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Effects of Complementary and Integrative Medicine on Cancer Survivorship

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Abstract Cancer survivorship has become a topic of great interest in the past few years. Unfortunately, even with successful treatment as well as good follow-up care, many patients continue to experience unmet physical, emotional, and spiritual needs as well as having an unsettling fear, fear of recurrence, a fear which most survivors share, even many years after their treatment ended. As a result, patients are continually looking for additional ways to address these needs and fears. Among the most popular approach is the use of complementary and integrative medicine (CIM). Most studies on CIM use among cancer patients and survivors concentrate on symptom improvement and improvement of quality of life and do not touch a crucial question if these therapies can affect patients' survival in terms of prolongation of life. Interestingly, in recent years, there are a growing number of studies that suggest that approaches such as mind-body interventions, enhanced general nutrition, nutritional supplements, physical activity, and other CIM approaches may have a positive effect on survival of cancer patients. Although additional studies are needed to confirm these findings, given the low cost of these CIM interventions, their minimal risk, and the potential magnitude of their effects, these approaches might be considered as additional important tools to integrate into cancer survivorship care plans.

Keywords Cancer survivorship · Unmet needs · Cancer care · Complementary medicine · Integrative medicine · Cancer prognosis · Nutrition · Nutritional supplements · Exercise · Mind body medicine

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Introduction

According to the U.S. National Cancer Institute (NCI), cancer survivorship is the process of living with, through, and beyond cancer. By this definition, cancer survivorship begins at diagnosis [1]. The number of "cancer survivors" in the U.S.A. continues to increase dramatically, from 3 million in 1971 to an estimate of over 14 million survivors as of 2014. These survivors represent approximately 4 % of the U.S. population, many of them 65 years or older. Because of advances in cancer treatment and care, the expectation of living at least 5 years after diagnosis and treatment has increased from approximately 50 % in the 1970s to 69.4 % in 2011 [2].

On the surface, cancer survivors emerge from their encounter with cancer and return to their regular lives after completing active treatment with surgery, radiation, chemotherapy, or other treatment options. With the completion of active treatment, frequent contact with the health care team ends and, for some cancer survivors, so does the sense of security that such contact provide [3]. Still patients face long-term effects of treatment which include fatigue, infertility, cognitive dysfunction, neuropathy, heart failure, kidney failure, cataracts, and

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second primary cancers [4]. Survivors may become lost during the transition to surveillance because of a lack of awareness about survivorship needs or poor coordination of care among oncologists and primary care physicians [3]. Even with state-of-the-science biomedical treatment, cancer patients' psychosocial needs, including those related to anxiety, depression, and issues related to shaken faith or changes in sexual functioning—can cause additional suffering, weaken adherence to prescribed treatments, and threaten patients' return to a state of well-being [5, 6].

In most survivorship care plans, a great deal of effort is focused on surveillance for cancer spread, recurrence, or second cancers [7–10]. On the other hand, patients often want to know what additional steps they can take to prevent late effects of treatments, prevent a recurrence, improve their quality of life and at the same time, prolong their life [11].

Several studies have shown that many survivors have a range of unmet needs, needs that are not quite appreciated by their treating physician [12–15]. In a multicenter, prospective survey of cancer patients from 66 centers in the U.K., 30 % of the participants reported at least five moderate-to-severe unmet needs, both at the end of treatment and 6 months later [12]. One of the leading unmet needs is learning how to cope with uncertainty and fear: fear of disease recurrence, fear of late treatment effects, and fear of death [13]. In an Australian study of 117 long-term (2–10 years) breast cancer survivors, approximately two thirds of the women reported at least one unmet need, most often involving existential survivorship issues, which were expressed as fear of recurrence [14]. Fear of recurrence can lead cancer survivors to over-interpret the significance of minor physical problems, such as a headache or joint stiffness. Patients often have difficulty in knowing what is "normal" and what needs to be reported to their health care provider. Addressing the fear of recurrence is the most common unmet need among survivors [13–15].

In order to address those unmet needs, many individuals choose to incorporate complementary and integrative medicine therapies such as meditation, acupuncture, yoga, and diet into their care [16•]. Patients are utilizing these treatments with a goal of gaining a sense of control and being more active participants in their care. By doing so, they seek to reduce the side effects of conventional cancer treatments and improving their quality of life [16•]. Cancer survivors are employing a menu of complementary and integrative medicine (CIM) practices to manage the chronic effects of treatments, reduce the risk of recurrence or second cancers, gain control over their lives, address co morbid conditions exacerbated by illness, and, ultimately, improve their quality of life [17, 18].

But the main question that some of these patients raise relate to survival. Patients wonder if different practices of CIM can affect recurrence, cancer mortality, and survival. This question seems to be the main issue that researchers need to address. Most studies on CIM concentrate on symptom improvement and improvement of quality of life and do not touch a crucial question that is commonly raised in clinical settings of integrative oncology practice: "Can we improve our survival if we integrate certain CIM practices?" [19]. In the next few pages, we try to address this essential question.

Complementary and Integrative Medicine and Cancer Survivorship

Complementary and integrative medicine (CIM) is a new term that is now replacing the term complementary and alternative medicine (CAM). It reflects the integration of the best conventional health care with evidence-based complementary modalities such as acupuncture, massage, mind-body medicine, nutrition and nutritional supplements, and other modalities [20].

Patients who have been affected by cancer utilize CIM on their own to address some of their unmet needs [20–25]. Population-based studies have shown that cancer survivors are more likely to use CIM than are people in the general population [21, 22]. Moreover, cancer survivors' use of CIM appears to have increased in recent years [23, 24]. In a large study published in 2008, 68 % of surveyed cancer survivors reported unmet needs, and individuals with at least one unmet need were 63 % more likely to use CIM [25]. Furthermore, the majority of those using CIM had not communicated this to their clinician [25].

A recent study suggests that this lack of communication between patients and physicians is changing [26]. More physicians are recommending CIM, and cancer survivors are using CIM more often because of recommendations from healthcare providers. Patients also are more likely to disclose their CIM use to their provider [26].

Complementary and Integrative Medicine and Psychosocial Distress

CIM use may indicate the presence of psychosocial distress; depression; or anxiety; perceived lack of social support; or an expectation of a poor outcome [27, 28]. If cancer care fails to address this type of cancer-related psychosocial distress [6], survivors may choose CIM as a mean of remedying this deficiency [26]. CIM use also may offer cancer survivors a sense of control in the face of an uncertain future [19, 29].

Surveys indicate that patients in general are looking for reliable information on CIM that they can integrate into their care [30–36]. In most instances, patients who use CIM are not disappointed in or dissatisfied with conventional medicine but want to do everything possible to regain their health and improve their quality of life [30–32].

Table 1 Lifestyle changes, complementary and integrative medicine—survival outcomes

Author	Cancer type	Intervention	Participants	Results
		Mind body		
Spiegel et al. [53]	Breast	Weekly supportive group therapy with self-hypnosis for pain	86 patients with metastatic breast cancer	A mean of 36.6 months in the intervention group compared with 18.9 months in the control group
Spiegel et al. [54]	Breast	Weekly supportive-expressive group therapy	Metastatic (n=122) or locally recurrent (n=3) breast cancer	ER-negative participants, survived longer (median, 29.8 months) than ER-negative controls (median, 9.3 months), ER-positive participants showed no treatment effect.
Giese-Davis et al. [44]	Breast	Supportive-expressive group therapy	125 women with metastatic breast cancer	Median survival time was 53.6 months for women with decreasing depression scores compared to 25.1 months for women with increasing depression scores.
Fawzy et al. [55, 56]	Melanoma	Psychoeducation intervention Groups of 7 to 10 patients met for 1.5 h weekly for 6 weeks	68 patients with malignant melanoma	At 5- to 6-year follow-up, participation in the intervention lowered the risk of recurrence by more than 2.5-fold (RR=2.66), and decreased the risk of death approximately 7-fold (RR=6.89). At the 10-year follow-up, a decrease in risk of recurrence was no longer significant, and the risk of death was 3-fold lower (RR=2.87) for those who participated in the intervention.
		Nutrition and nutritional supplements		
Thomson et al. [62]	Breast	Vegetable intake	3,080 breast cancer survivors	Baseline vegetable intake in the highest as compared to lowest tertiles was associated with an overall lower adjusted HR for recurrence of 0.69
Meyerhardt et al. [60]	Colon cancer stage III	Dietary glycemic load and total carbohydrate intake	1,011 stage III colon cancer patients reporting dietary intake during and 6 months after participation in an adjuvant chemotherapy trial.	Higher dietary glycemic load and total carbohydrate intake were statistically significant associated with an increased risk of recurrence and mortality
Ogunleye et al. [71]	Breast	Green tea—3 cups or more per day	5,617 cases of breast cancer	Increased green tea consumption was inversely associated with breast cancer recurrence (pooled RR=0.73; 95 % CI, 0.56–0.96).
Cui et al. [72]	Breast	Ginseng use as a complementary therapy	A cohort of 1,455 breast cancer patients	Regular users had a significantly reduced risk of death; adjusted hazard ratios associated with ginseng use were 0.71 (95 % CI, 0.52, 0.98) for total mortality and 0.70 (95 % CI, 0.53, 0.93) for disease-specific mortality/recurrence.
Matsui et al. [73]	Hepato cellular carcinoma	AHCC supplementation	269 consecutive patients with histologically confirmed HCC	The AHCC group had a significantly longer no recurrence period (HR, 0.639; 95 % CI), 0.429–0.952; P=0.0277) and an increased overall survival rate (HR, 0.421; 95 % CI, 0.253–0.701; P=0.0009) when compared to the control group
Kang et al. [74]	Breast	Soy intake	524 patients with breast cancer positive for estrogen and progesterone receptor and	Relative to post-menopausal patients in the lowest quartile of soy isoflavone intake, the risk of

Table 1 (continued)

Author	Cancer type	Intervention	Participants	Results
			receiving anastrozole as endocrine therapy	recurrence for post-menopausal patients in the highest quartile was significantly lower (HR=0.67; 95 % CI, 0.54–0.85, *p* for trend=0.02).
Shu et al. [75]	Breast	Soy intake	Population-based cohort study of 5,042 female breast cancer survivors in China	The hazard ratio associated with the highest quartile of soy protein intake was 0.71 (95 % CI, 0.54–0.92) for total mortality and 0.68 (95 % CI, 0.54–0.87) for recurrence compared with the lowest quartile of intake.
Kwan et al. [76]	Breast	Prudent diet (High intakes of fruits, vegetables, whole grains, and poultry) compared to Western diet (high intakes of red and processed meats and refined grains)	1,901 Life After Cancer Epidemiology Study participants diagnosed with early-stage breast cancer	Adherence to a prudent dietary pattern was associated with a statistically significant decreasing risk of overall death (*P* trend=0.02; HR for highest quartile=0.57; 95 % CI, 0.36 to 0.90) and death from non-breast cancer causes (*P* trend=0.003; HR for highest quartile=0.35; 95 % CI, 0.17 to 0.73).
Greenlee et al. [77]	Breast	Vitamins C and E	2,264 women in the Life After Cancer Epidemiology (LACE) cohort—women who were diagnosed with early-stage, primary BC.	Frequent use of vitamin C and vitamin E was associated with a decreased risk of BC recurrence (vitamin C: HR, 0.73; 95 % CI, 0.55–0.97; vitamin E: HR, 0.71; 95 % CI, 0.54–0.94); and vitamin E use was associated with a decreased risk of all-cause mortality (HR, 0.76; 95 % CI, 0.58–1.00)
Keum and Giovannucci [68]	General cancer	Over 2–7 years of duration, vitamin D supplementations	Meta-analyses of RCTs of vitamin D supplementation and total cancer incidence and mortality	Significantly reduced total cancer mortality
Bell et al. [69]	General cancer mostly lung, hematopietic, colorectal, breast, pancreas and others	Intake of long-chain ω-3 fatty acids	Study participants (*n*=70,495) were members of a cohort study (the Vitamins and Lifestyle Study) who were residents of Washington State aged 50–76 with 6 years follow-up	Higher combined intake of eicosapentaenoic acid and docosahexaenoic acid from diet and supplements was associated with a decreased risk of total mortality (HR=0.82, 95 % CI, 0.73, 0.93) and mortality from cancer (HR=0.77; 95 % CI, 0.64, 0.92)
Murphy et al. [70]	Nonsmall cell lung cancer (NSCLC)	Fish oil supplementation	Forty-six patients completed the study, *n*=31 in the SOC group and *n*=15 in the FO group (2.5 g EPA+DHA/day).	One-year survival tended to be greater in the FO group (60.0 % vs 38.7 %; *P*=0.15). Compared with SOC, supplementation with FO results in increased chemotherapy efficacy without affecting the toxicity profile
Tang et al. [61]	Bladder Ca	Cruciferous vegetables	A total of 239 bladder cancer patients. After an average of 8 years of follow-up	Significant inverse association was observed between bladder cancer mortality and broccoli intake, in particular raw broccoli intake (≥1 versus <1 serving per month; HR for overall death, 0.57; 95 % CI, 0.39–0.83;
Skuladottir et al. [78]	Lung	Vegetables and fruit	353 participants that had lung cancer using data on 57,053 participants in the Danish prospective cohort study, 'Diet, Cancer and Health'.	Increasing levels of intake of fruit and vegetables show a tendency toward decreased hazard of dying: the Cox proportional hazard model estimated a HR of 0.84 (95 % CI, 0.59–1.21)

Table 1 (continued)

Author	Cancer type	Intervention	Participants	Results
				for high intake of vegetables by current smokers and an HR of 0.81 (95 % CI, 0.58–1.15) for high intake of fruits with low intake as the reference. In contrast, high intake of potatoes increased the hazard of dying (HR, 1.51; 95 % CI, 1.12–2.23).
		Exercise		
Holmes et al. [79]	Breast	Women who reported 9–15 MET hours of physical activity per week	2,987 women with a diagnosis of breast cancer, monitored for up to 18 years	50 % reduction in risk of cancer-specific mortality (compared with women who reported less than 3 MET h/week).
Kenfield et al. [81]	Prostate cancer	Over 3 h/week of vigorous activity	2,705 men with non metastatic prostate cancer observed 1990–2008	*All cause mortality reduced by 49 % *Reduce risk of prostate cancer death by 61 %
Richman et al. [82]	Prostate cancer	Walking briskly for 3 h/week or more	1,455 men diagnosed with clinically localized prostate cancer	57 % lower rate of progression
Ruden et al. [92]	Glioma	Physical activity of over 9 MET h/week	243 patients with WHO grades 3 to 4 recurrent malignant glioma	Median survival was 13.03 months for patients reporting less than 9 MET h/week relative to 21.84 months for those reporting over 9 MET h/week.
Irwin et al. [96]	Breast cancer	in ≥9 or more MET-hous per week of physical activity after diagnosis	4,643 postmenopausal women diagnosed with invasive breast cancer	Women participating in ≥9 or more MET-hours per week of physical activity after diagnosis had lower breast cancer mortality (HR=0.61; 95 % CI, 0.35–0.99; P=0.049) and lower all-cause mortality (HR=0.54; 95 % CI, 0.38–0.79; P<0.01).
Jeon et al. [83]	Colon cancer	Physical activity after diagnosis	Prospective observational study of 237 patients with stage III colon cancer who had recurrence of disease	The hazard ratio comparing patients who reported at least 18 MET h/week of physical activity with those engaging in <3 MET h/week was 0.71 (95 % confidence interval, 0.46–1.11)
Chen et al. [80]	Breast	exercise during the first 36 months postdiagnosis follow-up median 4.3 years	4,826 women with stage I to III breast cancer identified 6 months after diagnosis	Exercise during the first 36 months postdiagnosis was inversely associated with total mortality and recurrence/disease-specific mortality with HRs of 0.70 (95 % CI, 0.56–0.88) and 0.60 (95 % CI, 0.47–0.76), respectively
		Integration—combining multiple CIM modalities		
Pierce et al. [87]	Breast cancer	Combination of consuming five or more daily servings of vegetables and fruits and accumulating 540+ MET min/week	1,490 women with diagnosis and treatment for early-stage breast cancer 1991–2000	Significant survival advantage (HR=0.56; 95 % CI, 0.31 to 0.98). 44 % reduction in risk for mortality
Andersen et al. [84••]	Breast	Psychologic interventions that address nutrition, stress reduction, and physical activity in the first year of diagnosis	227 women with median follow-up of 11 years	Patients in the intervention arm were found to have reduced risk of death from all causes (HR=0.51, P=0.028) a reduced risk of breast cancer recurrence (HR=0.55, P=0.034) and reduced risk of death from breast cancer (HR=0.44, P=0.016) compared with patients in the assessment-only arm.

Table 1 (continued)

Author	Cancer type	Intervention	Participants	Results
McCullough et al. [89]	Cancer all types	Following ACS guidelines: body mass index, physical activity, diet, and alcohol consumption	111,966 nonsmoking men and women in the Cancer Prevention Study-II Nutrition Cohort	The RR of all-cause mortality was lower for participants with high (7–8) versus low (0–2) scores of adherence to the ACS guidelines(men, RR=0.58; 95 % CI, 0.53–0.62; women, RR=0.58; 95 % CI, 0.52–0.64). Inverse associations were found with cancer mortality (men, RR=0.70; 95 % CI, 0.61–0.80; women, RR=0.76; 95 % CI, 0.65–0.89). Reduced risk of death from all causes was 42 % and from cancer 30 %
World Cancer Research Fund/American Institute for Cancer Research. Food, [58, 59]	Most cancer types	Nutrition, exercise, maintaining BMI	A panel of 21 experts from 11 countries review over 4,000 references extracted from systematic literature reviews from 9 institutions on food, nutrition, physical activity and their relationship to cancer	30–40 % of cancers can be prevented with nutrition, regular physical activity, and avoidance of obesity
Aleksandrova et al. [97•]	Colorectal cancer	healthy weight, physical activity, non-smoking, limited alcohol consumption and a healthy diet	347,237 men and women, 25 to 70 years old, provided dietary and lifestyle information at study baseline (1992 to 2000) data collected within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Over a median follow-up time of 12 years	Compared with 0 or 1 healthy lifestyle factors, the HR for CRC was 0.87 (95 % CI, 0.44 to 0.77) for two factors, 0.79 (95 % CI, 0.70 to 0.89) for three factors, 0.66 (95 % CI, 0.58 to 0.75) for four factors and 0.63 (95 % CI, 0.54 to 0.74) for five factors
Inoue-Choi et al. [94]	Cancer all types	Following WCRF/AICR cancer prevention guidelines (Nutrition, Exercise, Weight, Alcohol) with 5 years of follow-up	2,017 participants in the Iowa Women's Health Study who had a confirmed cancer diagnosis	Women with the highest (6–8) versus lowest (0–4) adherence score had lower all-cause mortality [HR=0.67; 95 % confidence of interval (CI), 0.50–0.94].
Vergnaud et al. [95]		Following WCRF/AICR cancer prevention guidelines (nutrition, exercise, weight, alcohol) With a median follow-up time of 12.8 years	378,864 participants from 9 European countries enrolled in the European Prospective Investigation into Cancer and Nutrition study	Participants within the highest category of the WCRF/AICR score (5–6 points in men; 6–7 points in women) had a 34 % lower hazard of death (95 % CI, 0.59, 0.75) compared with participants within the lowest category of the WCRF/AICR score (0–2 points in men; 0–3 points in women)
Hastert et al. [93•]	Post menopausal breast cancer	Following WCRF/AICR cancer prevention guidelines (nutrition, exercise, alcohol) with over 6.7 years of follow-up	30,797 post-menopausal women ages 50–76 years at baseline in 2000–2002 with no history of breast cancer.	Breast cancer risk was reduced by 60 % in women who met at least five recommendations compared to those who met none (HR, 0.40; 95 % CI, 0.25–0.65; *P* trend <0.001).

A study at MD Anderson Cancer Center looked at the benefits of using a consultation service to integrate CIM into cancer care. The researchers concluded that patients' primary concerns were related to the need to obtain reliable information on CIM and how to use it effectively and safely to improve their quality of life as well as affect their prognosis [19]. Patients stated that they wanted to do whatever they could to enhance their general well-being, reduce physical and emotional discomfort, and improve their coping mechanisms. They also valued support and guidance from "trusted individuals" in making choices about the proper use of CIM [37–41].

Addressing CIM-related questions and concerns seemed to empower patients and their families and provided significant relief to their distress [19, 29]. These findings are similar to those of a report from the U.K. that summarized a parallel experience of providing a CIM intervention consultation [41].

Complementary and Integrative Medicine: Safety, Efficacy, and Cancer Survival

Some clinicians worry that providing information about CIM may foster a sense of "false hope" or expose a patient to risky therapy. This concern is based on the small body of knowledge concerning CIM's safety and efficacy in cancer prevention and treatment [42].As a result of these concerns, many patients are told that there is nothing they can actively do to prevent cancer or improve outcomes after a cancer diagnosis [42]. However, new evidence from animal studies, epidemiological studies, and a few clinical trials has demonstrated that integrative approaches and lifestyle changes, including stress reduction, nutrition, and physical activity, can in fact influence cancer survivorship [42–83, 84••, 85–92, 93•, 94–96, 97•]. The studies summarized in Table 1 document the ability of mind–body interventions, exercise, nutritional therapy and certain nutritional supplements to influence the survival of patients affected by cancer.

Mind–Body Interventions

The most common emotional reactions during and after cancer treatment are stress, anxiety, depression, anger, and fear [43]. Untreated mood disorders can negatively affect a patient's quality of life, level of pain, and response to chemotherapy. Reducing negative emotions, such as depression, may contribute to a longer survival [44, 45].

Animal studies have shown that psychological distress is associated with faster tumor growth and spread [46, 47]. These types of studies cannot be performed on humans, but findings such as these on the effect of stress on tumor development may be relevant for clinicians and cancer researchers to consider.

A review of the literature found a strong association between stress, cancer morbidity, and cancer mortality [48]. In this study, researchers reviewed 165 studies suggesting that stress-related psychosocial factors are associated with a higher cancer incidence in general. Moreover, in a review of 330 studies, stress was associated with poorer survival and higher cancer mortality among patients diagnosed with cancer [48].

A recent study of 2,230 breast cancer survivors who had a median follow-up of 4.8 years found a lower mortality among women in the highest tertile of social well-being/QOL scores compared to those with the lowest scores. Women with higher QOL scores had a 38 % decreased risk of death and a 48 % decreased risk of breast cancer recurrence [49]. Based on these results, encouraging patients to become active participants in their own health may provide a sense of hope and reduce depression and anxiety [43].

If there is a connection between a patient's emotional status and quality of life and survival, the following question must be asked: Can easily accessible interventions that improve the emotional status of cancer patients also improve survival?

Mind–body interventions such as guided imagery, mindfulness meditation, and yoga are commonly used to reduce stress among cancer patients. A meta-analysis of 116 studies found that mind–body therapies reduced anxiety, depression, and mood disturbance in cancer patients [50]. Other researchers have reported the successful application of mind–body therapies such as relaxation techniques for treating anxiety, insomnia, and chemotherapy-related nausea; strengthening a sense of control; and countering feelings of hopelessness [51, 52].

Accumulating data do appear to support the belief that mind–body interventions improve quality of life and well-being, but the question remains: Can we actually affect survival by utilizing these mind–body interventions? A few studies have tried to address this crucial question. For example, Spiegel approached this issue in 1989 [53], when he evaluated an intervention among a group of 86 women with metastatic breast cancer. The 1-year intervention consisted of weekly supportive group therapy with self-hypnosis for pain. Both the treatment (n=50) and control groups (n=36) received routine oncologic care. At a 10-year follow-up, only three of the patients were alive; death records were obtained for the other 83. The survival duration from the time of randomization and onset of the intervention was a mean 36.6 months in the intervention group compared with 18.9 months in the control group [53].

Another study attempted to replicate these findings 10 years later but produced mixed results. A survival benefit was noticeable only among women with estrogen receptor (ER)-negative breast cancer. The women randomized to treatment survived longer (median, 29.8 months) than did the ER-negative controls (median, 9.3 months), but the ER-positive participants showed no treatment benefit [54].

Fawzy et al. [55] also addressed the effect of psychoeducational intervention on the survival of patients

with malignant melanoma. This intervention consisted of supportive expressive group therapy. At a 5- to 6-year follow-up, women who participated in the intervention experienced a 2.5-fold reduction (RR=2.66) in their risk of recurrence and decreased their risk of death by approximately 7-fold (RR=6.89).

At the 10-year follow-up, a decrease in the risk of recurrence was no longer significant. However, the risk of death remained significant and was 3-fold lower (RR=2.87) for those who had participated in the intervention [55, 56].

Boesen [57] attempted to replicate Fawzy's study [82] using a similar form of intervention among 258 Danish patients who had cutaneous malignant melanoma. In this study, psychoeducational support group did not increase survival or the recurrence-free interval among patients with malignant melanoma. However, nonparticipants in the study had a statistically significant (more than 2-fold) greater risk of death than did the study participants [57].

The clinical significance of the link between stress, emotions, and survival needs further evaluation; however, taking the results from the above studies into account, it is reasonable to conclude that in certain situations utilizing these mind–body interventions might affect survival with minimal risk and potentially significant benefit.

Nutrition

Nutrition has been discussed as a potentially important factor in cancer promotion and prevention. The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) report that 30–40 % of cancers can be prevented with proper food and nutrition, regular physical activity, and avoidance of obesity [58]. The evidence base supporting the health-related benefits of regular physical activity, plant-based diet, and weight control continues to expand [59].

The WCRF and AICR jointly recommend that all cancer survivors receive nutritional care from trained professionals, with the goal of following specific recommendations for diet and physical activity as a way to reduce risk of developing cancer [58]. In the organizations' combined document—*Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective Expert Report*—, the main recommendations call for consuming a greater variety of vegetables, fruits, whole grains, and legumes; aiming for meals that consist of two thirds (or more) vegetables, fruits, whole grains, or beans and one third (or less) animal protein; avoiding sugary drinks; and limiting consumption of energy-dense foods (particularly processed foods high in added sugar, low in fiber, or high in fat [58]). Additional studies that came after this report support these same conclusions [60, 61].

Moving from primary prevention to secondary prevention, several studies suggest that the same principles apply for both. The Women's Healthy Eating and Living (WHEL) study, conducted among 3,080 breast cancer survivors and administered by researchers at the University of Arizona, revealed a direct relationship between vegetable intake and cancer recurrence. Baseline vegetable intake in the highest versus lowest tertiles was associated with an overall lower adjusted hazard ratio (HR) for recurrence of 0.69; 95 % CI 0.55–0.87. The researchers concluded that baseline vegetable intake might be associated with the risk of breast cancer recurrence or with new events, even among women taking tamoxifen [62].

A recent Canadian study suggests that nutrition may play a role even among women with a genetic predisposition toward developing breast cancer, such as those who have a BRCA mutation. The researchers evaluated dietary diversity among a French–Canadian population. This population comprised 738 patients with incident primary breast cancer, including 38 BRCA mutation carriers. The research revealed a strong and significant interaction between BRCA mutations and diversity of vegetable and fruit intake (COR=0.27; 95 % CI=0.10–0.80; P=0.03) when the upper quartiles were compared to the lower quartiles. The authors concluded that vegetable and fruit diversity may be associated with a significant reduced risk of breast cancer among women with BRCA mutations [63].

The AICR adds that certain foods may be beneficial in cancer care in preventing recurrence including: beans, berries, cruciferous vegetables, flaxseed, garlic, green tea, tomatoes, and others [59, 61, 64–66]. The AICR emphasizes that no single food or food component by itself can protect against cancer, but the combination of foods in a predominantly plant-based diet may offer protection.

Accumulating evidence suggests that the minerals, vitamins, and phytochemicals in plant foods may interact in ways that boost their individual anti-cancer effects [59]. The cancer chemopreventive potential of naturally occurring phytochemicals is of great interest worldwide. Moreover, phytochemicals offer the advantages of safety, low cost, and oral bioavailability [65–67]. Even though the AICR emphasizes that no single foods by themselves can protect against cancer, some studies do suggest potential survival benefit with specific foods and supplements, such as vitamin D [68], omega 3 fatty acids [69, 70], green tea [71], ginseng [72], active hexose-correlated compound (AHCC) [73], soy [74, 75], and others. Additional studies with specific populations support the value of plant-based diet and vitamin use in decreasing the hazard of dying with breast and lung cancer patients [76–78].

Exercise

Regular physical activity has been recommended in many professional guidelines and in American Cancer Society publications [58, 59, 64]. Nonetheless, the potential benefits of exercise in terms of cancer survival have not been sufficiently

emphasized. One well-conducted study monitored 2,987 women with breast cancer for up to 18 years. The study results showed that women who reported 9–15 metabolic equivalent task (MET) hours of physical activity per week (equivalent to 3–5 h of brisk walking) had an impressive 50 % reduction in their risk of cancer-specific mortality compared with women who reported fewer than 3 MET h/week. Similar risk reductions were observed for breast cancer recurrence and all-cause mortality [79]. A more recent study with 4,826 women with stages I to III breast cancer, revealed that exercise during the first 36 months post diagnosis was inversely associated with total mortality and recurrence/disease-specific mortality with HRs of 0.70 (95 % CI, 0.56–0.88) and 0.60 (95 % CI, 0.47–0.76), respectively. The exercise–mortality associations were not modified by menopausal status, comorbidity, QOL, or body size [80].

In another study, 2,705 men with non-metastatic prostate cancer were observed for 18 years. Those who participated in regular vigorous physical activity had a reduction in all-cause mortality of 49 % [81]. An additional study of 1,455 men with clinically localized prostate cancer revealed that brisk walking for 3 h or more per week was significantly associated with a reduced rate of cancer progression (57 % lower among men who exercised versus those who did not) [82].

In a prospective observational study, researchers studied the impact of physical activity in 237 patients with stage III colon cancer who had recurrence of disease. They found that increasing total MET hours of physical activity per week was associated with a statistical significance trend for improved survival after recurrence. The benefit of the physical activity on patients' survival was not significantly modified by sex, body mass index (BMI), number of positive lymph nodes, age, baseline performance status, adjuvant chemotherapy regimen, or recurrence-free survival period [83].

Integration—Combining CIM Therapies Together

Stress reduction, nutrition, reduced alcohol intake, smoking cessation, and physical activity play important role in improving the survival of cancer patients [54–57, 62, 63, 71–75, 81, 82, 84••, 85–92, 93•, 94–96, 97•]. Questions regarding the ideal frequency and "dosage" of these elements are still under investigation. However, it may be that the combined effect of these approaches is more powerful than the effects of the individual components.

For example, a prospective study of 1,490 women who were treated for early-stage breast cancer between 1991 and 2000 found a significant survival advantage only for women who consumed five or more daily servings of vegetables and fruits *and* accumulated 540+ MET-minutes of exercise per week (equivalent to walking 30 min 6 days per week). The women who met these criteria had a significant survival advantage (HR=0.56; 95 % CI, 0.31 to 0.98) over those who did not. The approximately 50 % risk reduction associated with these healthy lifestyle behaviors was observed in both obese and non-obese cancer survivors [87].

Another study found an increasing survival benefit as patients increased their number of beneficial lifestyle activities [91]. The study objective was to investigate the single and combined effect of a Mediterranean diet, being physically active, moderate use of alcohol, and not smoking on all-cause and cause-specific mortality in elderly Europeans representing 11 countries. This cohort study lasted 12 years and involved 1,507 men and 832 women (all apparently healthy), aged 70 to 90 years.

The combined effect of these four behaviors lowered all-cause mortality to 0.35 (95 % CI, 0.28–0.44). Lack of adherence to this low-risk lifestyle was associated with an increase in population-attributable risk of 60 % for cancer-specific mortality [91].

An interventional study of cancer survivors revealed the same trend, suggesting that the combined effect of stress reduction, improved nutrition, physical activity, and smoking cessation instruction has a significant effect on survival. The study involved 227 women with localized breast cancer [84••]. Patients were randomly assigned to psychological intervention plus assessment or to assessment-only study arms. The intervention was overseen by a psychologist, conducted in small groups, and included strategies to reduce stress, improve mood, alter health behaviors, and maintain adherence to cancer treatment and care.

The study entailed 4 months of weekly sessions (intensive phase) followed by eight monthly sessions (maintenance phase). A total of 26 sessions (39 therapy hours) were held over a 12-month period. After a median of 11-years' follow-up, 62 of 212 women (29 %) had experienced disease recurrence, and 54 of 227 women (24 %) had died. As predicted, patients in the intervention arm experienced a reduced risk of breast cancer recurrence (HR=0.55, P=0.034) and death from breast cancer (HR=0.44, P=0.016) compared to patients in the assessment-only arm. Follow-up analyses also demonstrated that patients in the intervention arm had a lower risk of death from all causes (HR=0.51, P=0.028).

The researchers concluded that psychological interventions that address nutrition, stress reduction, and physical activity have a long-term positive effect on survivorship [84••]. A follow-up study that examined survival after breast cancer recurrence found that women in the intervention arm of the initial study lived longer. Intent-to-treat analysis also revealed a reduced risk of death following recurrence among women in the intervention arm (HR=0.41, P=0.014) [85].

Mixed-effects follow-up analyses with bio-behavioral data showed that all patients responded with significant psychological distress at recurrence. Thereafter, however, only women in the intervention arm improved (P values<0.023). Immune system indices (e.g., natural killer cell cytotoxicity, T cell

proliferation) were significantly higher for women in the intervention arm at 12 months (P values<0.017). These hazard analyses augment previous findings by documenting improved survival after recurrence for women in the intervention arm [85].

In another large study of 111,966 nonsmoking men and women in the Cancer Prevention Study-II Nutrition Cohort, participants completed diet and lifestyle questionnaires. A score ranging from 0 to 8 points was computed to reflect adherence to the American Cancer Society's cancer prevention guidelines regarding body mass index, physical activity, diet, and alcohol consumption, with 8 points representing optimal adherence. After 14 years of follow-up, researchers found that the relative risk (RR) of all-cause mortality was lower for participants with high scores (7–8) versus low scores (0–2) (men, RR=0.58; 95 % CI, 0.53–0.62; women, RR=0.58; 95 % CI, 0.52–0.64). Inverse associations were found also in cancer mortality (men, RR=0.70; 95 % CI, 0.61–0.80; women, RR=0.76; 95 % CI, 0.65–0.89). The researchers concluded that adherence to a combination of factors that include diet, physical activity, and limited alcohol consumption is associated with a lower risk of death from cancer, cardiovascular disease, and all causes in nonsmokers [89].

As these studies and many others suggest, the combined effect of nutrition, physical activity, smoking cessation, and stress reduction has a significant effect on survival [93•, 94–96, 97•]. Unfortunately, the reality is that widespread integration of these helpful lifestyle-related modalities is challenging to incorporate into the daily behavior of cancer survivors. Even though all the current guidelines recommend regular physical activity and a diet rich in vegetables and fruit, fewer than 5 % of patients actually follow these guidelines [90]. However, the increasing popularity of CIM may provide a window of opportunity to improve motivation, active lifestyle changes, and patients' survival by integrating these methods into conventional cancer care.

Conclusions

Despite advances in cancer care, patients continue to experience substantial levels of unmet physical, social, employment, financial, emotional, and spiritual needs and as a result utilize multiple CIM modalities to address these needs. Evidence is evolving that CIM interventions, especially those related to "lifestyle medicine" such as nutrition, nutritional supplements, stress reduction and exercise, may improve survival and reduce risk of recurrence. Although additional studies are needed to confirm these findings, given the low cost of these CIM and lifestyle interventions, their minimal risk, and the potential magnitude of their effects, these approaches ought now be considered as additional important tools to integrate into cancer survivorship care plans. Utilizing such established methods as motivational interviewing, group visits, and patient-centered care, utilizing psychologists, nutritionists, exercise physiologists, and health coaches are all potential methods of improving patient participation in their own self-care and improving their survival.

Compliance with Ethics Guidelines

Conflict of Interest Moshe Frenkel, Victor Sierpina, and Kenneth Sapire declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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