

# American Cancer Society nutrition and physical activity guideline for cancer survivors

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**Abstract:** The overall 5-year relative survival rate for all cancers combined is now 68%, and there are over 16.9 million survivors in the United States. Evidence from laboratory and observational studies suggests that factors such as diet, physical activity, and obesity may affect risk for recurrence and overall survival after a cancer diagnosis. The purpose of this American Cancer Society guideline is to provide evidence-based, cancer-specific recommendations for anthropometric parameters, physical activity, diet, and alcohol intake for reducing recurrence and cancer-specific and overall mortality. The audiences for this guideline are health care providers caring for cancer survivors as well as cancer survivors and their families. The guideline is intended to serve as a resource for informing American Cancer Society programs, health policy, and the media. Sources of evidence that form the basis of this guideline are systematic literature reviews, meta-analyses, pooled analyses of cohort studies, and large randomized clinical trials published since 2012. Recommendations for nutrition and physical activity during cancer treatment, informed by current practice, large cancer care organizations, and reviews of other expert bodies, are also presented. To provide additional context for the guidelines, the authors also include information on the relationship between health-related behaviors and comorbidities, long-term sequelae and patient-reported outcomes, and health disparities, with attention to enabling survivors' ability to adhere to recommendations. Approaches to meet survivors' needs are addressed as well as clinical care coordination and resources for nutrition and physical activity counseling after a cancer diagnosis.

**Keywords:** alcohol, cancer survivors, dietary patterns, nutrition, obesity, physical activity

## Introduction

Cancer is the second leading cause of death in the United States, disproportionately affecting racial, ethnic, socioeconomic, and geographic subgroups.<sup>1</sup> Over the past 30 years, there has been a decline in the overall cancer death rate of approximately 32%,<sup>1</sup> and cancer survivorship has increased over this same period, with 16.9 million survivors in the United States as of January 2019.<sup>2</sup> The absolute number of cancer survivors continues to increase due to several factors, including the aging of the US population.<sup>3</sup> In addition, temporal changes in behavioral patterns and other factors that influence risk for cancer, including smoking and obesity, affect cancer incidence and mortality.<sup>4</sup> Changes in screening practices have generally resulted in earlier cancer detection and treatment. For some types of cancer, improvements in treatment protocols and advancements in treatment as well as the use of targeted therapies and immunotherapies have dramatically increased survival rates. The overall 5-year relative survival rate for

all cancers combined is now 68%, although there is notable variability across racial groups and types of cancer.<sup>1</sup>

Evidence from laboratory and observational studies, although more limited than that for the development of cancer, suggests that modifiable risk factors, such as adiposity, physical activity, diet, and alcohol intake, may affect risk for recurrence and overall survival after diagnosis. The population of cancer survivors in which observational studies (and, to a lesser extent, intervention studies) have been conducted reflects both incidence and survival rates. For example, prostate cancer accounts for 27% of new cancer cases in men, whereas breast cancer accounts for 31% of new cases in women, and the 5-year relative survival rates are among the highest for these cancers (98% for prostate cancer, 90% for breast cancer).<sup>1</sup> Colorectal cancer (CRC) accounts for 8% of new cases in both men and women and is associated with a 5-year relative survival rate of 65%.<sup>1</sup> Therefore, substantially more investigations of the link between modifiable risk

factors and recurrence risk and survival have been conducted for the more common cancers with higher survival rates. In contrast, evidence is much more limited for cancers that are less common and/or have lower survival rates.

This is the third American Cancer Society (ACS) guideline with recommendations for relevant diet and physical activity factors for cancer survivors to be released. The audiences for this guideline are health care providers caring for cancer survivors as well as cancer survivors and their families. The guideline is intended to serve as a resource for informing ACS programs, additional ACS electronic and printed documents written with simpler terminology to be widely comprehensible by cancer survivors and their families, health policy, and the media. The first report,<sup>5</sup> published in 2006, was presented as a guide for informed choices with the aim of guiding patients and their health care providers in the interpretation of the scientific evidence available at that time. The second ACS guideline,<sup>6</sup> published in 2012, provided more

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Additional supporting information may be found online in the Supporting Information section at the end of the article.

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The first 4 authors and the last author are members of the Executive Committee.

**DISCLOSURES:** Cynthia A. Thomson reports honoraria from *Today's Dietitian* and Cancer Support Community and is a member of the Colorectal Cancer Alliance Scientific Advisory Board outside the submitted work. Kristen R. Sullivan reports salary support from a Centers for Disease and Control and Prevention's Center for State, Tribal, Local, and Territorial Support grant outside the submitted work. Carol L. Howe was supported by the American Cancer Society as an independent contractor during the conduct of the study. Lawrence H. Kushi reports grants from the National Cancer Institute; travel support from the Cancer Prevention Research Institute of Texas and the International Agency for Research on Cancer; and Advisory Board service at the National Cancer Institute, all outside the submitted work. Marian L. Neuhouser reports honoraria for her work as Associate editor for *Journal of Nutrition* (honoraria) and for serving on the internal advisory committee for NIH/NCI funded partnership grant between Fred Hutch and New Mexico State University to increase the capacity for cancer research at NMSU. Karen M. Basen-Engquist reports grants from the National Cancer Institute and the Cancer Prevention and Research of Texas; honoraria from the National Cancer Institute, the Gynecologic Oncology Group, the University of Kentucky, and the Yale University Transdisciplinary Research on Energetics and Cancer (TREC) training program; travel support from the National Cancer Policy Forum; the National Academies of Science, Engineering, and Medicine; and the Yale University TREC training program; participation on an independent safety monitoring board at Boston University; and service as president elect (2017–2019) and president (2019–2021) of the American Society of Preventive Oncology, all outside the submitted work. Justin C. Brown reports grants from the National Institutes of Health and grants and personal fees from the American Institute for Cancer Research outside the submitted work. Barbara L. Grant reports royalties from the Academy of Nutrition and Dietetics for a book chapter on oncology nutrition and service as a liaison representative from the Academy of Nutrition and Dietetics to the American College of Surgeons Commission on Cancer outside the submitted work. Sheri J. Hartman reports grants from the National Cancer Institute/National Institutes of Health and is chair of a Data Safety Monitoring Board outside the submitted work. She chairs a grant-based DSMB for a study at the University of Wisconsin and Northwestern University. It is not an institutional-based DSMB. Stacey A. Kenfield reports grants from the National Cancer Institute/National Institutes of Health outside the submitted work. Jeffrey A. Meyerhardt reports institutional research funding from Boston Biomedical; personal fees from Merck Pharmaceuticals and COTA Healthcare; and service on a grant review panel for the National Comprehensive Cancer funded by Taiho Pharmaceutical, all outside the submitted work. Linda Overholser reports grants from the Centers for Disease Control and Prevention and the National Cancer Institute as a coinvestigator in the Cancer Prevention and Control Research Network; royalties from Springer Publishing; and is a member of the National Comprehensive Cancer Network Survivorship Guidelines Panel, all outside the submitted work. Bernardine M. Pinto reports institutional funding from the National Cancer Institute/National Institutes of Health during the conduct of the study and grants or contracts from the Greenville Health System Health Sciences Center to her institution outside the submitted work. Mary E. Platke reports honoraria for providing an American Society for Parenteral and Enteral Nutrition webinar and from the Dartmouth Norris Cotton Center outside the submitted work. The sources of the honoraria are the organizations listed—ASPN and the Dartmouth Norris Cotton Cancer Center. Susan M. Gapstur reports grants from the National Cancer Institute/National Institutes of Health outside the submitted work. Marjorie L. McCullough reports consulting fees paid to her institution for service on the Cancer Advisory Group to Tufts University and the “Tools to be fit” colorectal cancer survivor study for R01 grants. All remaining authors report no conflicts of interest.

We express our gratitude to Jennifer Ligibel, MD, at Dana Farber Cancer Institute; Tracy Wiedt, MPH, at the American Cancer Society; and Jennifer Hoque, MA, at the American Cancer Society Cancer Action Network for their review and feedback on this article. We also thank Samantha Werts and Lauren Bates for developing supplemental materials on resources for the promotion of diet and physical activity for cancer survivors.

See Patient Page on pages 1–3, this issue.

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specific recommendations across cancer types and was a review of scientific literature based on a larger body of evidence.

This ACS guideline differs from earlier versions. The purpose is to provide evidence-based, cancer-specific recommendations for anthropometric parameters, physical activity, diet, and alcohol intake for reducing recurrence and increasing time to new disease and cancer-specific and overall mortality. The body of evidence on the relationship between modifiable risk factors and postdiagnosis recurrence and survival has increased substantially since the last version, especially in the form of systematic literature reviews and meta-analyses, which can add comprehensive evidence with a lower risk of bias than previous evidence syntheses. In addition, high-quality, systematic literature reviews and meta-analyses have been conducted by recognized scientific and advisory groups, and their recommendations are considered and presented in this report, which reduces redundancy and promotes a unified message for patients and health care providers. Notably, the focus of the evidence presented in this version of the ACS guideline is on reducing risk of recurrence and mortality and increasing disease-free survival for survivors of cancers for which evidence is available based on the systematic review described below. Evidence for intermediate outcomes from observational and intervention studies, such as biomarkers or potential mediators of cancer recurrence or progression, are not addressed in this report.

This report also includes information of relevance for cancer survivors, their families, and health care providers that was not subject to systematic review. Recommendations for nutrition and physical activity during active cancer treatment, informed by current practice and reviews of other expert bodies, are presented in the guideline. Other topical issues include the relationship between health-related behaviors and comorbidities, long-term sequelae, and patient-reported outcomes (PROs), with attention to enabling survivors' ability to adhere to recommendations. Information on clinical care coordination and resources for nutrition and physical activity counseling after a cancer diagnosis are also provided.

Although understanding how to help survivors make sustainable behavior change is critically important in operationalizing this guideline, a thorough discussion of evidence for specific interventions and strategies to support nutrition and physical activity behavior change in cancer survivors is beyond the scope of this review. The reader is referred to other reviews on this topic.<sup>7,8</sup> Supporting Table 1 provides a list of available nutrition and physical activity resources from national organizations for cancer survivors.

Many cancer survivors face environmental, social, and structural barriers that impact their ability to adhere to nutrition and physical activity recommendations. These include disparities in cancer care, food insecurity, targeted marketing, and lack of access to healthy food and opportunities to be physically active. Many of these issues disproportionately

impact people from diverse racial and ethnic backgrounds. We recognize that policies, systems, and environmental approaches are necessary to support behavior change and allow many survivors to adhere to nutrition and physical activity recommendations. Although some community and policy approaches to meet survivors' needs are discussed, a full systematic review of these approaches was not included in this guideline.

## Methods

Articles were identified and selected following standards outlined in the Institute of Medicine's (National Academy of Medicine) 2011 consensus study report *Finding What Works in Health Care: Standards for Systematic Reviews*<sup>9</sup> and reporting guidelines as detailed in "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement."<sup>10</sup> Although we did not conduct formal risk-of-bias analyses or rigorous data extraction and synthesis, we did follow systematic review standards for locating and selecting the articles that are analyzed in this guideline.

## Eligibility Criteria

Studies were included if they were systematic literature reviews, meta-analyses, pooled analyses of cohort studies, or randomized clinical trials (RCTs) with a sample size of at least 200 people. Included studies were those based on: 1) cancer survivors, with survivorship defined as beginning on the day of cancer diagnosis; 2) the outcomes mortality, cancer-free survival, cancer recurrence, or incidence of a second cancer; and 3) investigations of dietary factors, anthropometric parameters, physical activity, or alcohol consumption. Eligible studies included peer-reviewed publications in English during or after 2012, the year that the ACS published the last "Nutrition and physical activity guidelines for cancer survivors,"<sup>6</sup> and after 2014 for outcomes among breast cancer survivors, the year that the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Report on diet, nutrition, and physical activity in breast cancer survivors was published<sup>11</sup>; studies of physical activity published during or after 2018, after systematic literature reviews of the American College of Sports Medicine (ACSM) roundtable report on physical activity, sedentary behavior, and cancer prevention and control<sup>12</sup> and the 2018 "Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable"<sup>13</sup> were published. Exclusion criteria included conference abstracts, proceedings, dissertations, letters, commentaries or opinion pieces, and studies that did not meet the above criteria. Reviews that were nonsystematic (eg, did not provide systematic review methodology, searched only one database) were excluded. Studies were also excluded if exposures of interest could not be isolated from one another.

In addition to postdiagnosis exposure information, studies in which exposures were assessed before or at the time of diagnosis were retained because, with some exceptions, these may serve as a proxy for postdiagnosis behavior.

Together with a medical librarian (C.L.H.), the executive committee (C.L.R., C.A.T., M.L.M., and K.R.S.) iteratively generated lists of keywords and vocabulary terms (eg, MeSH, Emmtree) corresponding to: 1) the 4 key exposures addressed in this report—anthropometric parameters (eg, obesity, body mass index [BMI], body composition), physical activity, diet, and alcohol; 2) keywords and vocabulary terms for the concepts of cancer survivors; 3) outcomes of mortality, survival, recurrence, second cancer; and 4) the study types delineated above. Separate search strategies were developed for each of the 4 factors and were adapted for and conducted in the following 5 databases: Ovid/MEDLINE, Elsevier/Embase, Wiley/Cochrane Database of Systematic Reviews, EBSCO/Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Epistemonikos.org. Search dates were limited to articles published from January 1, 2012, through November 7, 2020, for the diet/anthropometric/alcohol searches; and from January 1, 2018, through November 7, 2020, for the physical activity/exercise searches. An English language filter was applied. The 4 search strategies conducted in Ovid/MEDLINE, analogous to the searches in the other 4 databases, are available in the Supporting Information.

## Study Selection

All records identified through the database searches were exported to the reference management software EndNote version X9 (Clarivate Analytics), in which results were deduplicated for each of the 4 sets of search results. Each member of the executive team independently screened the titles and abstracts of 2 of the 4 search results sets for relevance. Disagreements were resolved by consensus of the full executive team. Each member of the executive team then independently screened 2 sets of the full texts of those publications selected during the title/abstract screen, adhering to the detailed inclusion/exclusion criteria documented above. Disagreements were again resolved by consensus of the full team. Each member of the executive team was then assigned the finally selected articles for 1 of the 4 topic areas and categorized each article according to which cancer types were addressed within that article. After content experts and writers were identified and agreed to assigned sections, the articles were assigned and distributed.

## Results

For diet, we found 1356 records through the database searches (see Supporting Fig. 1). Of the 832 publications that remained after 524 duplicates were removed, 25 were selected for full text review, and 16 met the full set of inclusion

criteria. For anthropometric parameters, we found 1333 records through the database searches (see Supporting Fig. 2). Of the 856 publications that remained after 477 duplicates were removed, 19 were selected for full text review, and 15 met the full set of inclusion criteria. For physical activity, we found 814 records through the database searches (see Supporting Fig. 3). Of the 453 publications that remained after 361 duplicates were removed, 7 clinical trials with no published results and one title that was not available in English were removed, 11 were selected for full text review, and 9 met the full set of inclusion criteria. For alcohol, we found 152 records through the database searches, and 2 additional publications were recommended by the corresponding expert writing group (see Supporting Fig. 4). Of the 80 publications that remained after 74 duplicates were removed, 5 were selected for full text review, and all 5 met the full set of inclusion criteria.

## Nutrition and Physical Activity During Cancer Treatment and Recovery Immediately After Treatment

Nutrition and physical activity recommendations established recently by the ACS for the primary prevention of cancer are broadly relevant to survivors undergoing and immediately after cancer treatment.<sup>2,4</sup> Because achieving and maintaining a healthy weight might improve treatment tolerance, it is important to monitor voluntary or involuntary weight changes and adopt behavior changes to maintain or gain weight. Many patients have unique dietary and physical activity needs and abilities related to their specific cancer and immediate and long-term treatment. Cancer survivors under active treatment need to consult with their health care provider regarding potential dietary interactions, and patients should be assessed and managed as outlined in the sections below.

### Physical Activity

As previously reviewed,<sup>13,14</sup> there is sufficient evidence that exercise during cancer treatment is beneficial in managing several aspects of quality of life during cancer treatment. Although the evidence is sufficient for exercise prescriptions in the management of several cancer diagnoses or treatment-related side effects, such as anxiety, depression, physical function, and lymphedema, additional evidence for the management of other symptoms and side effects is still needed.<sup>13</sup> Specific recommendations for physical activity include aerobic exercise, resistance training, or a combination of both for expected patient benefits. Moreover, preliminary evidence suggests that exercise during cancer treatment may improve treatment tolerance<sup>15</sup> and response,<sup>16</sup> although current evidence is insufficient to make any recommendations.

Most studies support that exercise is generally safe for individuals undergoing cancer treatment. However, because most of these studies are randomized controlled trials that may include *healthier* participants than the general population of patients with cancer, it is important for patients who have cancer to seek medical evaluation to inform their individual exercise program during treatment.<sup>13,14</sup> This type of guidance is valuable in creating a safe and effective fitness plan for patients who have cancer with appropriate and tailored modifications related to specific cancer diagnosis or treatment-related issues, such as breast cancer-related lymphedema. Individuals undergoing cancer treatment are encouraged to be active members of their nutrition and physical activity care planning team. Interventions during and immediately after treatment should be individualized and realistic and should have scientific support.<sup>13,14</sup>

## Diet and Nutrition

Initial steps when establishing a nutrition care plan involve identifying a key person on the health care team responsible for nutrition care; this is followed by validated malnutrition screenings, nutrition-focused physical assessment, medical nutrition therapy interventions, and ongoing surveillance.<sup>17,18</sup> Although advances in cancer diagnosis and treatment have improved clinical outcomes, the inability to maintain adequate nutritional status because of cancer symptoms and treatment-related side effects is common and can negatively impact overall clinical outcomes.<sup>19</sup>

Several large cancer care organizations have published guidelines on nutrition and physical activity for clinicians and cancer survivors relevant to the treatment period and immediately after cancer treatment, as summarized below. An expert panel from the Academy of Nutrition and Dietetics examined various oncology-related diet and nutrition care questions in their Evidence Analysis Library, which guides nutritional care. In 2017, an update to these guidelines was published providing recommendations for the oncology health practitioner/Registered Dietitian Nutritionist (RDN) to follow when planning treatment-related care.<sup>20</sup> In addition, in 2017, the European Society of Enteral and Parenteral Nutrition published updated guidelines.<sup>21</sup> The section below provides an integrated summary of *clinician-focused recommendations* rated as strong based on the best evidence for optimal care in ambulatory settings where active curative or definitive treatment, including neoadjuvant and adjuvant therapy, is rendered. Readers are referred to the original sources for more detailed information:

- Those undergoing treatment and/or being followed in an ambulatory clinic should be screened for the risk of malnutrition on an ongoing basis using a validated tool, such as the Malnutrition Screening Tool.<sup>20</sup>

- Those who are at risk of malnutrition should be assessed by an RDN or Registered Dietitian and begin personalized nutritional counseling sessions. All interventions should be monitored at regular intervals. This process should be a component of a multidisciplinary team care plan.<sup>20</sup>
- Survivors need to maintain adequate nutritional intake, and symptoms related to the tumor and/or to the treatment that negatively impact nutritional intake, also known as *nutrition impact symptoms*, should be identified and managed.<sup>20,22</sup>
- If oral intake does not support adequate nutrient intake to meet energy expenditure, the Recommended Dietary Allowance for vitamins and minerals, and >1 g of protein per kilogram of body weight per day, then the use of an oral nutritional supplement should be implemented.<sup>20,22</sup>
- If intake remains insufficient, consideration should be given to additional nutrition support strategies, such as an enteral nutrition tube feeding regimen; and, if enteral nutrition support is contraindicated, parenteral nutrition support could be considered to meet nutritional needs.<sup>20,22</sup>

The National Comprehensive Cancer Network (NCCN) and the American Society for Clinical Oncology (ASCO) recently published guidelines for cancer survivors and their clinicians outlining diet, nutrition, and physical activity recommendations.<sup>14,17,18</sup> Highlights include:

- Recommendations to eat a healthy diet pattern, with adequate macronutrient and micronutrient content from both animal-based and plant-based food options but with a preference to plant-based diet patterns;
- Caution regarding the overuse and misuse of dietary supplements during and after treatment;
- Adherence to food safety procedures to avoid foodborne illnesses; and
- Being as physically active as possible.

## Long-Term Disease-Free Living or Stable Disease

There is growing evidence that being physically active, consuming foods that reflect a healthy dietary pattern, and avoiding obesity *after completion of cancer treatment* improves long-term survival. Since publication of the 2012 ACS guidelines on nutrition and physical activity for cancer survivors,<sup>6</sup> some health organizations, including the WCRF/AICR and the ACSM,<sup>11-13,23-25</sup> have published comprehensive, systematic literature reviews on the state of the science relating adiposity, physical activity, diet, and alcohol to recurrence and cancer-specific and overall mortality among cancer survivors.

The WCRF/AICR published its *Third Expert Report on Diet, Nutrition, Physical Activity and Cancer: A Global Perspective* in 2018,<sup>25</sup> in which it discussed evidence for survivors of breast<sup>11</sup> and other cancers, although comprehensive reviews for survivors of cancers other than breast cancer were not yet available. Given this lack of evidence, the WCRF/AICR panel judged that, unless otherwise advised by a health professional, following cancer prevention recommendations is unlikely to be harmful to survivors who have completed treatment.<sup>25</sup> The cancer prevention recommendations of the WCRF/AICR,<sup>25</sup> similar to the ACS guideline on diet and physical activity for cancer prevention<sup>4</sup> and the previous ACS guidance for survivors,<sup>6</sup> include maintaining a healthy body weight, being physically active, consuming a healthy diet, and avoiding or limiting alcohol consumption. Specific dietary recommendations in the ACS prevention guideline emphasize a dietary pattern rich in a variety of plant foods, such as vegetables, whole fruits, whole grains, and beans/legumes, but limited in or not including red and processed meats, sugar-sweetened beverages, highly processed foods, and refined grain products.<sup>4</sup> The WCRF/AICR's Third Expert Report also recommends the receipt of nutritional care and guidance on physical activity from trained professionals by all cancer survivors.<sup>25</sup>

In 2019, the ACSM roundtable report on physical activity, sedentary behavior, and cancer prevention and control published summary risk estimates for the association of prediagnosis and postdiagnosis physical activity and cancer-specific and all-cause mortality.<sup>12</sup> Being in the highest versus lowest categories of prediagnosis physical activity was associated with a statistically significant 18% lower risk of breast cancer-specific mortality based on a meta-analysis of 17 studies. Significant inverse associations were also noted for CRC. Postdiagnosis physical activity was significantly inversely associated with cause-specific and all-cause mortality among breast, colorectal, and prostate cancer survivors. The availability of data was limited for other cancers, with single studies suggesting benefits of physical activity on mortality outcomes for survivors of kidney, lung, and esophageal cancers; non-Hodgkin lymphoma; childhood cancer; and malignant glioma.<sup>12</sup> The ACSM published detailed physical activity guidelines for cancer survivors based on evidence for multiple cancer-related health outcomes, including anxiety, depression, fatigue, health-related quality of life, lymphedema, physical function, bone health, and sleep.<sup>13</sup>

It is important to emphasize that cancer survivors are at risk of other chronic diseases, including cardiovascular disease (CVD), diabetes, and osteoporosis, so guidelines developed for the prevention of these diseases<sup>26–30</sup> remain relevant for this population. Indeed, some cancer treatments heighten the risk of other chronic conditions.

The cancer-specific sections below specify evidence according to the timing of exposure assessment relative to cancer diagnosis (eg, prediagnosis or postdiagnosis). Observational studies provided the majority of studies included herein; these include prospective cohort data in which exposures could be assessed before or after a cancer diagnosis and/or secondary analyses of RCT data (eg, exposure assessed at diagnosis or study baseline). Because prediagnosis health behaviors may be similar to those after diagnosis, this document includes both and presents exposure timing separately when available. RCTs of health behavior (eg, physical activity, nutrition) interventions are also included, although these are less common. It is worth noting that most studies of anthropometric exposures examined BMI as a proxy for obesity, although BMI does not directly measure adiposity.

## Cancer-Specific Evidence for Long-Term Disease-Free Living or Stable Disease

### Breast Cancer

Breast cancer is the most commonly diagnosed cancer in women in the United States and is the second leading cause of cancer death among women. In 2022, it is estimated that 287,850 women will be diagnosed with breast cancer, and 43,250 will die from the disease.<sup>1</sup> Breast cancer survival has improved over time, and it is estimated that there are about 3.8 million breast cancer survivors in the United States.<sup>31</sup>

Research in breast cancer survivors provides the most substantial and robust body of evidence related to the effects of obesity, physical activity, diet, and alcohol in relation to cancer survival, recurrence, and the risk of second primary cancers among all cancer types. Even still, a comprehensive review of the literature published in 2014 by the WCRF/AICR<sup>11</sup> suggested that there was limited evidence to guide recommendations on these topics for breast cancer survivors. Nevertheless, the WCRF/AICR suggested that there was some evidence that there is better survival among women with breast cancer who have a healthy body weight, are physically active, eat foods containing dietary fiber, eat foods containing soy, or have lower fat or saturated fat intake.<sup>11</sup> Since that time, the body of evidence has increased significantly.

### Anthropometric parameters

For women diagnosed with breast cancer, most studies indicate that obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ), before, at the time of, or after diagnosis, is associated with a poorer prognosis, including recurrence and/or disease-specific or overall mortality.<sup>32–34</sup>

Two systematic reviews<sup>32,34</sup> and a large, pooled analysis<sup>33</sup> concluded that women who had a  $\text{BMI} \geq 30 \text{ kg/m}^2$  had a higher risk of recurrence as well as disease-specific and/or higher overall mortality compared with those who had a  $\text{BMI}$  from 18.5 to  $24.9 \text{ kg/m}^2$ . In their systematic

review, Parekh et al<sup>34</sup> included 11 studies of prediagnosis BMI in relation to disease-specific mortality that reported risk estimates ranging from a 20% to 200% higher risk for women who had a BMI  $\geq 30 \text{ kg/m}^2$  compared with those who had a BMI from 18.5 to  $24.9 \text{ kg/m}^2$ . They also included 22 studies of postdiagnosis BMI, most of which reported similar associations between BMI and mortality. In their pooled observational analysis of data from 22 clinical trials, including 3 trials of breast cancer, Greenlee et al<sup>35</sup> reported no association between having a BMI  $\geq 25.0 \text{ kg/m}^2$  and mortality after a breast cancer diagnosis. Obesity (BMI  $\geq 30 \text{ kg/m}^2$ ) was associated with a statistically significant increased risk of death (hazard ratio [HR], 1.34) only among breast cancer survivors who were treated with cyclophosphamide, doxorubicin, and 5-fluorouracil. Effect estimates from clinical trials were generally more modest than those from observational studies, but this may have been because of an overall healthier study population for inclusion in clinical trials.<sup>34</sup>

There remain many aspects of excess adiposity in relation to breast cancer outcomes that are not well understood, including associations with measures of adiposity other than BMI, such as body fat distribution (eg, waist-to-hip ratio and waist circumference) and body composition (eg, percentage body fat, muscle mass, fat mass index). Although weight gain throughout adulthood is associated with breast cancer risk, the relationship of weight gain before diagnosis on breast cancer outcomes is not well understood. Several studies suggest that weight gain after diagnosis is associated with greater breast cancer-specific mortality, but there is limited evidence that intentional weight loss after diagnosis may be beneficial. In their large, pooled analysis of  $>18,000$  estrogen receptor (ER)-positive breast cancer survivors, Nechuta et al<sup>33</sup> found that weight gain from before to after diagnosis was associated with a 24% higher risk of breast cancer recurrence (HR, 1.24; 95% CI, 1.00-1.53), and weight loss over this time frame was suggestive of lower risk (relative risk [RR], 0.67; 95% CI, 0.42-1.05). Conversely, a systematic review by Jackson et al<sup>32</sup> found that 4 of 5 observational studies indicated that weight loss in breast cancer survivors was associated with a higher risk of mortality. It is important to note that intentionality of weight loss was not assessed in these studies, and unintentional weight loss may be a result of cancer progression.

### **Physical activity**

**Prediagnosis physical activity.** In 2019, the ACSM roundtable report<sup>12</sup> concluded that physical activity, assessed before diagnosis, reduced risk of breast cancer-specific and all-cause mortality. This conclusion is supported by a more recent meta-analysis by Friedenreich et al<sup>36</sup> of recreational and total physical activity in 136 observational studies and secondary analyses of randomized controlled trials, 36 of

which were conducted among breast cancer survivors. Physical activity in the highest versus lowest activity categories was associated with a 14% (HR, 0.86; 95% CI, 0.78-0.94) and 18% (HR, 0.82; 95% CI, 0.76-0.87) lower risk of breast cancer mortality ( $n = 23$  studies) and all-cause mortality ( $n = 19$  studies), respectively. Physical activity reduced the risk of all-cause mortality regardless of BMI, and for patients with postmenopausal breast cancer, but not for those with premenopausal breast cancer. Evidence also supports an inverse dose-response relationship between physical activity and breast cancer-specific or all-cause mortality.<sup>36,37</sup> Greater amounts of physical activity, particularly moderate-to-vigorous-intensity physical activity, conferred a greater risk reduction for breast cancer-specific and all-cause mortality; however, the increasing benefits leveled off at higher amounts of physical activity. Apart from the dose of physical activity, when considering the domain, both recreational physical activity (eg, walking, running, etc) and total physical activity (recreational, transportation, occupational, and household) were associated with reduced breast cancer-specific and all-cause mortality.<sup>36</sup>

**Postdiagnosis physical activity.** Postdiagnosis physical activity confers a greater risk reduction than prediagnosis activity among premenopausal and postmenopausal women for breast cancer-specific and all-cause mortality.<sup>12,36</sup> Comparing the most active versus least active categories, the meta-analysis by Friedenreich et al of observational studies and RCTs<sup>36</sup> found a 37% (HR, 0.63; 95% CI, 0.50-0.78) and 42% (HR, 0.58; 95% CI, 0.52-0.65) lower risk of breast cancer-specific mortality ( $n = 13$  studies) and all-cause mortality ( $n = 17$  studies), respectively. Survival benefits were seen for breast cancer survivors with a BMI  $<25 \text{ kg/m}^2$  and  $\geq 25 \text{ kg/m}^2$  for both cancer-specific and all-cause mortality. Like prediagnosis physical activity, postdiagnosis activity reduced the risk of all-cause mortality for postmenopausal breast cancer survivors, but not for premenopausal breast cancer survivors. Consistent with results obtained by Friedenreich et al,<sup>36</sup> a meta-analysis by Spei et al<sup>38</sup> of 10 observational studies of breast cancer survivors that compared women who had the highest levels of recreational physical activity with those who had the lowest levels also found reduced risks of all-cause and breast cancer-specific mortality of 42% and 40%, respectively. Subgroup analyses that compared high versus low physical activity and overall mortality according to ER status found a significant inverse association among women with ER-positive breast cancer (HR, 0.47; 95% CI, 0.25-0.88) and a similar inverse but nonsignificant trend for women with ER-negative breast cancer (HR, 0.50; 95% CI, 0.38-0.66).<sup>38</sup> Furthermore, a meta-analysis by Morishita et al<sup>39</sup> of 8 RCTs showed that physical activity interventions (aerobic,

resistance, or combined) led to a 24% decreased risk of all-cause mortality. Two of the 8 RCTs included by Morishita et al<sup>39</sup> examined cancer recurrence, with a significant 48% reduced risk of recurrence. A meta-analysis by Akdeniz et al<sup>40</sup> of 12 population-based cohort studies examining modifiable risk factors and the risk of contralateral, new, primary breast cancers revealed no data on physical activity, suggesting the need for future studies to examine the impact of physical activity on the risk of a second, new, primary breast cancer.

Several meta-analyses have looked at the amount of physical activity and mortality risk among breast cancer survivors. In general, there is a significant inverse dose response for postdiagnosis physical activity and mortality. In their meta-analysis, Friedenreich et al<sup>36</sup> calculated dose-response curves and reported steep declines in the risk for cancer-specific and all-cause mortality, up to approximately 10 metabolic equivalent (MET) hours per week. This level of activity is consistent with physical activity guidelines to engage in 150 minutes per week of moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity.<sup>36</sup> Lee's<sup>37</sup> meta-analysis of 2 prospective studies supports the benefits of meeting physical activity guidelines versus not meeting guidelines because the author found a 21% and 28% reduced risk of breast cancer-specific and all-cause mortality, respectively. Lee<sup>37</sup> suggested that the amount and intensity of physical activity in patients with breast cancer may need to be higher than current recommendations (150 minutes per week of moderate-to-vigorous physical activity) and that the recommendations be increased to 300 minutes per week of moderate-intensity physical activity. However, the analyses of intensity and amount grouped low amounts of activity into <300 minutes per week, and the results were based on 2 studies for the various combinations of amount (dose) and intensity of physical activity. Consistent with the steep decline in risk seen in the dose-response curves reported by Friedenreich et al,<sup>36</sup> a meta-analysis by Wang et al<sup>41</sup> from 9 studies of multiple cancer types, 3 of which included breast cancer survivors, showed that even low amounts of physical activity were associated with a reduced risk of mortality compared with no activity. Importantly, Lee<sup>37</sup> conducted a meta-analysis of 2 prospective studies and found that decreasing physical activity from before to after diagnosis was associated with a 236% increased risk of all-cause mortality (RR, 2.36; 95% CI, 1.09–5.12).

Both recreational and total physical activity, at both prediagnosis and postdiagnosis, have been found to consistently provide protection for cancer-specific and all-cause mortality.<sup>36</sup> Conclusions about other physical activity domains, such as occupational, transportation, and household physical activity, cannot be reached because they have been less studied. Similarly, no clear recommendations can be made regarding the domain(s) of physical activity that

could contribute to the dose of 10 MET hours per week (approximately 3 hours of walking per week) identified in dose-response analyses.<sup>36</sup>

Across these reviews of individual studies,<sup>36–41</sup> the authors point to study limitations, such as variations in physical activity assessments, reliance on self-report (questionnaires and interviews), various cutoff points for the amount of activity, and the possibility of reverse causation. Nonetheless, taken together, these studies highlight the importance of breast cancer survivors engaging in any amount of physical activity they can, increasing their activity level when possible, and especially not decreasing physical activity after their diagnosis and treatment.

Apart from physical activity, there is increasing interest in the impact of sedentary behavior on health. A systematic review by Swain et al<sup>42</sup> of 9 prospective studies on the association between postdiagnosis sedentary behavior in cancer survivors and all-cause mortality only identified one study with breast cancer survivors. That study did not find a significant relationship between sedentary time and all-cause mortality. Notably, across all 9 studies, sedentary behavior was measured by self-report, and the quality of the evidence was classified as *low*, highlighting the need for more observational and interventional research to understand whether time spent being sedentary increases the risk for breast cancer-specific mortality or all-cause mortality and whether this is a potential intervention target for breast cancer survivors.

As pointed out in several of these reviews,<sup>12,38,41</sup> the mechanisms for the protective effects of physical activity on breast cancer-specific mortality may include reduced exposure to estrogen and androgen, the effects of insulin and insulin-related factors, and reduced inflammation. Physical activity may affect these pathways directly or indirectly by its effects on reducing body weight. The lower risk for all-cause mortality may be linked to other benefits of physical activity through reduced cardiovascular risk (eg, improved exercise capacity) and reduced risk for other comorbidities.

### Diet

There is a growing literature examining dietary patterns and outcomes in breast cancer survivors to capture the totality of diet rather than focusing on individual nutrients or foods. Dietary patterns that have been investigated include *a priori* indices, such as those based on dietary recommendations like the Healthy Eating Index (HEI),<sup>43</sup> to reflect diets consistent with US dietary guidelines for Americans, or an alternative Mediterranean diet score,<sup>44</sup> to reflect a Mediterranean-style eating pattern. Other studies explore dietary patterns identified from study populations, so-called *a posteriori* patterns, named according to constellations of food intake choices, such as those resembling a

*prudent* (healthy) or *Western* (unhealthy) dietary pattern. The more healthful dietary patterns are generally aligned with recommendations for cancer prevention (eg, those of the ACS<sup>4</sup> or the WCRF/AICR<sup>25</sup>), CVD prevention, and health promotion.<sup>30,45</sup> High-quality dietary patterns generally are characterized by a predominance of plant-based foods, including vegetables and fruit, and whole grains, and de-emphasize red and processed meat intake and refined grains; whereas Western dietary patterns generally are characterized by more red and processed meat intake as well as greater intakes of refined grain products and added sugars.

**Prediagnosis dietary patterns.** Three systematic literature reviews<sup>46–48</sup> found relatively few studies with mixed results that reported on prediagnosis dietary patterns and their influence on recurrence or mortality after breast cancer. However, to the extent that evidence may exist, the reviews suggest that a healthy dietary pattern may decrease overall mortality risk, whereas a more Western dietary pattern may be detrimental. In contrast, in a separate meta-analysis of 4 studies comparing vegetarians with nonvegetarians, Molina-Montes et al<sup>47</sup> reported a meta-analysis HR of 0.99 (95% CI, 0.67–1.44), indicating no benefit for vegetarian patterns per se.

**Postdiagnosis dietary patterns.** Three systematic literature reviews suggest that healthful dietary patterns after diagnosis are associated with decreased risk of overall mortality and nonbreast cancer mortality after breast cancer. Jochems et al<sup>46</sup> identified 11 separate studies that reported on some aspect of dietary patterns and breast cancer outcomes, with 3 suggesting inverse associations of healthful dietary patterns such as the HEI-2005 or a prudent dietary score with overall mortality. For nonbreast cancer-related mortality, 2 studies reported both an increased risk associated with a Western dietary pattern and inverse associations with prudent dietary patterns. Two other studies reported inverse associations with healthy diet scores, including the HEI-2005, the Dietary Approaches to Stop Hypertension score, and the Alternative Healthy Eating Index. In the systematic literature review conducted by Terranova et al,<sup>48</sup> 6 of the same studies were identified with the similar conclusion that better overall diet quality is associated with decreased risks of overall mortality and nonbreast cancer mortality but that there was insufficient evidence regarding associations with breast cancer-specific mortality or recurrence. In their systematic review, Molina-Montes et al<sup>47</sup> focused on vegetarian and other mostly plant-based diets. In 3 studies representing 6 prospective cohorts, no association between a vegetarian (vs nonvegetarian) diet and breast cancer mortality

was observed. A meta-analysis of 2 studies suggested a 13% lower risk of all-cause mortality with greater concordance with a Mediterranean dietary pattern.<sup>47</sup> Finally, the systematic review by Jochems et al<sup>46</sup> identified 2 randomized trials of dietary interventions among breast cancer survivors: the Women's Intervention Nutrition Study and the Women's Healthy Eating and Living Study (WHEL). The Women's Intervention Nutrition Study dietary intervention was focused on dietary fat reduction, whereas the WHEL dietary intervention was focused on increasing fruit and vegetable intake; both can be regarded as variations on promoting more healthful dietary patterns. Both studies suggested only modest effects of the dietary interventions on reducing total mortality; a meta-analysis of the 2 results suggests an HR for overall survival of 0.90 (95% CI, 0.75–1.09) and an HR for disease-free survival of 0.89 (95% CI, 0.78–1.02).

In an additional systematic literature review by Schwedhelm et al<sup>49</sup> that did not make clear distinctions between prediagnosis and postdiagnosis dietary patterns, a meta-analysis of 3 studies reported an HR of the association with overall mortality of 0.76 (95% CI, 0.60–0.95) for a high versus low prudent dietary pattern intake and an HR of 1.44 (95% CI, 1.17–1.77) for a high versus low Western dietary pattern. An additional meta-analysis of 3 studies that used a priori healthy dietary pattern scores reported an HR for overall mortality of 0.74 (95% CI, 0.60–0.90).<sup>49</sup>

**Dietary fat intake.** In addition to the WCRF/AICR 2014 review,<sup>11</sup> Makarem et al<sup>50</sup> published a contemporaneous systematic literature review in which they identified 18 studies that reported associations related to total or subtypes of dietary fat intake and mortality after breast cancer, although the number of studies reporting on any specific fat type variable was smaller. Regarding prediagnosis intake, Makarem et al<sup>50</sup> noted that, among the 7 identified studies reporting on total fat intake, only one found an association that was statistically significant, indicating an association between higher fat intake and higher breast cancer-specific mortality. For saturated fat intake, one of 2 studies suggested a positive association with overall mortality; for monounsaturated fat intake, 2 of 2 studies suggested a positive but nonstatistically significant association with overall mortality; and, for polyunsaturated fat intake, among 5 studies, one reported a positive association with overall mortality, whereas another reported an inverse association with overall mortality.<sup>50</sup> The results of the other 3 studies are not clear. There is limited evidence that prediagnosis fat intake is associated with mortality after breast cancer.

For postdiagnosis fat intake, Makarem et al<sup>50</sup> noted that one of 4 studies reported a positive association of total fat intake with overall mortality, and 2 of 5 studies reported a

positive association with breast cancer-specific mortality. For saturated fat intake, one of 3 studies reported a positive association with overall mortality, and the 2 studies examining breast cancer-specific mortality reported nonsignificant positive associations. Two of 2 studies reporting on the associations of *trans*-fat intake with overall mortality reported positive associations, with HRs of 1.45 (95% CI, 1.06-1.99) and 1.78 (95% CI, 1.35-2.32). The latter of these 2 studies also examined breast cancer-specific mortality and found a nonsignificant positive association (HR, 1.42; 95% CI, 0.89-2.52). For monounsaturated fat, one of 2 studies reported a significant inverse association of intake with overall mortality, whereas neither of the 2 studies examining breast cancer-specific mortality reported an association. For polyunsaturated fat intake, 3 studies reported positive associations with breast cancer-specific mortality, whereas 4 studies found no associations with overall mortality. The one exception was a study that reported a significant inverse association of eicosapentaenoic acid and docosahexaenoic acid intake with overall mortality, whether examining intake from food only (eg, fish) or including supplement intake.<sup>50</sup>

Overall, based on the reviews by Makarem et al<sup>50</sup> and the WCRF/AICR,<sup>11</sup> there is mixed and limited evidence that fat intake or subtypes of fat intake may be associated with mortality after breast cancer. Although there was an intriguing observation in these reviews that *trans*-fat intake was associated with an increased risk of death after breast cancer, this association was based on only 2 studies.

**Soy foods.** The WCRF/AICR 2014 review<sup>11</sup> concluded that there was limited evidence that soy foods may decrease risk of outcomes after breast cancer. Since that time, 2 systematic literature reviews reported on these associations.<sup>51,52</sup> Qiu and Jian<sup>52</sup> identified 11 studies that examined the association of prediagnosis soy food intake and soy protein or estimated soy isoflavone intake with breast cancer outcomes. In meta-analyses of 8 studies, those authors calculated that the RR of high versus low soy intake with overall mortality was 0.84 (95% CI, 0.71-0.98). For breast cancer-specific mortality, the meta-analysis RR for high versus low soy food intake was 0.89 (95% CI, 0.74-1.07) across 5 studies. For soy isoflavone intake, the comparable RR for overall mortality, including 7 studies, was 0.81 (95% CI, 0.66-0.99); and, for breast cancer-specific mortality, the comparable RR (including 3 studies) was 0.92 (95% CI, 0.76-1.12).<sup>52</sup> Two studies reported on the association of soy isoflavone intake from foods and breast cancer recurrence; the meta-analysis RR was 0.73 (95% CI, 0.60-0.87).<sup>52</sup> Finally, for the 3 studies reporting on food sources of soy protein intake, the meta-analysis RR for overall survival was 0.73 (95% CI, 0.49-1.10).<sup>52</sup>

Qiu and Jiang<sup>52</sup> identified 2 papers that reported on postdiagnosis soy intake. One was a pooled analysis by Nechuta et al of data from 3 studies—the WHEL trial, the Shanghai Breast Cancer Survivor Studies, and the Life After Cancer Epidemiology (LACE) study—and the other was from the Breast Cancer Family Registries Study. The meta-analysis RR for overall mortality comparing high versus low soy isoflavone intake was 0.80 (95% CI, 0.62-1.04).<sup>52</sup> A pooled analysis by Nechuta et al<sup>53</sup> (also analyzed in the review by Qiu and Jiang<sup>52</sup>) also reported on breast cancer-specific mortality, with an RR of 0.83 (95% CI, 0.64-1.07), and on breast cancer recurrence, with an RR of 0.75 (95% CI, 0.61-0.92). The analyses from that report<sup>53</sup> suggested that the findings related to recurrence were somewhat stronger for patients with ER-negative breast cancer, but the test for interaction by ER status was not significant.

As described by Nechuta et al,<sup>53</sup> the amount of soy foods consumed differs substantially in east Asian populations compared with populations in the United States or Europe. For example, in the After Breast Cancer Pooling Project (ABCPP), almost 90% of breast cancer survivors in Shanghai reported consumption of  $\geq 10$  mg soy isoflavones per day, whereas 84% of breast cancer survivors in 2 US studies reported consumption of <4 mg per day. Even so, the effects of soy isoflavone consumption of  $\geq 10$  mg per day, compared with <4 mg per day, were remarkably similar in the Shanghai and US women. For example, for recurrence, the HR for women in Shanghai was 0.69 (95% CI, 0.47-1.01), whereas, for the US women, it was 0.76 (95% CI, 0.58-0.99).<sup>53</sup>

### Alcohol

The 2014 summary report from the WCRF/AICR<sup>11</sup> indicated that no inferences could be made regarding alcohol intake and outcomes after breast cancer. Since that report, there have been 3 systematic literature reviews reporting on the association of alcohol intake with breast cancer outcomes.<sup>40,49,54</sup> In addition, a pooled analysis in the ABCPP<sup>33</sup> combining data from 3 studies (the WHEL trial, the LACE study, and the Nurse's Health Study) focused on postdiagnostic exposures and late events (>5 years) among survivors of ER-positive breast cancer.

**Overall mortality.** In a meta-analysis of 21 studies by Schwedhelm et al,<sup>49</sup> the RR of high versus low alcohol intake was 0.94 (95% CI, 0.85-1.04); no distinction was made between prediagnosis and postdiagnosis intake. An analysis from the ABCPP<sup>33</sup> found a similar association with overall mortality for postdiagnosis alcohol intake (RR, 0.93; 95% CI, 0.75-1.17).

**Recurrence.** In 7 studies in their systematic review, Schwedhelm et al<sup>49</sup> also examined the risk of breast cancer recurrence. The RR comparing high versus low alcohol intake was 1.21 (95% CI, 1.06-1.39). Again, no distinction was made between prediagnosis and postdiagnosis alcohol intake. Simapivapan et al<sup>54</sup> also conducted a systematic review on the impact of alcohol intake on recurrence or second primary breast cancers. For recurrence, Simapivapan et al<sup>54</sup> included 8 studies examining prediagnosis alcohol intake, 2 of which reported an increased risk of recurrence with higher versus lower alcohol intake. Five studies examining postdiagnosis alcohol intake were also included in that review, 2 of which reported pooled results from the ABCPP. One of the 3 individual studies reviewed (the LACE study) reported an increased risk of recurrence (HR, 1.35; 95% CI, 1.00-1.83 for  $\geq 6$  g vs no alcohol) with higher versus lower postdiagnosis alcohol intake, whereas the other 2 individual studies reported either no association or a nonstatistically significant increased risk. An ABCPP 2013 pooled analysis of 3 studies (including the LACE study) included in the review by Simapivapan et al<sup>54</sup> found no association of drinking  $\geq 6$  g alcohol per day versus none and breast cancer recurrence among all women. However, an increased risk was observed among postmenopausal women (HR, 1.19; 95% CI, 1.01-1.40), but not premenopausal women (HR, 0.91; 95% CI, 0.72-1.16; *P* for interaction = .027). Consumption of 0.36 to <6 g per day (<1/2 a drink per day) was inversely associated with recurrence among premenopausal women (HR, 0.75; 95%, 0.59-0.94). In addition, among women who had ER-negative tumors at diagnosis, light alcohol consumption was associated with a lower risk of recurrence (HR, 0.70; 95% CI, 0.53-0.92), and regular consumption was not associated with risk. In a 2016 analysis from ABCPP,<sup>33</sup> the RR of a late recurrence (ie,  $\geq 5$  years after diagnosis) among women with ER-positive breast tumors, for one drink per day (12 g of alcohol per day) was 1.28 (95% CI, 1.01-1.62) compared with nondrinkers.

**Second primary breast cancer.** In one review,<sup>54</sup> 3 prospective studies examining prediagnosis alcohol intake and the risk of second primary breast cancer were null. A review of contralateral breast cancer risk factors<sup>40</sup> identified 3 studies reporting associations with prediagnostic alcohol intake, with a meta-analysis RR of 1.15 (95% CI, 1.02-1.31) for ever versus never alcohol intake; however, this estimate includes one case-control study.

### Summary

Overall, systematic reviews indicate that greater obesity, whether prediagnosis or postdiagnosis, is associated with higher risk of recurrence, breast-cancer specific mortality, and overall mortality. Whether weight loss that is independent of disease-associated weight loss affects breast

cancer outcomes is less clear. There is strong and consistent evidence that physical activity, both prediagnosis and postdiagnosis, is associated with reduced risk for breast cancer-specific and all-cause mortality. Studies indicate that increasing activity, and not decreasing activity, after diagnosis have positive effects on breast cancer outcomes. More healthful dietary patterns after diagnosis are associated with lower risk of overall and nonbreast cancer mortality, whereas less healthful dietary patterns after diagnosis are associated with increased risk of these mortality end points. Soy food consumption before diagnosis is associated with lower risk of overall mortality. There is also consistent evidence, albeit from fewer studies, that soy intake, whether prediagnosis or postdiagnosis, or postdiagnosis soy isoflavone intake is associated with a lower risk of recurrence. The evidence that fat intake or its subtypes are associated with mortality is inconsistent and limited. Existing evidence suggests that there is no association of alcohol intake and overall mortality in breast cancer survivors, although that evidence is limited. The evidence for alcohol consumption, including postdiagnosis, in relation to breast cancer recurrence is inconsistent overall. However, possible heterogeneous associations by ER-receptor and menopausal status warrant further investigation.

## Cancers of the Upper Aerodigestive and Digestive System

Cancers of the upper aerodigestive tract (UADT) (eg, oral cavity, pharyngeal) and digestive system (eg, the gastrointestinal [GI] tract, including the esophagus, stomach, small bowel, colon, rectum, and anus, and the liver, gall bladder, biliary tract, and pancreas) constitute nearly 21% of newly diagnosed cancers annually in the United States.<sup>1</sup> In total, 397,040 new cases of GI cancers are projected in 2022, accounting for 183,150 deaths.<sup>1</sup> Colorectal cancer (CRC) is the most common GI cancer,<sup>1</sup> and rates are declining by about 2% per year for those aged 50 years and older; however, they are increasing by 1.5% annually in those younger than 50 years.<sup>55</sup> There are an estimated 1.5 million Americans living with a history of CRC.<sup>2</sup>

### Anthropometric parameters

The majority of studies examining BMI and mortality in UADT and digestive system cancers have focused on esophageal,<sup>56,57</sup> colorectal,<sup>34,56,58,59</sup> gastric,<sup>56,58</sup> oropharyngeal,<sup>56</sup> and pancreatic cancers.<sup>56,57</sup> Most studies have compared overweight (BMI 25.0-29.9 kg/m<sup>2</sup>) and/or obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) with BMIs from 18.5 to 24.9 kg/m<sup>2</sup>.

For esophageal cancer, in one meta-analysis by Liu and Zhang,<sup>57</sup> higher versus lower BMI at diagnosis was associated with a 17% (HR, 0.83; 95% CI, 0.68-0.98) lower risk of death; for every 5-unit increment in BMI,

there was a 3% lower risk of all-cause mortality. In another meta-analysis by Han et al,<sup>56</sup> high versus low BMI measured either before or at diagnosis was associated with a 23% (HR, 0.77; 95% CI, 0.66–0.88) lower risk of all-cause mortality. For CRC, patients who had a BMI in the overweight range, compared with those who had a BMI from 18.5 to 24.9 kg/m<sup>2</sup>, had a reduced risk of all-cause mortality.<sup>56,59</sup> For patients who had a BMI in the obese category, compared with those who had a BMI from 18.5 to 24.9 kg/m<sup>2</sup>, data were conflicting, with some meta-analyses showing no relation with all-cause mortality<sup>59</sup> and others showing a positive relationship.<sup>58,60</sup> The association for obesity compared with a BMI from 18.5 to 24.9 kg/m<sup>2</sup> for CRC-specific mortality was also conflicting. Some meta-analyses reported an increased risk of mortality with BMI measured prediagnosis but no association with BMI measured at diagnosis.<sup>34,58</sup> For gastric<sup>56,57</sup> and oropharyngeal cancers,<sup>56</sup> high versus low BMI at diagnosis was unrelated to all-cause mortality. For pancreatic cancer, the meta-analysis by Liu and Zhang<sup>57</sup> examined a BMI at diagnosis  $\geq 30$  kg/m<sup>2</sup> compared with a BMI from 18.5 to 24.9 kg/m<sup>2</sup> and found no association between BMI and all-cause mortality. In another larger meta-analysis, Han et al<sup>56</sup> demonstrated that obesity was associated with a 22% increased risk of mortality (HR, 1.22; 95% CI, 1.01–1.43), although no increased risk was seen for patients who were overweight. In one subanalysis by Han et al<sup>56</sup> (24 studies, 17,145 survivors), which combined all of the digestive system cancers together but excluded pancreatic cancer, the authors found that, compared with patients who had a BMI from 18.5 to 24.9 kg/m<sup>2</sup>, those with overweight in adulthood had a 24% reduction (HR, 0.76; 95% CI, 0.67–0.85) and those with obesity had a 15% reduction (HR, 0.85; 95% CI, 0.72–0.98) in the risk of death. The highest BMI at the time of diagnosis and in adulthood showed an 18% lower risk of death (HR, 0.82; 95% CI, 0.71–0.92).<sup>56</sup>

BMI is a proxy for obesity but does not directly measure adiposity. Visceral adiposity (VAT), the more metabolically active of the adipose tissue compartments, which could potentially affect cancer survival, was examined by Xiao et al<sup>61</sup> in one systematic review focusing on both CRC and pancreatic cancer in relation to mortality. In the majority of studies included by Xiao et al,<sup>61</sup> higher VAT (either those above the median compared with those below the median or high adiposity [ $>130$  cm<sup>2</sup>] compared with those without high adiposity) was associated with an increased risk of mortality for patients with CRC. In the studies of patients with pancreatic cancer (which primarily compared the highest quartile or tertile with the lowest), results were inconsistent, with only 1 of 5 studies reporting a significant increased relationship with mortality.

### Physical activity

Survivors of CRC who are physically active after diagnosis have a lower risk of CRC-specific mortality and all-cause mortality. A meta-analysis by Qui et al<sup>62</sup> of 18 prospective cohort studies that included 31,873 survivors of CRC reported a 36% lower risk of CRC-specific mortality (HR, 0.64; 95% CI, 0.47–0.88) and a 37% lower risk of all-cause mortality (HR, 0.63; 95% CI, 0.54–0.74) between the highest versus the lowest levels of postdiagnosis self-reported physical activity. In a meta-analysis of dose response in which the risk of bias was low to moderate, Qui et al<sup>62</sup> reported that each 10 MET-hour per week increase in postdiagnosis physical activity (eg, approximately 3 hours per week of brisk walking or 1.5 hours per week of bicycling) was associated with a 24% lower risk of CRC-specific mortality and a 21% lower risk of all-cause mortality. The benefits of specific physical activity types, such as aerobic or muscle-strengthening activities, were undetermined. The evidence quantitatively summarizing the effects of postdiagnosis physical activity was insufficient for other UADT and digestive system cancer sites.

Survivors of CRC who report more sedentary behavior after diagnosis have a higher risk of CRC-specific mortality.<sup>42</sup> Sedentary behaviors are characterized by sitting or lying and often include screen-based activities. A meta-analysis of 3 prospective cohort studies that included 6791 survivors of CRC<sup>42</sup> reported a 53% increase in the risk of CRC-specific mortality (HR, 1.53; 95% CI, 1.14–2.06) among those who reported more versus less sedentary behavior, which was defined variably across studies; however, the quality of the evidence was low. The evidence quantitatively summarizing the effects of postdiagnosis sedentary behavior was insufficient for other UADT and digestive system cancer sites.

### Diet

The evidence supporting associations of diet and survival among UADT or digestive system cancer survivors is focused primarily on dietary patterns and dietary indices.<sup>63</sup> Vegetables and fruits are considered a mainstay to a healthy diet pattern. In a meta-analysis of 5 cohort studies (5472 survivors) by Hurtado-Barroso et al,<sup>64</sup> a higher vegetable intake before diagnosis of head and neck cancer (oral cavity, pharynx, and larynx) was associated with 25% (HR, 0.75; 95% CI, 0.65–0.87) lower mortality in survivors. In contrast, studies of high fruit and vegetable consumption have either not shown outcomes in other GI cancers or have shown associations only in single studies.<sup>49,64</sup> The 2 major dietary patterns that have been reported in studies of GI cancer survivors are often categorized as prudent/healthy/plant-based diet and Western/unhealthy diet. Prudent dietary patterns are characterized by a higher intake of fruits, vegetables, cereals, nuts, legumes, and nonfat dairy products.

Western dietary patterns are characterized by a higher intake of red and processed meats, refined grains, sweets, desserts, and high-fat dairy products. Neither prediagnosis nor post-diagnosis prudent dietary patterns are associated with cancer recurrence or all-cause mortality in CRC survivors.<sup>46,49,64</sup> In contrast, at least 3 observational studies have shown that higher Western or processed meat diet patterns before or after diagnosis are associated with increased CRC recurrence and/or all-cause mortality.<sup>46,49,64</sup>

Dietary indices examined in observational studies mostly include the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension diet score, and the Mediterranean Diet score.<sup>46,49,64</sup> Meta-analyses of the limited number of studies have not shown consistent associations of these indices with outcomes in patients with CRC. The 2007 WCRF/AICR dietary score<sup>65</sup> is derived based on recommendations to eat a diet rich in whole grains, vegetables, fruit, and beans; limit consumption of energy-dense foods and avoid sugary drinks; eat mostly foods of plant origin; limit intake of red meat and avoid processed meat; and limit alcoholic drinks.<sup>66</sup> One study reported that a prediagnosis diet consistent with the WCRF/AICR recommendations was associated with 30% lower CRC mortality and 21% lower all-cause mortality.<sup>66</sup>

#### **Alcohol**

To date, there are limited data on associations between alcohol intake and overall mortality and/or cancer recurrence among survivors of UADT and digestive system cancers.<sup>49</sup> In a meta-analysis by Kim et al,<sup>67</sup> prediagnosis consumption of <30 g ethanol per day (<2 drinks per day) was associated with a lower risk of all-cause mortality in a dose-response analysis, whereas only light (>0 to <12.5 g per day) versus no consumption before diagnosis was associated with lower CRC-specific mortality. Postdiagnostic alcohol consumption was not associated with survival.<sup>67</sup> In their systematic review and meta-analysis of cohort studies, Schwedhelm et al<sup>49</sup> noted that higher intake of alcohol among hepatocellular carcinoma survivors was associated with increased all-cause mortality rates (RR, 1.21; 95% CI, 1.07-1.36). Similar increases in all-cause mortality rates were observed for laryngeal and pharyngeal cancers (RR, 1.48; 95% CI, 1.08-2.02) and head and neck cancer (RR, 1.39; 95% CI, 1.10-1.76).<sup>49</sup>

#### **Summary**

Higher BMI is not consistently associated with survival after GI cancer; relationships differ by cancer type, time of BMI measurement, and cancer outcome. There are no data that address whether intentional weight loss after a GI cancer diagnosis will improve outcomes. More direct measures of adiposity and muscle mass are needed to add rigor to the investigation of these relationships, in that some evidence supports a role for higher VAT driving greater all-cause mortality after CRC. Greater physical

activity is associated with improved overall and CRC-specific survival, and lower sedentary time also is associated with lower CRC-specific mortality; evidence for other GI cancers is limited and inconclusive. A Western dietary pattern is related to worse survival after CRC; evidence is limited for other GI cancers. Prediagnosis alcohol consumption of <30 g per day is associated with lower overall and CRC-specific mortality; there is no association between postdiagnosis alcohol consumption and survival outcomes. Available evidence supports limiting or avoiding alcohol after laryngeal, head and neck, or hepatic cancer because alcohol may increase all-cause mortality among survivors of these cancers.

### **Genitourinary Cancers**

In this section, we review cancers of the urinary tract and male reproductive cancers (female reproductive cancers are reviewed separately below). The genitourinary system includes the kidneys, urinary bladder, ureters, urethra, and in men, the prostate, penis, and testis. The estimated numbers of new cases in the United States for these cancers in 2022 are as follows: prostate (268,490), urinary bladder (81,180), kidney (79,000), testis (9910), ureter and other urinary organs (4010), and penis (2070).<sup>1</sup> Prostate cancer is the most commonly diagnosed cancer in males but ranks second for mortality and is estimated to account for 11% of the expected cancer deaths among men in 2022.<sup>1</sup>

#### **Anthropometric parameters**

**Prostate cancer.** The overall evidence that overweight and obesity impact the progression to advanced prostate cancer with increased mortality is inconclusive. In a pooled observational analysis of data from 22 phase 1 and 2 clinical trials ( $n = 11,724$ ) in the Southwest Oncology Group, Greenlee et al<sup>35</sup> analyzed the associations between BMI at study enrollment and cancer mortality across 14 cancer types. Deviating from previous observational studies, these data documented that patients who had prostate cancer with overweight ( $BMI \geq 25 \text{ kg/m}^2$ ) or obesity ( $BMI \geq 30 \text{ kg/m}^2$ ) treated with androgen-deprivation therapy ( $n = 942$ ) had a lower risk of death (HR, 0.79;  $P = .01$ ).

A 2012 systematic literature review by Parekh et al<sup>34</sup> evaluated the relationship between prediagnosis and postdiagnosis BMI and prostate cancer survival ( $n = 6$  studies). Two of the studies evaluated prediagnosis BMI and found that men with obesity ( $BMI \geq 30 \text{ kg/m}^2$ ) had a significantly higher risk of death compared with those with a healthy BMI, with an HR of 1.95 (95% CI, 1.17-3.23) after adjusting for age, smoking, BMI measurement time, cancer stage at diagnosis, and Gleason grade and an HR of 2.64 (95% CI, 1.18-5.92) after adjusting for age, race, smoking, Gleason grade, cancer stage and prostate-specific antigen at diagnosis, and treatment, respectively.

Men with obesity were also at greater risk of metastasis (HR, 3.61; 95% CI, 1.73-7.51). In the same systematic review,<sup>34</sup> 4 studies evaluating postdiagnosis prostate cancer BMI and site-specific mortality had inconsistent results. Contrasting these findings, both the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) study, with a mean follow-up of approximately 4 years, and the Mayo Clinic Prostatectomy Registry, with follow-up of 10 years, found no associations between BMI and prostate cancer-specific mortality. A limitation in interpreting results for most studies is that few prostate cancer studies control for tumor pathologic features.

**Bladder cancer.** In the Greenlee et al pooled observational analysis,<sup>35</sup> bladder cancer patients with overweight who were treated with Bacillus Calmette-Guerin ( $n = 443$ ) had a significantly lower risk of death (HR, 0.69;  $P = .02$ ). In a systematic review of 105 studies, Zuniga et al<sup>68</sup> examined modifiable risk factors and cancer recurrence, progression, cancer-specific mortality, and all-cause mortality for patients with nonmuscle-invasive bladder cancer. Of these, 18 studies assessed BMI and bladder cancer prognosis. The summary of evidence supported that overweight or obesity ( $BMI \geq 25 \text{ kg/m}^2$ ) is associated with an increased risk of both disease recurrence and progression for patients with nonmuscle-invasive bladder cancer.<sup>68</sup> Inconclusive results were noted with BMI and cancer site-specific mortality and all-cause mortality. Two cohort studies suggested that measurement of adiposity and muscle mass by computerized tomography (CT) scans, versus anthropometry, serve as better predictors of clinical outcomes in patients who undergo cystectomy because these measurements capture both fat and skeletal muscle mass. Indeed, sarcopenia was associated with an increased risk of all-cause mortality (HR, 1.67; 95% CI, 1.11-2.50), whereas BMI alone showed no association.<sup>68</sup> As acknowledged by the authors, the use of a single database (PubMed; and references of publications identified) was a limitation of their systematic review.

**Kidney cancer.** In the Greenlee et al pooled observational analysis,<sup>35</sup> patients with renal cancer who had a higher BMI at the time of diagnosis and were treated with  $\alpha$ -IFN 9 ( $n = 145$ ) showed no association between baseline BMI and the risk of death. A 2016 systematic review of imaging (CT/magnetic resonance imaging) studies was conducted by Xiao et al<sup>61</sup> to assess VAT and cancer survival in several cancers, including 5 studies of renal cell carcinoma. In 4 of 5 renal cell carcinoma cohort studies, either higher VAT was predictive of survival or lower VAT was associated with poorer survival.

**Testicular cancer.** No systematic reviews assessing the associations between adiposity, body weight, body

composition, weight change, and testicular or other male genital cancer outcomes have been reported.

### Physical activity

Evidence examining postdiagnosis physical activity or sedentary behavior in relation to cancer survival outcomes in genitourinary cancers is limited. Benke et al<sup>69</sup> conducted a systematic review and meta-analysis of 48 cohort studies and 24 case-control studies examining the associations between physical activity and prostate cancer incidence and mortality. Four cohort studies examined postdiagnosis physical activity and prostate cancer-specific mortality and reported that higher physical activity was associated with a 31% reduced risk of prostate cancer-specific mortality (RR, 0.69; 95% CI, 0.55-0.85); the benefit was largely attributed to recreational activity. Friedenreich et al<sup>36</sup> conducted a systematic review and meta-analysis of 136 studies examining the associations of prediagnosis and postdiagnosis physical activity with cancer-specific and overall survival for all cancers and by tumor site, identifying the same 4 cohort studies of prostate cancer-specific mortality as Benke et al<sup>69</sup> and reporting the same 30% risk reduction. Among 5 cohort studies examining physical activity and all-cause mortality, there was a 40% risk reduction for the most active versus least active prostate cancer survivors (HR, 0.60; 95% CI, 0.46-0.79).

In terms of other genitourinary cancers, Friedenreich et al<sup>36</sup> identified only one study that examined postdiagnosis physical activity and survival in patients with kidney cancer. That study reported that the most active versus least active kidney cancer survivors had a nonsignificant 43% risk reduction in kidney cancer-specific mortality (HR, 0.57; 95% CI, 0.24-1.33) and a significant 40% risk reduction in all-cause mortality (HR, 0.60; 95% CI, 0.38-0.96). Swain et al<sup>42</sup> conducted a systematic review of 33 studies examining postdiagnosis sedentary behavior and health outcomes in cancer survivors, including 9 studies that examined mortality. One study of kidney cancer survivors demonstrated a higher risk of overall mortality for the most versus least sedentary (HR, 1.19; 95% CI, 0.96-1.47). Finally, a single study of prostate cancer survivors included by Swain et al<sup>42</sup> reported a decreased risk of overall mortality among those with the most versus least sedentary occupational activity (HR, 0.72; 95% CI, 0.50-1.04).

### Diet

A systematic review and meta-analysis of cohort studies in cancer survivors by Hurtado-Barroso et al<sup>64</sup> reported on associations between fruit and vegetable intake with cancer recurrence, mortality, and all-cause mortality. However, only one study was identified for prostate cancer; an Italian study of 777 men with median follow-up

of 12.7 years, the results of which suggested lower cancer-specific and overall mortality with high levels of raw vegetable intake, as well as lower overall mortality with greater fruit intake prediagnosis. The review included 2 inconclusive studies of fruit and vegetable intake in patients who had bladder cancer, with one study suggesting that greater prediagnosis fruit intake may reduce risk for first recurrence of bladder cancer. Regarding bladder cancer, the Zuniga et al review<sup>68</sup> concluded that limited evidence suggests that beverages including coffee, green tea, or cola, and artificial sweetener do not appear to be associated with outcomes among patients with nonmuscle-invasive bladder cancer.

Jochems et al<sup>46</sup> reviewed dietary patterns and indices in cancer survivors and identified 2 studies among men with prostate cancer. One of those studies, the Physician's Health Study, examined adherence to a Western diet after prostate cancer diagnosis in 926 men with nonmetastatic prostate cancer and found that adherence was associated with a 2.5-fold increased risk of prostate cancer-specific mortality (HR, 2.53; 95% CI, 1.00-6.42) and a 67% increased risk of all-cause mortality (HR, 1.67; 95% CI, 1.16-2.42). A prudent diet was associated with a 36% lower risk of all-cause mortality (HR, 0.64; 95% CI, 0.44-0.93).<sup>46</sup> The second report completed in the Health Professionals Follow-up Study enrolled a cohort of 4538 nonmetastatic prostate cancer survivors and reported that following the Mediterranean diet pattern after diagnosis was associated with a 22% lower risk of all-cause mortality (HR, 0.78; 95% CI, 0.67-0.90), whereas there was a lack of association between this diet and the risk of prostate cancer outcomes.<sup>46</sup>

### **Alcohol**

No systematic reviews or meta-analyses that met our inclusion criteria have reported on the associations of alcohol intake with outcomes among those with prostate or any other genitourinary cancers.

### **Summary**

Evidence for factors related to nutrition and physical activity that may influence survival from genitourinary cancers is inconsistent and, for some of the less common genitourinary cancers, nonexistent. The totality of the evidence in systematic reviews does not definitively support an association of body weight, BMI, or body composition with prostate cancer progression or prostate cancer-specific mortality. Data are inconclusive for bladder cancer in terms of cancer-specific and overall mortality; recurrence and progression are associated with overweight/obese status for noninvasive disease. However, higher BMI may increase recurrence or progression risk in patients with bladder cancer and is inversely associated with kidney cancer

survival. There is consistent evidence that physical activity is associated with lower prostate cancer-specific and overall mortality. Systematic review analyses of diet patterns and genitourinary cancers are few and suggest that Western, as opposed to prudent, diet patterns are associated with higher prostate cancer-specific and overall mortality, and a Mediterranean-style dietary pattern is associated with lower all-cause mortality among prostate cancer survivors. No systematic reviews that met our inclusion criteria have been conducted evaluating alcohol intake and genitourinary cancer outcomes.

## **Gynecologic Cancers**

Gynecologic cancer refers to any cancer that originates in women's reproductive organs, including the cervix, ovary, uterus, vagina, and vulva. In 2022, it is estimated 115,130 new cases of gynecologic cancer will be diagnosed in the United States.<sup>1</sup> Endometrial cancer (which comprises the vast majority of uterine corpus cancers) is the most common gynecologic malignancy in the United States, with an estimated 65,950 new cases and 12,550 deaths in 2022.<sup>1</sup> The prognosis for endometrial cancer is related to the stage of disease at diagnosis, with a 95% survival rate if diagnosed with localized disease.<sup>1</sup> Ovarian cancer is the most lethal of the gynecologic cancers, and it is estimated that 29,880 women will be diagnosed with, and 12,810 will die of, this disease in 2022.<sup>1</sup> At least half of ovarian cancers are diagnosed at an advanced stage, when the prognosis is poor, with an overall 5-year survival rate of 49%. For the 19% of women diagnosed with localized ovarian cancer, the 5-year survival rate is 93%.<sup>1,55</sup> Invasive cervical (also called *uterine cervix*) cancer is estimated to be diagnosed in 14,100 women in 2022 and result in death in approximately 4280 women.<sup>1</sup> The role of nutrition and physical activity in gynecologic cancer prognosis is largely unknown.

### **Anthropometric parameters**

**Endometrial cancer.** Obesity is established as a strong risk factor for the development of several cancers, and one of the strongest associations is with endometrial cancer.<sup>70</sup> However, studies on the role of obesity in endometrial cancer prognosis are limited and inconclusive. Among studies covered in 2 systematic reviews by Arem and Irwin<sup>71</sup> and Secord et al,<sup>72</sup> approximately one-half found that a higher prediagnosis BMI is associated with a higher risk of all-cause mortality among endometrial cancer survivors, whereas the other one-half reported no association between prediagnosis BMI and survival. Pooling these studies together suggests that a 10% increase in endometrial cancer survivors' BMI is associated with 9% higher odds of all-cause mortality.<sup>72</sup> A few studies included by Arem and Irwin<sup>71</sup> examined the relationship between

BMI and progression-free survival among endometrial cancer survivors, and none indicated an association. A recent, large meta-analysis by Petrelli et al<sup>60</sup> exploring the associations between obesity (BMI  $\geq 30 \text{ kg/m}^2$ ) and mortality found that women with endometrial cancer who had a BMI  $\geq 30 \text{ kg/m}^2$  at diagnosis had a 20% higher risk of all-cause mortality compared with those without obesity, but no association with risk of endometrial cancer-specific mortality or recurrence was demonstrated. The role of weight change from prediagnosis to postdiagnosis in endometrial cancer survival is unknown.

**Ovarian cancer.** The association between BMI and ovarian cancer survival is poorly understood. One pooled analysis by Greenlee et al,<sup>35</sup> using data from 22 clinical trials of common treatments in multiple cancer sites within the Southwest Oncology Group, suggested poorer ovarian cancer survival for women with higher BMI on a paclitaxel regimen (HR, 1.18). However, the sample size was relatively small ( $n = 241$ ), and the results were not statistically significant. A systematic literature review by Xiao et al<sup>61</sup> evaluated the association of visceral fat with cancer survival, but only one small study of ovarian cancer was identified ( $n = 46$  patients with advanced ovarian cancer), which found no association with progression-free survival or overall survival. Petrelli et al,<sup>60</sup> in a recent meta-analysis of studies evaluating obesity (BMI  $\geq 30 \text{ kg/m}^2$ ) at diagnosis and ovarian cancer survival, found no association with recurrence (including 2 studies) or with ovarian cancer-specific mortality or all-cause mortality (including 4 studies) for women with obesity versus women without obesity.

#### Physical activity

No systemic reviews or meta-analyses on the role of physical activity or sedentary behavior in the prognosis of endometrial cancer, ovarian cancer, or other individual gynecological cancers were available at the time of this report. One meta-analysis by Friedenreich et al,<sup>36</sup> however, pooled results from studies of ovarian, endometrial, and cervical cancer survivors to explore the potential role of prediagnosis and postdiagnosis physical activity in female reproductive cancer survival. That analysis revealed no indication of an association between prediagnosis physical activity and cancer-specific or all-cause mortality among female reproductive cancer survivors. However, survivors of female reproductive cancers who were the most physically active postdiagnosis had a 33% lower risk of all-cause mortality compared with the least physically active female reproductive cancer survivors.<sup>36</sup> There were not enough studies to explore the association between postdiagnosis physical activity and site-specific cancer mortality. There are currently no reviews or meta-analyses on the role of

sedentary behavior in the prognosis of female reproductive cancers.

#### Diet

**Endometrial cancer.** No systematic reviews or meta-analyses on the role of diet in the prognosis of endometrial cancer were available at the time of this report.

**Ovarian cancer.** Limited evidence is available for the role of diet in ovarian cancer prognosis. Meta-analyses of vegetable and fruit consumption and the prognosis for cancer survivors by Hurtado-Barroso et al<sup>64</sup> showed that high vegetable and fruit intake before a diagnosis of ovarian cancer was associated with 22% (HR, 0.78; 95% CI, 0.66–0.91) and 18% (HR, 0.82; 95% CI, 0.70–0.96) lower overall mortality, respectively (based on 4 studies). The findings suggested a dose response, with those consuming  $\geq 400 \text{ g}$  per day of vegetable and fruits experiencing the greatest overall survival. By contrast, a single study within a review by Molina-Montes et al<sup>47</sup> indicated that vegetarian (plant-based) dietary patterns were not associated with ovarian cancer-specific mortality. A 2018 systematic review by Yeganeh et al<sup>73</sup> of lifestyle modification on gynecologic cancer recurrence identified no published results from RCTs that assessed the effect of lifestyle interventions, including those related to diet, on cancer recurrence or survival.

#### Alcohol

No systemic reviews or meta-analyses on the role of alcohol in the prognosis of endometrial cancer, ovarian cancer, or other gynecological cancers were available at the time of this report.

#### Summary

In summary, although the current evidence is limited and inconclusive, there is emerging evidence that obesity may be associated with lower survival after an endometrial cancer diagnosis, and early but limited evidence suggested that physical activity after diagnosis may improve survival from gynecological cancers. For ovarian cancer, there is not sufficient evidence on the role of behaviors such as diet, physical activity and alcohol consumption to guide recommendations for ovarian cancer survivors at this time. No systematic reviews or meta-analyses on the role of modifiable risk factors in the prognosis of cervical, vaginal, or vulvar cancers were available at the time of this report. Further studies are needed before public health recommendations that are specific to gynecological cancers can be made.

#### Lung Cancer

In 2022, an estimated 236,740 Americans will be diagnosed with lung cancer, and 130,180 will die from the disease.<sup>1</sup>

Lung cancer is the second most common cancer (excluding nonmelanoma skin cancer) and the number one cause of cancer death among men and women in the United States.<sup>1</sup> There were 517,350 lung cancer survivors living in the United States by 2018.<sup>2</sup> Although smoking cessation is still a top priority, other modifiable risk factors might also play a role in long-term survival outcomes among lung cancer survivors.

### **Anthropometric parameters**

The relationship between body weight, BMI, body composition, and lung cancer survival is complex. Because smoking is an important risk factor for the disease, and smokers tend to have a lower BMI, this may potentially confound the association of BMI and cancer survival. Research on BMI at diagnosis and lung cancer prognosis is limited and inconsistent. In a study of patients who were treated with certain chemotherapeutic drugs, there was some evidence of a survival advantage for patients with higher BMI.<sup>35</sup> Greenlee et al,<sup>35</sup> in a pooled analysis of 22 clinical trials investigating the relationship of BMI and cancer survival, included 2 studies of nonsmall cell lung cancer and found that overweight ( $BMI \geq 25$  vs  $<25 \text{ kg/m}^2$ ) was associated with a lower risk of mortality among patients with nonsmall cell lung cancer who received treatment with carboplatin and paclitaxel. However, higher BMI was not associated with mortality among patients who received treatment with cisplatin and vinorelbine. In another meta-analysis, Petrelli et al<sup>60</sup> found that patients with lung cancer who had obesity, compared with patients who did not, had lower overall mortality (11 studies: HR, 0.86; 95% CI, 0.76-0.98) and cancer-specific mortality (3 studies: HR, 0.53; 95% CI, 0.30-0.92). However, the majority of studies included patients with advanced lung cancer, in whom significant weight loss is common; therefore, the findings should be interpreted with caution.

### **Physical activity**

Evidence linking postdiagnosis physical activity or sedentary behavior to lung cancer survival is very limited. Friedenreich et al<sup>36</sup> conducted a systematic review and meta-analysis of 136 observational studies or randomized trials examining the associations of prediagnosis and post-diagnosis physical activity with cancer-specific and overall survival for all cancers and by tumor site. In 2 prospective cohort studies, self-reported postdiagnosis physical activity was associated with a statistically significant 24% risk reduction in all-cause mortality for the most versus least physically active patients with lung cancer (HR, 0.76; 95% CI, 0.60-0.97). Similarly, in 5 prospective cohort studies, higher self-reported prediagnosis physical activity was associated with a statistically significant 19% reduced risk of lung cancer mortality (HR, 0.81; 95% CI, 0.75-0.87).

Moreover, Morishita et al<sup>39</sup> conducted a systematic review and meta-analysis of 8 randomized controlled trials examining the effects of physical activity on recurrence and overall survival across all cancer survivor groups. The one trial of 111 patients with lung cancer reported no effect of a 2-month exercise program designed to increase physical activity by 3 MET hours per week on overall mortality. Overall, evidence for an association between physical activity and lung cancer survival is very limited and inconclusive. Robust data and studies to inform on the role of sedentary behavior and lung cancer survival are not available at this time.

### **Diet**

Research on diet and lung cancer outcomes to date have largely focused on intake of fruits, vegetables, and vegetarian dietary patterns. In a recent systematic literature review and meta-analysis by Hurtado-Barroso et al<sup>64</sup> of 28 cohort studies, including 2 studies among lung cancer survivors, no association was found between fruit and vegetable consumption and all-cause mortality in patients with lung cancer. Another meta-analysis of dietary patterns and cancer survival by Molina-Montes et al<sup>47</sup> found no association between consuming a vegetarian diet (reported no consumption of any meat or fish) before diagnosis and lung cancer-specific mortality.

### **Alcohol**

No systemic reviews or meta-analyses on the role of alcohol in the prognosis of lung cancer were available at the time of this report.

### **Summary**

In summary, the evidence on anthropometric parameters, physical activity, and diet in relation to lung cancer prognosis remains limited. Despite some beneficial associations between being physically active and having a higher BMI with lung cancer-specific survival in patients who have lung cancer, more studies are needed to confirm these associations. No systematic reviews, meta-analyses, or RCTs of alcohol consumption and lung cancer survival were identified. Importantly, current evidence has assessed exposures before diagnosis as drivers of survival-related outcomes more than it has evaluated behaviors or behavior changes after diagnosis.

### **Hematological Cancers**

Hematological cancers are a group of malignancies originating from cells of the bone marrow and the lymphatic system. The 3 major types of hematological cancers are leukemia, lymphoma, and multiple myeloma. In 2022, there will be an estimated 184,130 new cases of hematological cancer, accounting for 9.6% of new cancers, and 57,810 deaths from hematological cancers in the United States.<sup>1</sup> The survival

rates for hematopoietic and lymphoid cancers have improved over the last several decades; for example, the 5-year relative survival rate for chronic myeloid leukemia increased from 22% in the mid-1970s to 71% for those diagnosed from 2011 through 2017.<sup>1</sup> Similar to the solid malignancies, however, there are significant disparities in incidence and survival for patients with hematological cancers across racial and ethnic groups.<sup>74</sup>

There is limited understanding of the origins of these malignancies and risk factors. The association between exposure to ionizing radiation and leukemia is well established, and cigarette smoking is also a known risk factor for leukemia.<sup>75</sup> Recent evidence suggests that lower fruit and vegetable consumption may contribute to risk for non-Hodgkin lymphoma.<sup>76</sup>

Studies on the role of modifiable risk factors in hematological cancer prognosis are also limited. Seven of the systematic reviews, meta-analyses, and large pooled cohort and clinical trials in survivors that met our criteria included patients with hematological cancers. In these systematic reviews, which included several cancer types, patients with hematological cancers comprised a small proportion of the total number of patients and studies in the analyses.

#### **Anthropometric parameters**

In the pooled analysis of 22 clinical trials by Greenlee et al,<sup>35</sup> one trial in patients with acute myelogenous leukemia and one trial in patients with non-Hodgkin lymphoma were included, and BMI at the time of cancer diagnosis was not significantly associated with prognosis in either study.

#### **Physical activity**

In a systematic review and meta-analysis of the association between physical activity and mortality that included 136 studies and 11 cancer sites, Fredenreich et al<sup>36</sup> reported that a protective effect of prediagnosis physical activity was observed in 6 studies of patients with hematological cancers (described as leukemia, lymphoma, myeloma, and other hematopoietic cancers; HR, 0.82; 95% CI, 0.76–0.90). Postdiagnosis physical activity was not significantly associated with mortality in the single study that examined that relationship in patients with hematological cancers. Postdiagnosis sedentary behavior was not associated with mortality in the single study of patients with hematological cancers in a systematic review and meta-analysis of 33 studies of that relationship in various cancer sites by Swain et al.<sup>42</sup>

#### **Diet**

Two studies of patients with non-Hodgkin lymphoma were included by Jochems et al<sup>46</sup> in their systematic review of patients with common cancers who had a 10-year survival rate

of >50% to examine the association between dietary patterns/indices and food groups and mortality/cancer recurrence. Evidence for associations between dietary factors and mortality in the patients with non-Hodgkin lymphoma in those 2 studies was inconsistent. A systematic review and meta-analysis by Molina-Montes et al<sup>47</sup> of 26 studies of plant-based dietary patterns and cancer-related mortality or survival did not include any patients with hematological cancers among their postdiagnosis cohorts. The association between fruit and vegetable consumption and cancer recurrence, mortality, and all-cause mortality in 28 studies of patients with cancer was the focus of a systematic review and meta-analysis by Hurtado-Barroso et al<sup>64</sup> that included 3 studies of patients with non-Hodgkin lymphoma. Null results for prediagnosis vegetable and fruit consumption in relation to survival from non-Hodgkin lymphoma or any cause were reported for those studies.

#### **Alcohol**

A meta-analysis by Schwedhelm et al<sup>49</sup> of 117 cohort studies that investigated the effects of adherence to diet quality indices, dietary patterns, and food and beverage consumption on overall mortality and cancer recurrence among adult cancer survivors included patients with non-Hodgkin lymphoma (but not other hematological cancers) across 4 studies. In a meta-analysis of those 4 studies, the highest versus lowest prediagnosis alcohol consumption was associated with higher mortality (HR, 1.33; 95% CI, 1.10–1.63), but associations with other dietary patterns or foods were not observed. Although 3 of the 4 studies controlled for smoking, only one examined alcohol associations stratified by smoking history; in that study, no association of alcohol consumption and mortality among nonsmokers was observed.

#### **Summary**

There is some evidence for a protective effect of prediagnosis physical activity and an adverse effect of prediagnosis alcohol intake on prognosis in patients with hematological cancers, although confounding by tobacco should be ruled out. Evidence is sparse and does not support benefits of dietary recommendations for these patients at this time, and further research is needed.

#### **Childhood Cancer**

The ACS estimates that 10,470 children in the United States younger than 15 years and 5480 adolescents (aged 15–19 years) will be diagnosed with cancer in 2022; and 1050 children and 550 adolescents will die from the disease.<sup>1</sup> Although general diet and physical activity recommendations for children being treated for cancer are largely similar to the recommendations for adults outlined in this guideline, a unique concern for children is to maintain normal growth and development during and after treatment.

Families should work closely with dietitians, rehabilitation specialists, and physical therapists at their cancer treatment facility for dietary intake and physical activity recommendations tailored to the child's specific needs to maintain appropriate growth and development milestones.

Significant advances in the treatment of childhood cancers over the past 50 years have dramatically improved long-term survival rates. Survival rates vary by cancer site and treatment regimen, but current overall 5-year survival rates are 85% among children and 86% among adolescents.<sup>1</sup> As a result, there are currently more than 400,000 survivors of cancers diagnosed during childhood and adolescence living in the United States.<sup>2</sup> However, because of the intensity of the chemotherapy and/or radiation regimens that have been used to treat many types of childhood cancers in the past, survivors of childhood cancer have been found to be at higher risk of developing chronic health conditions, such as CVD and second cancers.<sup>77</sup> Childhood cancer survivors also tend to experience these chronic health conditions at earlier ages compared with people who do not have a history of cancer.<sup>78</sup> Therefore, efforts to prevent or delay the development of these conditions by maintaining a healthy body weight, making healthy dietary choices, and engaging in regular physical activity are especially important for survivors of childhood cancer. Fortunately, the risk of these secondary chronic health conditions is decreasing as treatment regimens with lower toxicity profiles have become available.<sup>74,79</sup>

Research on the role of diet and physical activity in minimizing the risk of chronic health conditions and improving overall outcomes for survivors of childhood cancers is currently limited. A systematic review and meta-analysis of 136 observational studies or randomized trials examining prediagnosis and postdiagnosis physical activity by Friedenreich et al<sup>36</sup> found only one study of childhood cancer survivors. That large study of 15,450 adult participants in the Childhood Cancer Survivor Study found that individuals who reported regular postdiagnosis exercise had significant reductions in the risk of all-cause mortality and cancer recurrence compared with those who did not exercise regularly postdiagnosis.

The recommendations outlined in this document are consistent with the *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* (version 5.0, October 2018) from the Children's Oncology Group,<sup>80</sup> which recommend that survivors of childhood cancers maintain a healthy body weight and make healthy choices about diet and exercise to reduce the risk of certain types of adult cancers and other chronic health conditions.

## Recommendations and Summary of Evidence

Cancer survivors can benefit from diet and physical activity assessment and counseling across the continuum of

**TABLE 1. American Cancer Society Guideline on Diet and Activity for Cancer Survivors 2022**

General recommendations for cancer survivors:

- Nutritional assessment and counseling should begin as soon as possible after diagnosis, with the goal of preventing or resolving nutrient deficiencies, preserving muscle mass, and managing side effects of treatments that may adversely affect nutritional status.
- Physical activity assessment and counseling should begin as soon as possible after diagnosis, with the goal of helping patients prepare for treatments, tolerate and respond to treatments, and manage some cancer-related symptoms and treatment-related side effects.

Recommendations to improve long-term health and increase the likelihood of survival:

- Avoid obesity and maintain or increase muscle mass through diet and physical activity.
- Engage in regular physical activity, with consideration of type of cancer, patient health, treatment modalities, and symptoms and side effects.
- Follow a healthy eating pattern that meets nutrient needs and is consistent with recommendations to prevent chronic disease.
- Follow the general advice of the American Cancer Society *Guideline for Diet and Physical Activity for Cancer Prevention* to reduce risk of a new cancer.

survivorship, from diagnosis and treatment through long-term health and survival postdiagnosis. Table 1 summarizes general recommendations that are supported by current scientific evidence.

Nutritional counseling can help to manage treatment-related side effects, such as nausea, vomiting, and appetite loss, and thus prevent nutrient inadequacies and loss of muscle mass caused by these side effects. Many cancer survivors are able to exercise before, during, and after treatments, although some short-term restrictions may apply after major surgery or stem cell transplantation. Physical activity during and after treatment can improve anxiety, depressive symptoms, fatigue, physical functioning and health-related quality of life. The American College of Sports Medicine provides guidance on specific doses of aerobic and resistance training that could improve these common cancer-related health outcomes.<sup>14</sup> Individual physical activity recommendations may need to be adapted in consideration of patient health and treatment-related symptoms and side effects because of potential impacts on exercise tolerance and safety. The ultimate aim is to achieve the current physical activity recommendations for health (150–300 minutes per week of moderate-intensity or 75–150 minutes per week of vigorous-intensity physical activity, and muscle-strengthening activities on 2 or more days a week). There is insufficient evidence for an association between alcohol intake and overall and cancer-specific mortality across all cancer types to warrant a general recommendation that is specific for cancer survivors. However, there are some types of cancer for which this association has been observed. Also, alcohol intake is an

**TABLE 2. American Cancer Society Guideline on Nutrition and Physical Activity for Cancer Prevention Recommendations for Individuals**

1. Achieve and maintain a healthy body weight throughout life.
<ul style="list-style-type: none"> <li>Keep body weight within the healthy range and avoid weight gain in adult life.</li> </ul>
2. Be physically active.
<ul style="list-style-type: none"> <li>Adults should engage in 150–300 min of moderate-intensity physical activity per wk (or 75–150 min of vigorous-intensity physical activity); striving to meet or exceed the upper limit of 300 min is ideal.</li> <li>Children and adolescents should engage in at least 1 h of moderate-intensity or vigorous-intensity activity each d.</li> <li>Move more and sit less.</li> </ul>
3. Follow a healthy eating pattern at all ages.
<ul style="list-style-type: none"> <li>A healthy eating pattern includes:           <ul style="list-style-type: none"> <li>Foods that are high in nutrients in amounts that help achieve and maintain a healthy body weight;</li> <li>A variety of vegetables—dark green, red, and orange, fiber-rich legumes (beans and peas), and others;</li> <li>Fruits, especially whole fruits with a variety of colors;</li> <li>Whole grains.</li> </ul> </li> <li>A healthy eating pattern limits or does not include:           <ul style="list-style-type: none"> <li>Red and processed meats;</li> <li>Sugar-sweetened beverages;</li> <li>Highly processed foods and refined grain products.</li> </ul> </li> </ul>
4. It is best not to drink alcohol.
<ul style="list-style-type: none"> <li>People who do choose to drink alcohol should limit their consumption to no more than 1 drink per d for women and 2 drinks per d for men.</li> </ul>

established cause of several types of cancer, so the avoidance of alcohol consumption is among the recommendations for cancer prevention and thus is relevant to reduce risk for a new cancer in cancer survivors.

The ACS guideline for diet and physical activity for cancer prevention recommendations are listed in Table 2. The summary of evidence for adiposity, physical activity, diet, and alcohol after diagnosis for specific cancer types is presented in Table 3. In summarizing the findings, *only* systematic reviews that met the guideline methodology for inclusion and that identified a significant association are listed. Importantly, the table calls attention to the lack of quality systematic reviews for many cancers, suggesting additional research is needed to advance recommendations going forward.

### Late Effects and Patient-Reported Outcomes: Issues Affecting Uptake of Physical Activity and Nutrition Guidelines

Adopting healthy behaviors for diet and physical activity can have many positive impacts on quality of life and symptoms related to cancer treatment. For example, exercise can improve quality of life<sup>81</sup> and specific symptoms, such as fatigue.<sup>82</sup> Structured exercise programming may also be a strategy to improve cardiovascular fitness after

cancer therapy.<sup>83</sup> Some studies have specifically confirmed that adherence to the previous version of the ACS guideline for physical activity and nutrition for cancer survivors can improve health-related quality of life<sup>84</sup> and reduce the risk for the development of metabolic syndrome.<sup>85</sup> The latter is significant because metabolic syndrome also increases risk for other comorbidities, including diabetes and CVD, which remains a leading cause of morbidity and mortality in the United States, even among cancer survivors.<sup>86</sup>

### Health Promotion Counseling in Cancer Survivors

Individuals with a history of cancer are not necessarily following nutrition and physical activity guidelines to a greater extent than their peers without a cancer history when it comes to meeting current recommendations for healthy behaviors.<sup>87–90</sup> Gaps in assessing and counseling survivors on dietary<sup>91</sup> and alcohol intakes<sup>92</sup> and physical activity<sup>12,13</sup> may be partly to blame. Even those cancer survivors with known risk factors for CVD report not having discussions about health promotion with their health care providers.<sup>93</sup> Counselors should tailor communications and strategies appropriate to the health literacy and numeracy of the individual to improve accessibility of information. Health literacy can be influenced by many factors, including age, education, cognitive abilities, and language. For example, older individuals may have more limited health literacy and numeracy compared with their younger counterparts.<sup>94</sup>

### Late and Long-Term Effects Can Serve as Barriers to Guideline Adherence

Adherence to the ACS guideline among cancer survivors is suboptimal. An RCT of breast cancer survivors demonstrated only moderate adherence.<sup>95</sup> The reasons for this inadequate adherence to diet and physical activity guideline recommendations are varied. To some extent, they may not differ from those of individuals without a history of cancer, such as sociodemographic factors, time, or access to resources. However, the late and long-term effects of cancer themselves may function as barriers to adopting healthy behaviors and be underrecognized in the cancer survivor population. A recent survey found that late and long-term effects of cancer treatment may overshadow other barriers,<sup>96</sup> and this may be especially true for the implementation of physical activity recommendations.<sup>96–99</sup> Peripheral neuropathy, sequelae of avascular necrosis, cardiomyopathy, or other functional impairments, such as partial limb amputations or lymphedema, may provide unique risks for certain types of physical activity.

### The Role of Patient-Reported Outcomes

The wide range of late and long-term effects of cancer and its treatment together with the documented importance of adopting healthy diet and physical activity behaviors necessitates an individualized approach to assessing for possible

**TABLE 3. Summary of Adiposity, Physical Activity, Diet, and Alcohol After Diagnosis and Cancer Survivorship Guideline Evidence 2022<sup>a,b,c,d</sup>**

CANCER SITE	ADIPOSITY	PHYSICAL ACTIVITY	DIET	ALCOHOL
Breast	<ul style="list-style-type: none"> <li>Postdiagnosis obesity (BMI <math>\geq 30 \text{ kg/m}^2</math>) is associated with a higher risk for recurrence and for disease-specific and overall mortality</li> <li>The role of weight loss after diagnosis, independent of disease and treatment-related weight loss, and survival is unclear at this time</li> <li>Decreasing physical activity after diagnosis is associated with higher all-cause mortality</li> </ul>	<ul style="list-style-type: none"> <li>Physical activity is associated with lower risk of breast cancer-specific and all-cause mortality</li> </ul>	<ul style="list-style-type: none"> <li>Healthy postdiagnosis diet patterns/more plant-based diets are associated with lower overall and nonbreast cancer-specific mortality</li> <li>There is insufficient evidence to support that a healthy diet pattern (including a vegetarian diet) is associated with breast cancer recurrence or breast cancer-specific mortality</li> <li>A Western diet pattern after diagnosis is associated with higher overall and nonbreast cancer mortality</li> <li>Dietary fat and subtypes of fat have shown inconsistent and generally nonsignificant associations with breast cancer outcomes</li> <li>Limited data that soy isoflavone intake after diagnosis is associated with lower risk of breast cancer recurrence; evidence does not support a protective association with mortality</li> </ul>	<ul style="list-style-type: none"> <li>Existing evidence suggests lack of an association of alcohol intake with overall mortality among breast cancer survivors</li> <li>Alcohol intake after breast cancer diagnosis has been inconsistently associated with recurrence</li> </ul>
Upper aerodigestive and gastrointestinal				
Colorectal cancer (CRC)	<ul style="list-style-type: none"> <li>BMI in the overweight range (25–29.9 <math>\text{kg/m}^2</math>), compared with normal range (18.5–24.9 <math>\text{kg/m}^2</math>), is associated with lower all-cause mortality</li> <li>Obesity shows an inconsistent association with mortality after CRC diagnosis</li> <li>Higher visceral adiposity is associated with greater all-cause mortality</li> <li>Conflicting evidence regarding BMI and CRC-specific survival</li> </ul>	<ul style="list-style-type: none"> <li>Higher physical activity after diagnosis is associated with lower CRC-specific and all-cause mortality</li> <li>Lower sedentary time associated with lower CRC-specific mortality</li> </ul>	<ul style="list-style-type: none"> <li>Western diet pattern (high processed meat dietary patterns) after CRC diagnosis is associated with higher risk for CRC recurrence and all-cause mortality</li> <li>AHEI, DASH, and Mediterranean diet scores are inconsistently associated with outcomes after CRC diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>Existing evidence suggests lack of an association of alcohol intake after diagnosis and all-cause mortality</li> <li>Higher alcohol intake after laryngeal, pharyngeal, or head and neck cancer is associated with higher all-cause mortality</li> </ul>
Esophageal/oral/pharyngeal, head and neck/gastric cancers				

TABLE 3. (Continued)

CANCER SITE	ADIPOSITY	PHYSICAL ACTIVITY	DIET	ALCOHOL
Hepatic				• Higher alcohol intake is associated with greater all-cause mortality
Pancreatic	• Limited and somewhat conflicting evidence suggests obesity may be associated with higher all-cause mortality			
Genitourinary				
Bladder	• BMI $\geq 25 \text{ kg/m}^2$ is associated with higher recurrence and progression risk in nonmuscle-invasive disease • Inconclusive for bladder cancer-specific and overall mortality			
Kidney	• Most studies of visceral adiposity tissue (VAT) suggest higher VAT is associated with greater overall survival	• Higher postdiagnosis physical activity is associated with lower prostate-cancer and overall mortality	• Existing evidence suggests a Western (as opposed to prudent) diet pattern is associated with higher prostate-specific and all-cause mortality; a Mediterranean diet pattern is associated with lower all-cause mortality	
Prostate	• Evidence is inconclusive that obesity is associated with mortality or disease progression • Relationships may vary, depending on treatment regime (eg, ADT)			
Gynecological		• Postdiagnosis, higher physical activity is associated with lower all-cause mortality		
Female reproductive combined (cervix, endometrium, ovary)		• See above for combined gynecological cancer findings		
Endometrial	• Majority of evidence suggests that BMI $\geq 30 \text{ kg/m}^2$ at diagnosis is associated with higher all-cause mortality • Higher BMI has not been associated with endometrial cancer mortality, or progression-free survival, or recurrent disease	• See above for combined gynecological cancer findings		
Ovarian	• Limited evidence of a relationship between obesity and ovarian cancer outcomes does not support an association with ovarian cancer-specific or all-cause mortality	• See above for combined gynecological cancer findings		

(Continues)

**TABLE 3. (Continued)**

CANCER SITE	ADIPOSITY	PHYSICAL ACTIVITY	DIET	ALCOHOL
Lung	<ul style="list-style-type: none"> <li>Obesity is associated with lower overall mortality after lung cancer diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>Limited evidence suggests postdiagnosis physical activity may be associated with lower lung cancer-specific and all-cause mortality</li> </ul>		

Abbreviations: ADT, androgen-deprivation therapy; AHEI, Alternative Healthy Eating Index; BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension.

<sup>a</sup>The information included in this table reflects postdiagnosis exposures (not prediagnosis) given that after diagnosis is a time period wherein related health behaviors are actionable.

<sup>b</sup>No evidence regarding testicular cancers was available for inclusion.

<sup>c</sup>Blank cells indicate insufficient evidence supporting an association with the identified exposure and the specific cancer. Absence of evidence of an association is not evidence of no association.

<sup>d</sup>Obesity is defined as a BMI  $\geq 30 \text{ kg/m}^2$ .

barriers. PROs offer a way to do this in clinical practice in a systematic fashion. A wide array of PROs relevant to cancer survivorship care is available.<sup>100,101</sup>

These could be used to help assess the effectiveness of interventions designed to improve long-term cancer outcomes. Prehabilitation<sup>102</sup> in cancer care, which is a proactive approach to cancer treatment and focuses on using baseline assessments to help guide interventions to improve outcomes, may provide a good model for doing so. Although traditionally focused on improving short-term outcomes during cancer treatment, a recent systematic review of prehabilitation programs described both the potential for and limitations of current prehabilitation interventions<sup>103</sup> to help affect long-term outcomes in survivorship. Prehabilitation in combination with posttreatment rehabilitation efforts may be more effective at reducing morbidity and adverse clinical outcomes.<sup>103</sup> Notably, individuals with comorbid conditions other than cancer were largely excluded from many studies evaluating the impact of prehabilitation programs.<sup>103</sup> But the significant prevalence of comorbid conditions in patients with cancer<sup>104</sup> and the variation of these comorbidities further highlight the need for an individualized approach. Other organizations, such as the American Heart Association, recognizing the importance of CVD as both a potential significant late effect of cancer treatment as well as prevalent comorbid condition, have published guidance around the use of cardio-oncology rehabilitation to improve outcomes for patients with cancer.<sup>105</sup> Therefore, there are various potential clinical structures into which PROs could be incorporated to assess and monitor adherence to current clinical guidelines.

Cancer survivors experience multiple symptoms, and symptom burden is a key modifiable barrier to the adoption of healthy behaviors.<sup>106,107</sup> Many symptoms linger into the posttreatment period and may last up to 10 or more years after completion of cancer treatment.<sup>106,107</sup> For example, among patients completing chemotherapy, the median severity of pain and fatigue was 6 on a zero to 10 scale,<sup>108</sup> and sustained levels of these symptoms remain over the course of a year after the diagnosis of cancer.<sup>109</sup> This transitional period may be an opportune time for intervention. Others have documented persistent pain and peripheral neuropathy.<sup>110-112</sup> The completion of chemotherapy regimens was rated as moderately to extremely stressful by 48% of breast cancer survivors<sup>107,113</sup>; and >60% had problems with fatigue and sleep.<sup>82</sup> Depressive symptoms were reported by 67% of cancer survivors<sup>114</sup>; and, between 2010 and 2013, in total, 2.5 million cancer survivors in the United States were taking medications for depression, anxiety, or both.<sup>88</sup> Disparities with these PROs exist, with Hispanic and Black cancer survivors often reporting higher numbers of symptoms and greater psychological distress than non-Hispanic Whites.<sup>115</sup> Latinas report an average of 5.5 symptoms (range, 1-12),

with these symptoms associated with poor adherence to national guidelines for nutrition and physical activity to prevent cancer.<sup>116–120</sup> Recognizing that symptoms may be a barrier to the adoption of healthy behaviors, integrated approaches that manage symptoms while promoting the uptake of healthy behaviors are needed to optimize long-term outcomes for survivors.

## Health Disparities and Health Equity for Cancer Survivors

Cancer survivors face physical, emotional, psychosocial, and financial challenges as a result of cancer diagnosis and treatment.<sup>121,122</sup> Although all survivors face these challenges, certain groups remain disproportionately affected. For instance, cancer survivors from rural areas, particularly Black and American Indian populations, experience greater poverty and racism—both systemic and structural—and often lack access to culturally competent care in accordance with guidelines, including availability, accessibility, and affordability of health care services, which results in lower survival.<sup>123</sup> Hispanic individuals have the lowest health insurance prevalence of any racial and/or ethnic group<sup>124</sup>; many individuals may be undocumented and have unique challenges when accessing health care, particularly cancer care. Cancer health disparities, defined as *measurable differences in cancer outcomes in population groups*, continue to be a significant public health concern in the United States.<sup>125</sup> Cancer health disparities research in cancer survivors to date has largely focused on racial, ethnic, and rural populations. Research in health disparities is expanding to include disparities by age, sexual orientation and gender identity, social determinants of health (eg, access to care, language, health literacy, education), socioeconomic status, environmental exposures, and geography.<sup>125</sup> This inclusive approach has highlighted the importance of health equity, in which everyone has a fair and just opportunity to prevent, find, treat, and survive cancer.<sup>126</sup> From this perspective, health disparities are preventable results of structural discrimination and marginalization that, if left unaddressed, will continue to reinforce inequities in health outcomes.<sup>125</sup>

ASCO released a policy statement in 2020<sup>125</sup> to support reductions in health disparities and improvements in health equity in cancer care. That statement provides recommendations in key areas, including ensuring equitable access to high-quality care, ensuring equitable research, addressing structural barriers (eg, promoting workforce diversity, community partnerships, and addressing institutional discrimination), and increasing awareness and action (eg, policy solutions). Before this statement, in 2017, ASCO provided a position statement for sexual and gender minority populations as well as including recommendations

for increased patient education and support, workforce development and diversity, quality-improvement strategies, policy solutions, and research strategies.<sup>127</sup> In 2020, the American Association for Cancer Research inaugural *Cancer Disparities Progress Report* was published.<sup>128,129</sup> That report provided specific recommendations for research to improve cancer health disparities for individuals who receive suboptimal access and cancer care treatment to improve health equity. This includes providing a robust, sustained, and predictable funding increase for the federal agencies and programs that are tasked with reducing cancer health disparities; implementing steps to ensure that clinical trials include a diverse population of participants; supporting programs to make sure that the health care work force reflects and appreciates diverse communities it serves; prioritizing cancer control initiatives; and working with members of the Congressional Tri-Caucus, (comprised of the Congressional Asian Pacific American Caucus, the Congressional Black Caucus, and the Congressional Hispanic Caucus) to pass provisions included in the Health Equity and Accountability Act.

Reducing cancer disparities and achieving health equity is an overarching goal of the ACS and the ACS Cancer Action Network.<sup>130</sup> The ACS and the ACS Cancer Action Network health equity principles are evidence-based and categorized into the areas of people, place, and partnerships. Within the context of *people*, it is recommended to use a mixed-methods approach, eg, use quantitative and qualitative data to identify populations at greatest need and prioritize research in this area. This includes embracing diversity and inclusion by accepting, respecting, and valuing different people and creating an inclusive and collaborative environment with communities that are affected by health disparities. *Place* includes addressing structural and social determinants of health; understanding the historical, social, cultural, and economic history of communities before aligning research, events, programs, and policies that may impact them; and implementing sustainable community solutions. Finally, *partnerships* leverage the power of volunteers, engaging partners in different sectors and preventing and addressing unintended consequences in populations affected by the development, evaluation, and implementation of solutions. Addressing unintended consequences ensures that gaps in health disparities are not widened but advances health equity efforts.

As part of addressing social determinants of health, it is important to consider food insecurity, which is defined as *the disruption of food intake or eating patterns because of lack of money and other resources*.<sup>131</sup> According to the US Department of Agriculture's Economic Research Service,<sup>132</sup> 10.5% of all US households experienced food insecurity throughout 2019. The prevalence of food insecurity is twice as high among Hispanic and Black individuals compared

with non-Hispanic White individuals. Furthermore, 34.5% of households with incomes below the federal poverty line experienced food insecurity. Data on food security among cancer survivors are scarce. A study by Charkhchi et al<sup>133</sup> using data from the Behavioral Risk Factor Surveillance System showed that patients with cancer had a higher likelihood of experiencing food insecurity (odds ratio, 1.39; 95% CI, 1.02-1.91) compared with individuals without chronic conditions, even after controlling for sociodemographic characteristics. Although data are lacking on levels of food insecurity among patients with cancer for different sociodemographic groups, it is possible that inequities exist given that food insecurity is influenced by factors such as income, employment, disability, and race/ethnicity. For example, one study by Gany and colleagues<sup>130,134</sup> of primarily Latino (45%) and Black (41%) patients with cancer, the majority of whom had incomes below the national poverty level (82%), reported that 41% of patients were food-insecure, and 17% had very low food security. Therefore, as a community, we must recognize that, to meet dietary guidelines, we must address food equity as a goal for all cancer survivors. Efforts to screen for and address food insecurity among patients with cancer and survivors need to be prioritized as a strategy to eliminate continued disparities and inequities in cancer outcomes.

As noted in the section below on community influences on survivor nutrition and physical activity, in this guideline and the ACS guideline for cancer prevention,<sup>4</sup> it is recommended that researchers, clinicians, and communities work collaboratively at national, state, and local levels to develop, advocate for, and implement policy and environmental changes that increase access to affordable, nutritious foods; provide safe, enjoyable, and accessible opportunities for physical activity; and limit access to alcoholic beverages for all individuals. However, we must account for health inequities that cancer survivors face for myriad of reasons, including social/cultural context, food insecurity, and environment (eg, neighborhood safety). Ultimately, coordinated efforts, including policy changes that address structural racism and barriers to engagement in healthy behaviors, are necessary to reduce the burden of cancer disparities and improve health equity across the cancer care continuum.

## Community Influences on Survivor Nutrition and Physical Activity

A multitude of influences in community and clinical environments affect a population's diet and physical activity, and these influences have a similar impact on healthy behaviors in both cancer survivors and the general population. Research on these factors has been reviewed in the ACS guideline for diet and physical activity for cancer prevention.<sup>4</sup> Briefly,

the factors include limited access to healthy food options (and excessive access to foods of low nutritional value/high-energy density) and resources/facilities to support exercise, advertising, and promotion of nutrient-poor/energy-dense foods and alcohol, and a built environment that discourages physical activity.

Some of these issues may be particularly acute for cancer survivors. For example, the economic burden of cancer diagnosis, treatment, and survivorship<sup>135,136</sup> may contribute to food insecurity<sup>133</sup> and an inability to access healthy food or afford exercise or nutrition programs or counseling. Survivors, particularly those living in small communities and rural areas, may have difficulty finding programs that meet their unique needs after cancer diagnosis. In an effort to learn about healthy behaviors after cancer, many survivors turn to the internet for information.<sup>137,138</sup> Evidence-based information on nutrition and physical activity for cancer survivors is available online through sources such as the ACS, ACSM, and AICR. However, there is also a plethora of misinformation on internet sites—and on social media sites in particular.<sup>139,140</sup> Survivors report difficulty accessing credible nutrition information online<sup>138</sup> and may be especially vulnerable to claims that specific behavior changes can cure their cancer or extend survival. One study of cancer-related nutrition and meal planning content in Pinterest<sup>141</sup> found that a substantial proportion claimed a particular food or recipe prevented, treated, or cured cancer. Approximately one-half of those posting content were for-profit, and only 35% of posts included a disclaimer.<sup>141</sup> Without efforts by social media platforms to flag and manage such misinformation, it is likely to flourish and can potentially overwhelm the evidence-based information that exists.

## Availability of Survivor-Specific Education and Counseling for Diet and Physical Activity

Most cancer survivors prefer to receive information about diet, alcohol, weight management, and physical activity from their health care team,<sup>17,138,142</sup> and such discussions can positively influence behavior changes.<sup>143,144</sup> However, culturally appropriate and relevant resources are often lacking. Furthermore, many oncology care providers cite lack of time as a barrier to providing counseling on these topics and acknowledge that they have inadequate training and knowledge about available resources.<sup>145-147</sup> Some cancer survivors indicate that nutrition information obtained from providers is often inadequate or conflicting.<sup>138</sup>

Resources exist to help guide providers in counseling patients on healthy behaviors. For example, ASCO has published a statement supporting oncology providers addressing obesity and healthy behaviors with patients<sup>146</sup> and has an online toolkit to help providers. ACSM has

published guidelines for counseling cancer survivors about exercise.<sup>147</sup> For such resources to be used more broadly and integrated into the culture of cancer care, information and skills training about nutrition, physical activity, and weight management should be included in oncology training and should become a part of continuing medical and nursing education.

Oncologists and oncology nurse professionals are unlikely to have the time and training to provide everything a survivor needs to make behavior change. Effective and reliable professionals and programs are needed to provide ongoing support for survivors' behavioral changes. The Academy of Nutrition and Dietetics has an Oncology Nutrition Dietetic Practice Group for RDNs or Registered Dietitians working in oncology, but a survey conducted by Trujillo et al<sup>148</sup> of these professionals highlighted the limitations of current resources. The survey found that the ratio of RDNs to patients with cancer in responding cancer centers was 1:2308, which was much lower than the 1:120 ratio recommended for each patient with cancer to receive evidence-based care to improve quality-of-life and nutrition outcomes.<sup>148</sup> Similar workforce shortages are evident for exercise professionals. ACSM has a specialty certification for Cancer Exercise Trainer, but the number of professionals certified by these programs is insufficient to meet the needs of the growing population of patients with cancer and cancer survivors.

### Nutrition and Physical Activity Programs: Who Pays?

Insurance coverage for diet and physical activity services and programs is limited, which is a major factor influencing their availability and accessibility for cancer survivors. For individuals with documented health needs, insurance coverage for rehabilitative services, which can include exercise to improve physical conditioning, is required under the Essential Health Benefit regulations of the Affordable Care Act.<sup>149</sup> However, this requirement only applies to certain types of private insurance plans, and access to these services can still be limited by cost in the form of copayments or deductibles. There is no coverage requirement for oncology nutrition services in the Affordable Care Act; and, although some insurance plans cover oncology nutrition, the Centers for Medicare & Medicaid Services programs, which cover a large proportion of cancer survivors, do not. Most cancer centers do not bill for these services,<sup>148</sup> and nutrition and physical activity counseling and programs are typically covered by overhead or philanthropy and thus may be vulnerable to cutbacks, particularly during difficult financial times. This lack of a sustainable payment model limits the availability of services.<sup>145,147</sup> Diet and physical activity services outside of

the clinical setting are not typically covered by private health insurance or Medicare, although some community organizations provide exercise programs for patients with cancer and survivors at low or no cost, usually supported by philanthropy (eg, Livestrong at the YMCA).<sup>150–152</sup>

There are several opportunities to increase access to programs for patients with cancer and survivors. Payment models are moving from traditional fee-for-service payment systems toward systems that focus on value-driven care, which rewards improved care quality and reduced costs. These models may incentivize the delivery of physical activity, nutrition, and weight management services to patients, particularly if quality measures used to justify value are expanded to include measures focused on physical functioning, nutritional status, and weight status. Additional research is needed on the effectiveness and cost-effectiveness of various behavior-change programs and services for cancer survivors, including determining which programs and services are most effective for whom and how these services affect the value equation.<sup>153</sup> Engagement of payers is needed in the formulation of research questions so that research results can better inform their decisions about benefit design and coverage.

### Clinical Care Coordination

The benefits of incorporating and continuing healthy behaviors after a diagnosis of cancer are clear and have been presented in this guideline. To ensure that individuals with a history of cancer are benefitting from evidence-based guidance regarding physical activity and diet, health care providers must be proactive about assessing health behaviors in these individuals, counseling, and referring to appropriate health care professionals and evidence-based programs. Doing so presents multiple challenges and opportunities for care coordination.

### Primary Care and Oncology

It is well known that coordination of cancer survivorship care between oncology and primary care is challenging for a variety of reasons<sup>154–156</sup>; however, consistent messaging with regard to healthy behaviors over the course of the survivorship trajectory by both specialties could go a long way toward facilitating needed support for cancer survivors. Currently, this messaging is not happening in a systematic fashion. Instead, health behavior counseling appears to depend on several factors if it happens at all.<sup>118,157–159</sup> A 2009 survey of CRC survivors by Haggstrom et al<sup>158</sup> suggested that this type of counseling was more likely to happen at primary care follow-up visits versus oncology follow-up visits. Survivors who are younger or more educated, as well as those with more comorbidities, may be more likely to receive advice about health behaviors,<sup>159</sup> but

even young cancer survivors have indicated that their informational needs around diet and physical activity are not being met.<sup>160</sup> There is some evidence that cancer survivors may not be receiving this advice as often as those individuals without a history of cancer.<sup>161</sup>

Although oncology teams and primary care teams have their own competing demands for clinical care, each type of provider is uniquely positioned to reinforce the importance of physical activity and healthy dietary choices to their patients living with and beyond cancer. Smith et al,<sup>162</sup> in a recent survey of long-term cancer survivors, suggest that shared care is the preferred approach in general for the majority of survivors, whereas primary care follow-up is favored slightly when it comes to the provision of preventive care and the management of comorbid health conditions.

### **Approaches to Facilitate Shared Health Promotion Activities for Cancer Survivors**

To promote a shared care approach for the health promotion of cancer survivors, there are a few approaches to consider. First, there must be concerted efforts to promote education among oncology and primary care professionals about the benefits of dietary and exercise interventions for cancer survivors. Second, strategies that can be used in clinical settings have been proposed to assist teams caring for cancer survivors to assess and promote healthy behaviors, including developing systems to routinely assess these behaviors in patients with cancer, reassess these behaviors at regular intervals, and advise and arrange mechanisms to optimize survivors' likelihood of engaging in efforts to improve their diet, activity, and related cancer-preventive health behaviors.<sup>163,164</sup> Recent changes to the Commission on Cancer survivorship care program accreditation provide an opportunity to expand such services, although it is important to emphasize that most patients are not receiving their care in such settings. Cancer prehabilitation initiated before the initiation of cancer treatment, oncology rehabilitation during and after cancer treatment, and cardio-oncology rehabilitation<sup>105</sup> include approaches that advocate for using baseline assessments to help guide and plan tailored, structured exercise programming (and may also include dietary recommendations). Importantly, referrals are happening at a rate far below what would be anticipated given the known prevalence of such symptoms: a circumstance that must be addressed.<sup>165</sup> Third, technology can serve to promote coordination in diet and exercise counseling and interventions. For example, electronic health records can have integrated prompts to ask patients about exercise and/or provide links to an algorithm to refer to an appropriate level of exercise supervision.<sup>164</sup> Such strategies may also be useful for nutrition counseling. When primary care physicians and oncologists,

as well as other health care providers, use the same electronic health record system, this can lead to multiple touch-point opportunities. Furthermore, electronic health records could have built-in decision support tools that can guide referral touch points. Expanding the base of health care professionals, including oncology nurses, Registered Dietitians, exercise physiologists, and rehabilitation specialists, will also facilitate referrals. The use of telehealth offers greater capacity through remote consultation with appropriate professionals, whose numbers may be limited in rural or underserved areas.<sup>166</sup>

### **Reaching Beyond the Clinic for Maximal Impact**

Finally, given the known strains the oncology workforce is already facing to care for cancer survivors well into the survivorship phase,<sup>167</sup> nutrition and physical activity interventions must use all possible resources, including those available not solely in oncology and/or primary care settings but also those in the community.<sup>168</sup> Home-based and community-based programs show promise to help with health promotion efforts for cancer survivors, although the evidence base is still growing.<sup>169</sup>

To ensure that any interventions or practice adaptations implemented for cancer survivors do not increase health disparities for those who live in communities at risk (eg, medically underserved and/or rural communities where evidence-based resources are more scarce) or for those survivor populations that are under-represented in cancer survivorship research, strategies exist to help build an evidence base that closes these gaps. For example, the inclusion of community-based participatory research methods<sup>170</sup> in research and program development could be an effective strategy to ensure that all voices, perspectives, and communities are being considered. And dissemination and implementation research expertise are crucial to encourage broader external validity and pragmatic considerations when it comes to translating evidence into clinical practice.

### **Closing Comments and Relevant Issues**

Several factors constrain the development of a comprehensive guideline for reducing risk for recurrence and mortality among cancer survivors. Although systematic reviews with meta-analysis provide one of the higher levels of scientific evidence in research, high-quality evidence for associations from systematic literature reviews, meta-analyses, pooled analyses, and randomized controlled trials is limited for cancers that are less common and/or have low survival rates. For all cancers, systematic reviews are inherently limited by the heterogeneity of the studies available for inclusion, which further limits the ability to conduct meta-analyses of the data. In addition, systematic literature reviews and meta-analyses combine studies that may or may not adequately

address confounding. Pooled analyses of original data can more readily address potential issues of confounding and bias. Systematic literature reviews on the relationship between alcohol intake and survival (except for breast cancer) are particularly limited.

Reliance on BMI as an indicator of adiposity, which is the most common anthropometric parameter examined in clinical and epidemiological studies, is inherently limited. This indicator does not differentiate between lean and fat tissue mass and does not provide information about the amount or location of adiposity. Body fat distribution and low skeletal muscle mass likely contribute to mortality in cancer survivors, and relevant high-quality data on these measures are limited. More research is needed to evaluate the complex interactions between body composition and cancer progression, recurrence, site-specific mortality, and all-cause mortality. Moreover, future research should expand beyond body composition to include other components of health-related fitness such as aerobic fitness, muscular fitness, flexibility, and balance.<sup>171</sup>

There is a need to expand the evaluation of physical activity and risk for recurrence and mortality among survivors, including type of activity, dose, intensity, and time frame, across the cancer survivorship continuum. More systematic literature reviews and meta-analyses of dietary patterns,

rather than individual nutrients, foods, and bioactive food components, would provide useful evidence for translation to recommendations for cancer survivors.

The vast majority of studies of associations between these risk factors and survival are based on data collected at or before diagnosis. For most individuals, the assumption can be made that these behaviors do not readily or significantly improve after diagnosis without substantial intervention efforts. Evidence to support this assumption is based on comparisons of healthy behaviors of cancer survivors and population controls<sup>161,172,173</sup> as well as dietary data collected from control groups in randomized controlled trials. Therefore, prediagnosis dietary and other behaviors have value in contributing to the evaluation of associations. Nonetheless, there is a need for more evidence from interventions from diagnosis onward.

Finally, reductions in health disparities and improvements in health equity are necessary for more cancer survivors to be informed of and apply these recommendations and thus reduce risk for recurrence and increase survival. Community and clinical environments can greatly impact a patients' behavior, so these factors are critical in the application of these recommendations. A comprehensive evaluation of effective policy, systems, and environmental approaches translatable to policymakers is needed to facilitate further action. ■

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