer diagnosis.
Richman et al, 2010	Prospective	1294	Prostate	Intakes of processed and unprocessed red meat, fish, total poultry, and skinless poultry were not associated with prostate cancer recurrence or progression. Men with high poultry intake had a 4-fold increased risk of recurrence.
Friedenreich et al, 2015	Prospective cohort	830	Prostate	Postdiagnostic activity was associated with a significantly lower all-cause mortality risk and lower prostate cancer—specific mortality risk.
Dickerman et al, 2019	Prospective	2299	Prostate	Estimated 10-y risks of mortality were reduced with more activity levels.
Yang et al, 2015	Prospective	926	Prostate	The Western pattern was significantly related to a higher risk of prostate cancer—specific and all-cause mortality. The Prudent diet pattern was associated with a significantly lower all-cause mortality.
Kenfield et al, 2014	Prospective	4538	Prostate	There was no association between the Mediterranean diet after diagnosis and risk of lethal or fatal prostate cancer.

CRC, colorectal cancer; DASH, dietary approaches to stop hypertension; RCT, randomized controlled trial.

associated risk in earlier transformation from MGUS to MM in obese individuals.[45] In 2 pivotal studies, obesity was associated with a younger age at time of transformation from MGUS to MM.[45,46] The exact mechanisms driving this are not well known although hypothesized to be related to concomitant comorbid conditions.

IMPACT OF LIFESTYLE FACTORS ON SURVIVORSHIP OUTCOMES

In the survivorship after cancer, the most common malignancy studied is breast followed by colorectal cancer. Comparedwithother malignancies, there is a plethora of studies in patients with breast cancer, being the most commonly studied malignancy in the survivorship setting. Within physical activity, RCTs were mostly educational or physical intervention based and results all trended to significance. RCTs in physical activity in breast cancer reported improved overall survival and weight loss but were inconsistent in QOL and improved understanding of healthy lifestyle (Table 2).[47-51] RCTs in dietary interventions in breast cancer found differences in risk of death and weight loss but not in breast cancer—related events.[49,52,53] Prospective studies in physical activity and breast cancer reported decreased risks of death especially in hormone-responsive breast cancer.[48,54-56] However, reduced risk of recurrence was not clearly found[57] (Table 3).

There were more prospective studies in diet and breast cancer than physical activity. In general, a healthier diet, such as following the American Cancer Society guidelines, reduced (mostly saturated or animal) fat intake, plant-based diet, diabetes reduction, anti-inflammatory, and Mediterrainean diet (among others) was mostly associated with reduction risk of recurrence or death, with few exceptions that reported no difference (Table 3).[58-67]

The second most commonly studied cancer is surviorship was colorectal cancer. There were mostly prospective trials on physical activity after colon cancer, and these studies found improved disease-related survivial for more active suriviors regardless of priagnostic activity.[68-72] One RCT found no significant differences between group for functional assessment changes before and after exercise intervention.[73] Studies of diet in survivors with colorectal cancer disfavored a western dietary pattern because it was associated with worse disease-free and overall survival and poor diet quality of processed foods and high sugar intake.[74,75] Instead, a higher American Cancer Society nutrition score, lower dietary hyperinsulinemia index, anti-inflammatory diet, and the Mediterranean diet were associated with positive outcomes, including lower risk of mortality, sometimes from colorectal cancer—specific mortality or other disease-related surivival.[72,76,77]

Moving forward, studies combining physical activity and diet interventions or observations will likely show promise as lifestyle changes are multifactorial, and we cannot out-eat poor activity or out-exercise poor diet. Although, theoretically, we have some idea as to the biochemical mechanisms behind diet and activity, further research might also focus on understanding how diet andphysical activity biochemically change mortality outcomes. In general, more RCTs and prospective studies are needed in less common cancers, but some of these are underway. Ultimately, studies that combine qualitative QOL outcomes and more numerical oncologic outcomes such as recurrence risk/mortality might help us understand the “bigger picture” of the effect of diet and exercise on cancer survivorship.

DISCUSSION

This narrative review emphasizes the importance of lifestyle on cancer prevention, prognosis, and survivorship. Although lifestyle factors do not independently influence cancer development, they are exogenous components that can modulate the underlying mechanisms that drive oncogenesis and, thereby, likely play a critical role in primary cancer risk and health outcomes after diagnosis. The studies presented in this review indicate that a signficant reduction in cancer incidence and all-cause mortality can be achieved through modification of diet and physical activity. It should be recognized we use the term lifestyle broadly in this review, given the diverse variation of interventions; hence, each intervention (ie, specific dietary and physical activity modifications) and associated cancer outcome should be critically reviewed for relevance in particular patient populations.

ALthough the role of healthy lifestyle on prevention and prognosis in cancer patients is generally well-established, the impact of lifestyle modifications on cancer survivorship is less elucidated. This review focused on the impact of lifestyle factors on survivorship in patients with breast and colorectal cancer because research in other malignancies is limited. Within the breast and colorectal cancer realm, the literature does show a trend toward improved disease-related survival and overall survival in patients adhering to WCRF/AICR guidelines. Such findings may be similar across other cancer types; however, more RCTs and prospective studies are needed to further clarify this. Moreover, some smaller studies have shown no beneficial effect of certain lifestyle interventions on cancer recurrence and QOL. Future research would benefit from larger cohort studies with longer follow-up times to ascertain the role of lifestyle modification on cancer survivorship.

Cancer development is associated with dysregulatory mechanisms of normal cellular processes, driven by both endogenous and environmental factors. Recent data have shown the contribution of obesity on oncogenesis through alterations in various pathways, culiminating in a state of chronic inflammation that leads to ongoing oxidative stress, proinflammatory cytokine and akipokine release, insulin resistance, and alterations in cellular microenviornment.[78] An understanding of obesity-related oncogenesis is therefore critical because we aim to reverse these dysfunctinal pathways through lifestyle modifications such as physical activity, weight loss, and dietary modifications.

Many studies to date have systematically reviewed the relationship of individual lifestyle factors on both incidence and all-cause mortality of cancer, giving us invaluable information to encourage patients to lead healthy lifestyles. Despite this, the volume of information can be overwhelming for clinicians to access, summarize, and apply in clinical practice. This narrative review provides clinicians a resource of the largest known studies to date, thus enabling evidence-informed counseling on diet and physical activity, with site-specific interventions.

There is limited research available investigating the impact of combined lifestyle intervention, which we identify as a potential area of future research. Although our review supports the impact of single lifestyle modifications on risk reduction in cancer incidence, more research is needed to identify the effects of multiple lifestyle interventions, applied simulataneous or sequentially, to investigate synergistic effects of the applied interventions. This includes stress and social support, that is, the mind-body connection, which has been implicated in the development of cancer incidences and progress. There is currently limited understanding of the impact of these 2 factors on the full reach of their impact on biological effects. To fill these gap, we need robust systems—based designed RCTs evaluating the effects of comprehensive lifestyle modifications on cancer prevention and prognosis. It would require patients to be followed up over decades, randomized to their "regular" lifestyle versus intervention with diets and physical activity, social support and stress interventions that are broadly feasible, implementable, and disseminable. Indeed, this would be an arduous but an impactful endeavor.

In summary, this narrative review highlights the potent clinical impact of lifestyle modification (specifically diet and physical activity) on cancer outcomes and reviews the oncogenic mechanisms modulated by lifestyle medicine, as both endogenous and exogenous factors. Although plenty of primary data exist, they are limited to cancer subtype, breadth and uniformity of interventions, and high-quality holistic interventions incorportating multimodal approaches (such as including stress modification in addition to diet and activity). This makes global and detailed recommendations difficult to acertain for the practicing clinician. This narrative review helps to summarize the key studies in the field of lifestyle medicine as they specifically relate to cancer, which can guide clinical practive recommendations and future research design.

POTENTIAL COMPETING INTERESTS

The authors declare no conflicts of interest.

Abbreviations and Acronyms: **AICR,** American Institute for Cancer Research; **MGUS,** monoclonal gammopathy of undetermined significance; **MM,** multiple myeloma; **QOL,** quality of life; **RCT,** randomized controlled trial; **WCRF,** World Cancer Research Fund

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