

Impact of Diet, Body Mass Index, and Physical Activity on Cancer Survival

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Abstract With the increase in the number of cancer patients worldwide in the coming years, the need for knowledge on the influence of lifestyle factors on cancer survival is increasing. In this paper, the current knowledge on diet, body mass index, and physical activity in relation to cancer outcome is summarized. Also, challenges are identified to be addressed to provide evidence-based recommendations for cancer patients. Studies in patients with breast, colorectal, or prostate cancer show that the influence of dietary factors on survival remains to be determined. Adiposity and a lack of physical activity, however, appear to influence cancer outcome negatively.

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Subsequent studies should focus on more detailed aspects of these lifestyle factors, such as body composition and dose of exercise, and on the timing with respect to diagnosis and treatment. Research should be directed toward investigating diet and physical activity simultaneously and on how changes in health behavior can be established.

Keywords Diet · Body mass index · BMI · Physical activity · Survival · Cancer survival · Colorectal cancer · Breast cancer · Prostate cancer

Introduction

Of all individuals who are diagnosed with cancer, more than 50% will live 5 years or longer after diagnosis [1, 2]. The number of cancer survivors will increase steadily in the coming years due to screening practices, more advanced treatment options, and improved follow-up after treatment. Besides functional limitations and psychosocial problems related to cancer diagnosis and treatment, cancer survivors face the possibility of second cancers, long-term effects of cancer treatment, and comorbid conditions such as diabetes and cardiovascular disease [3, 4]. Particularly relatively soon after diagnosis or treatment, many patients will be interested in dietary or other lifestyle changes that could improve their prognosis.

We do know on the basis of more than 10,000 experimental and observational studies that overweight, an unhealthy diet (i.e., low in vegetables and fruits and high in [processed] red meat), alcohol intake, and lack of physical activity significantly influence the risk of developing certain types of cancer [5, 6]. However, what about those who have cancer? Does it still make sense to change one's lifestyle after cancer has been diagnosed? Which lifestyle changes do cancer patients make and what

should we recommend? In contrast to the wealth of current evidence on the role of diet and physical activity in the etiology of cancer, only a few well-designed studies have been conducted thus far to assess whether similar modifiable risk factors influence outcomes of patients already diagnosed with cancer. Current recommendations for cancer survivors are based on the recommendations to reduce cancer risk and emphasize achieving and maintaining a healthy weight; regular physical activity; and consumption of a diet rich in vegetables, fruit, and whole grains and limited in red meat and alcohol. Also, the use of foods instead of supplements is recommended. However, it is acknowledged that the evidence for these recommendations is limited.

During the past decade, the focus of researchers as well as funding agencies has broadened from cancer prevention only to include cancer survival. The number of publications on diet, physical activity, and cancer survivorship is rapidly increasing [7]. During the past few years, results of these studies have been extensively reviewed [8–16, 17••, 18–21].

This paper summarizes the conclusions from previous reviews and discusses results from the most recent studies on the role of diet, body mass index (BMI), and physical activity before, during, and after treatment on cancer recurrence, cancer-specific death, and all-cause mortality. As the majority of studies focused on three of the most frequently occurring types of cancer in the Western world (i.e., breast, colorectal, and prostate cancer), those types of cancer are reviewed. In this paper, ongoing challenges and the next steps that need to be taken are identified to provide evidence-based recommendations for cancer survivors.

What Do We Know?

Breast Cancer

Diet

As reviewed by several authors, some, but not all, observational studies on breast cancer outcome showed favorable effects of pre- and postdiagnosis high intake of vegetables, fruits, and whole grains on overall death and death from non-breast cancer causes, but not breast cancer-specific death [17••, 21]. A few years ago, two large dietary intervention studies were conducted among women diagnosed with breast cancer: the WHEL (Women's Healthy Eating and Living) and the WINS (Women's Intervention Nutrition Study) [22, 23]. WHEL focused on a plant-based dietary pattern that included a reduction in dietary fat, while WINS focused on reduced dietary fat intake. Overall, the results of these trials indicated that dietary interventions among breast cancer survivors without weight loss or increased physical activity are not sufficient to improve breast cancer prognosis [22, 23].

Secondary analyses in WHEL showed that specific subgroups may benefit from increased vegetable and fruit consumption [24–26], but these results need to be confirmed by others.

Several recent observational studies focused on specific components in plant foods and breast cancer outcome, such as dietary fiber [27] and specific plant-based phytoestrogens. Buck et al. [28, 29••] recently investigated enterolactone, the main metabolite of lignans, the most important class of phytoestrogens in Western diets, and showed that high estimated prediagnostic and postdiagnostic serum levels were associated with increased overall survival in postmenopausal breast cancer patients. The consumption of soy, an important source of phytoestrogens in an Asian diet, in relation to breast cancer outcome has been controversial, as some previous studies showed harmful effects on breast cancer recurrence [30]. Results from three recent studies showed that postdiagnostic intake of isoflavone, the major component of soy, was not associated with second breast cancer risk and may decrease the risk of overall mortality [31, 32••, 33]. Based on those findings, there is no need to advise against soy consumption in breast cancer patients.

Although consumption of alcoholic drinks clearly increases breast cancer risk, studies are not consistent concerning alcohol and breast cancer outcomes [21]. Alcohol intake may increase risk of breast cancer recurrence and breast cancer-related mortality, although this is not observed in all studies. Moderate intake of alcohol after diagnosis may, however, decrease the risk of death from comorbidities such as cardiovascular disease [21]. In 2010, Kwan and coworkers [34••] published a study based on the LACE (Life after Cancer) study, a prospective cohort study including 1,897 women with early-stage breast cancer. The authors observed that drinking 6 or more g/day (~one half of a drink) of alcohol compared with no drinking after breast cancer diagnosis was not associated with all-cause mortality. However, it was associated with a decreased risk of non-breast cancer mortality and an increased risk of recurrence and breast cancer-specific death [34].

Vitamin D is postulated to be associated with decreased cancer risk and improved survival [35••]. A nested case-control study of 512 matched pairs within the WHEL study, however, did not provide support for an association between blood concentrations of 25-hydroxyvitamin D (25[OH]D) after treatment and the recurrence of breast cancer. On the other hand, a prospective cohort study conducted in Germany and including 1,295 incident postmenopausal breast cancer patients showed that lower 25(OH)D concentrations (<35 nmol/L) were associated with poorer overall survival and distant disease-free survival than higher concentrations (≥55 nmol/L). The authors suggest that the relevant time frame of and the effect of chemotherapy on serum 25(OH)D measurements in breast cancer survival studies deserve further investigation [36].

Body Mass Index

It is certainly not new information that excess weight among breast cancer patients increases the risk of contralateral breast cancer, other primary cancers, and all-cause mortality, as these topics have been reviewed extensively over the past years [8, 17••, 19, 21, 35••]. A recent retrospective study by Ewertz and colleagues [37] is probably the largest to date and included data from 18,967 women, all enrolled in adjuvant chemotherapy trials in Denmark. It confirmed that obesity at diagnosis of early-stage breast cancer is an independent prognostic factor for the development of distant metastases and death after the diagnosis of breast cancer [37].

Weight gain and changes in body composition are known to be important side effects of certain breast cancer treatments [38]. An increase in fat mass in combination with a loss or no change in muscle mass is often observed. Besides this “sarcopenic” obesity, chemotherapy may impair muscle strength, which may lead to “dynapenic” obesity. Weight gain as well as unfavorable changes in body composition have been associated with recurrence risk or decreased survival in some, but not all, studies [38].

Physical Activity

Increased physical activity is associated with improved breast cancer prognosis [8, 21]. In the large Women’s Health Initiative study [39], the risk of all-cause and breast cancer-specific mortality was decreased in postmenopausal breast cancer survivors participating in moderate to vigorous intensity recreational physical activity (e.g., brisk walking, bicycling, or swimming) approximately 3 h/w before or after a breast cancer diagnosis compared with nonactive women. Furthermore, the risk of all-cause mortality declined by 33% in women who increased their physical activity level to—or maintained their level at—3 h or more per week (including women who had been inactive at baseline) compared with women who stayed or became inactive. These findings suggest that adopting an active lifestyle after diagnosis can improve overall longevity and prognosis. This is in accordance with the recent findings from the After Breast Cancer Pooling project, which included data from four studies of breast cancer survivors ($n=13,302$) [40]. Engaging in at least 10 metabolic equivalent task (MET) h/week of physical activity postdiagnosis was associated with a 27% reduction in all-cause mortality and a 25% reduction in breast cancer mortality compared with women who were active for less than 10 MET h/week. Risk of breast cancer recurrence was not associated with recreational physical activity [40].

Colorectal Cancer

Diet

There are not enough studies on diet and outcomes in colorectal cancer survivors to draw firm conclusions. Moreover, most studies were impaired by retrospective dietary assessment, small patient groups, heterogeneous populations including all stages of disease, and/or limited capacity to adjust for other prognostic factors. There is only one prospective observational study, published a few years ago, on postdiagnostic diet, BMI, and physical activity to date among a relatively homogeneous population of 1,009 stage III colorectal cancer patients [41]. This study was embedded in an adjuvant chemotherapy trial; diet was assessed midway through therapy and 6 months after therapy. A Western dietary pattern characterized by high intake of red meat, fat, refined grains, and desserts was associated with worse disease-free and overall survival. Patients in the highest quintile of this Western pattern experienced nearly a three times worse disease-free survival as compared with those in the lowest quintile on that pattern. A prudent pattern high in vegetables, fruits, poultry, and fish was not associated with colorectal cancer outcomes in this study [41].

As far as vitamin D is concerned, two prospective cohort studies, the Nurses’ Health Study and the Health Professionals Follow-Up Study, showed a 40% to 50% lower risk with higher 25(OH) vitamin D concentrations in serum for colorectal cancer-specific mortality and all-cause mortality, respectively [39]. In particular, colorectal cancer patients with stage IV disease may be at risk of vitamin D deficiency [42].

Body Mass Index

Risk of colorectal cancer recurrence, all-cause mortality, and colorectal cancer-specific mortality has been found to be elevated for patients who are underweight as well as for those who are overweight before or at the time of diagnosis, as extensively reviewed [9, 12]. Recent analyses in the Cancer Prevention Study nutrition cohort for these end points confirmed these findings [43]. However, higher postdiagnostic BMI did not affect survival outcomes in that study [43], as is observed in most [9], but not all, studies [44].

Abdominal adiposity may be more strongly associated with colon cancer prognosis than BMI [45]. To our knowledge, there are no recent studies on pre- and postdiagnostic body composition and fat distribution and its association with colorectal cancer outcome.

Physical Activity

Colorectal cancer patients who are regularly physically active after diagnosis experience more favorable survival than

those who are not [9, 14–16]. Prediagnostic physical activity levels are not consistently associated with outcomes of colorectal cancer [14]. However, those who increased levels of physical activity after diagnosis, compared with those who did not change, decreased their cancer-specific mortality and overall mortality [14].

Prostate Cancer

Diet

As recently reviewed by Davies et al. [20], the paucity of data on dietary intake and prostate cancer outcome makes it impossible to draw conclusions. In a prospective observational study (CaPSURE [Cancer of the Prostate Strategic Urologic Research Endeavor]) among approximately 1,300 localized prostate cancer patients, postdiagnostic intakes of specific foods were associated with an increased risk of prostate cancer progression (whole egg and poultry with skin) or a decreased risk (cruciferous vegetables), while other foods did not show associations [46, 47].

Body Mass Index

Within a recent meta-analysis including 6 prospective studies with a total of more than 18,000 patients, a 5-kg/m² increase in BMI was associated with 20% higher prostate cancer-specific mortality [48]. Androgen deprivation therapy has been found to be associated with changes in body composition similar to those induced by chemotherapy in breast cancer [49], yet the consequences of these changes on prostate cancer outcome have not been studied.

Physical Activity

Few studies focused on physical activity and prostate cancer outcome [20]. Within the Health Professionals Follow-Up Study, 2,705 men diagnosed with nonmetastatic prostate cancer were prospectively observed [50]. Men who were physically active had a lower risk of all-cause and prostate cancer-specific mortality. Men exercising vigorously before and after diagnosis had the lowest risk. The CaPSURE study showed that men who walked briskly for 3 h/week or more had a 57% lower rate of progression than men who walked at an easy pace for less than 3 h/week [51].

Summarizing, the evidence linking adiposity and lack of physical activity before and after diagnosis to worse breast, colorectal, and possibly prostate cancer prognosis is starting to become convincing. Up to now, data on dietary factors in cancer prognosis appear less convincing.

Ongoing Challenges and Steps to Be Taken

Diet

A healthy diet is certainly recommendable to cancer patients; however, we are not yet able to formulate evidence-based guidelines for specific foods and nutrients. To be able to do that, we need more observational data on the influence of pre- and postdiagnostic diet on cancer outcome to plan and conduct feasible and effective dietary intervention trials among cancer survivors. We need more information about what patients do after diagnosis. Do they change? If yes, when and what do they change? An ongoing prospective study among breast cancer survivors in the United Kingdom (the DietCompLyf [The Role of Diet, Complementary Treatments and Lifestyle in Breast Cancer Survival] study) recently showed that the intake of fruits and vegetables, whole grains, and lean sources of protein increased significantly after diagnosis, while consumption of high-fat and high-sugar products, red meat, coffee, some alcoholic drinks, and refined grains significantly decreased [52]. In this study, dietary habits were only assessed once—1 year after diagnosis. We are currently evaluating the role of diet in colorectal cancer recurrence and survival (the COLON study). In this prospective study, we assess diet and lifestyle habits at least four times (i.e., shortly after diagnosis and 6 months, 2 years, and 5 years after diagnosis) to be able to study changes in habits during and after colorectal cancer treatment [53]. One of the important questions that remains unanswered is whether it makes a difference to change one's diet after diagnosis.

Body Mass Index

Although results on adiposity appear convincing enough to recommend weight loss or maintenance of a healthy weight to cancer survivors, most results thus far come from observational studies rather than from randomized clinical trials [7]. It appears that only a few survivors succeed in sustained weight loss after diagnosis, which limits the power to detect the effects of weight loss on the risk of recurrence. Ongoing and future interventions will have to address whether weight loss is beneficial for survivors. In the United States, the ENERGY (Exercise and Nutrition to Enhance Recovery and Good Health for You) trial is currently ongoing; within this randomized controlled trial among 800 breast cancer survivors, women are counseled to lose weight through increased physical activity and a healthy diet (<http://clinicaltrials.gov> [NCT01112839]). The ENERGY trial is designed as a vanguard study for a fully powered trial of 2,500 women to address the effect of the intervention on cancer outcomes. The budget of the ENERGY trial (1.4 million dollars) highlights the extent of resources needed to perform interventions.

However, if effective interventions will beneficially affect the number of recurrences and other health parameters, the medical care costs to these survivors will be reduced. Thus, future research should also assess the costs and benefits of these interventions.

An important point of discussion is the timing of the intervention. The American Cancer Society recommends that weight loss can already begin during cancer therapy (in case women or men are seriously overweight) [54]. However, this is a matter of debate, as weight loss during therapy can also be a sign of undernutrition and may lead to cachexia. As therapy may induce sarcopenia, which may increase the risk of several comorbidities, cancer recurrence, as well as functional decline, it may be especially beneficial to focus on preserving lean body mass, but also on muscle strength, and not on weight loss as such during and after therapy. The challenge is to convince women and men to take part in these interventions during a period so emotionally and physically demanding as cancer therapy.

Physical Activity

Recommendations on appropriate physical activity already have been endorsed as an important part of cancer therapy by several American (US National Comprehensive Cancer Network, the American Cancer Society, and the American College of Sports Medicine) [55] and European institutions. Endurance as well as resistance exercise during active treatment is encouraged. However, reports on exercise intervention trials among cancer patients sometimes lack the appropriate details on the precise exercise prescription and adherence to the prescription, limiting the reproducibility of the intervention and the ability to determine the dose of exercise received by the participants [56]. Also, few intervention studies have addressed exercise and a healthy diet at the same time, although stronger effects may be expected from this combination. In observational analyses of the WHEL study, for instance, the combination of high physical activity (~3 h/week) and a diet high in vegetables and fruit (>5 daily servings) was associated with higher breast cancer survival rates than adherence to only one or no healthy behaviors [57]. From the patient perspective, it is best to have a multidisciplinary lifestyle intervention to get the largest possible benefit. From a scientific perspective, insight into the contribution of all the different aspects of a lifestyle program is desired.

For observational studies as well as interventions on diet, BMI, and physical activity, a major challenge will be the recruitment of diverse, representative samples of the population at large [13]. For instance, it is very difficult to recruit participants from all socioeconomic classes into observational or experimental studies after cancer survival, as more highly educated, healthier cancer survivors are more likely

to participate. If we want to translate the findings from these studies into practice, we must make sure that effective lifestyle interventions are suitable, applicable, and affordable for cancer survivors from all socioeconomic classes.

For evidence-based recommendations to be formulated for all cancer survivors, we do need more studies on other types of cancer. Although there are some studies on cancer of the endometrium, ovaries, head, and neck, evidence is too limited to draw conclusions [21, 55, 58]. In general, but especially for rarer cancers, (inter)national cooperation is essential.

Conclusions

A healthy lifestyle, including a healthy diet and sufficient physical activity, is certainly recommendable to cancer patients during and after treatment. However, there remains an urgent need for well-designed studies investigating the effects of improved diet, weight management, and increased physical activity on cancer survivorship. Whereas the overall influence of diet on cancer survival remains to be determined, studies on adiposity and physical activity can now focus on more detailed aspects, such as the timing of exposure and the specific dose/duration needed. Also, more research is needed on the combination of different lifestyle changes simultaneously. One of the most profound challenges will be to determine how to change one's lifestyle during treatment as well as for one's life. Needless to say, this ultimate challenge is not restricted to cancer patients.

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