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Recommendations for Obesity Clinical Trials in Cancer Survivors: American Society of Clinical Oncology Statement

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INTRODUCTION

Observational evidence suggests that obesity and related factors, such as inactivity and poor dietary quality, may significantly increase the risk of developing and dying as a result of cancer.¹⁻¹² More than 200 studies have evaluated the relationship between body weight and cancer risk. Evidence has demonstrated that obese individuals are at greater risk of developing cancer. Observational reports have also evaluated the relationship between body weight and related factors, such as physical activity, at the time of cancer diagnosis and cancer prognosis.^{2-5,13,14} Most of these studies evaluating the relationship between obesity and prognosis have focused on women with early-stage breast cancer, in whom obesity and inactivity have been fairly consistently linked to higher rates of cancer-specific and all-cause mortality. A number of recent reports have also suggested that obesity and inactivity are associated with poor outcomes in other common malignancies, including prostate,^{4,11} colon,⁴ and gynecologic cancers.^{15,16}

Recognizing the growing evidence linking obesity to unfavorable cancer outcomes and the public health risks posed by the obesity epidemic, the American Society of Clinical Oncology (ASCO) convened a working group in 2012 to evaluate the evidence and help develop ASCO policies and initiatives in this area. The following year, the ASCO Board of Directors identified obesity as a strategic issue for the society and adopted a position statement that laid out several key priorities, including the need to foster the development of a robust research agenda to evaluate whether lifestyle change (or other interventions) after cancer diagnosis improves outcomes. A related goal was to determine the best methods to help cancer survivors make behavioral changes.

In November 2014, ASCO convened the Research Summit on Advancing Obesity Clinical Trials in Cancer Survivors. The meeting involved key stakeholders in the study of obesity and cancer, including

obesity researchers, oncology providers, clinical trialists, patient advocates, governmental and private funding organizations, payers, and representatives from health systems. The primary objectives of the summit were to review and summarize the available literature, identify gaps, define research priorities, discuss the logistic and financial barriers to research in this field, and develop a roadmap for the design and implementation of studies with the potential to generate data that could support the incorporation of weight management and physical activity programs into standard oncology practice. This article summarizes key conclusions of the ASCO summit and provides recommendations for the development of a coordinated research agenda of obesity clinical trials in cancer survivors.

BACKGROUND

Although consistent data from observational studies link obesity to increased cancer incidence and mortality,^{5,9,13,15} there have been few large-scale trials testing the impact of changes in energy balance (ie, weight, caloric intake, or physical activity) on cancer risk or prognosis. There are currently no data that provide definitive evidence that weight loss, calorie restriction, or increased exercise will prevent cancer or lower the risk of cancer-specific mortality. However, there have been hundreds of small trials in patients with cancer summarized in several recent reviews and meta-analyses, that evaluate the feasibility and benefits of weight loss and physical activity interventions with regard to intermediate end points and patient-reported outcomes.¹⁷⁻²⁴ Most of these studies have focused on patients with early-stage breast cancer, although several recent studies have focused on patients with prostate, colorectal, and gynecologic cancers. These randomized trials have demonstrated that weight loss and physical activity interventions are feasible in cancer survivors and can lead to improvements in outcomes such as body composition, physical fitness, body image, fatigue, quality of life, and biomarkers linked to cancer outcomes.

Funding for research of energy balance trials in cancer survivors has grown over the past decade worldwide. The two major funders of these trials in the United States are the National Cancer Institute (NCI) and the American Cancer Society (ACS). At the NCI, the number of grants addressing diets, weight, and physical activity doubled from 2003 to 2010, accounting for 3.1% of all NCI grants and 4.2% of the total research grants budget in fiscal year 2010.²⁵ The ACS has also funded grants focused on nutrition and physical activity; between fiscal years 2003 and 2012, the ACS funded 94 grants, with a total budget of more than \$51 million, focused on weight, diet, and physical activity. For both organizations, most of this funding has been directed toward cancer prevention, rather than cancer control in cancer survivors, and has largely supported observational projects evaluating the relationship of obesity and related factors with regard to cancer risk and outcomes. However, recent trends suggest an increase in funding for energy balance interventional projects focused on lifestyle change after cancer diagnosis.²⁶ Most of these projects have evaluated end points such as the feasibility of inducing changes in diet, weight, or physical activity or the impact of these changes on quality of life or intermediate end points such as biomarkers linked to cancer risk. Few projects have focused on the impact of lifestyle change on the risk of cancer recurrence or related mortality.

In addition to funding energy balance research, the ACS has developed nutrition and physical activity guidelines for cancer survivors.²⁷ These guidelines call for maintenance of a healthy body weight, regular physical activity regardless of body mass index, and modest weight loss for overweight and obese cancer survivors. ASCO has also developed a toolkit for patients and providers to increase awareness regarding the links between obesity and cancer and to help patients make healthy lifestyle changes after cancer diagnosis.²⁸ Despite these guidelines, reports assessing body weight and physical activity patterns in cancer survivors have suggested that only one third engage in the recommended levels of physical activity, and more than 70% of cancer survivors are overweight or obese.^{29,30}

Although trials have demonstrated that energy balance interventions are feasible in cancer survivors, ongoing behavioral support is needed to implement and sustain changes in weight and physical activity. Obtaining such support is hindered by the lack of reimbursement for energy balance interventions in cancer survivors, in part

attributable to the lack of data demonstrating improvements in cancer-specific outcomes as a result of these interventions. If effective, the incorporation of weight management and physical activity programs into cancer care has the potential to improve outcomes in millions of patients with cancer around the world. These programs are resource- and time-intensive, necessitating commitments from payers, patients, and providers. To engage these groups, data are needed to provide definitive evidence that weight loss and increased physical activity improve cancer prognosis and to demonstrate effective methods of implementing lifestyle interventions in large, diverse groups of cancer survivors.

A key question was identified at the ASCO obesity research summit: How do we move from conducting observational studies and small randomized trials testing the feasibility and short-term benefits of lifestyle change in cancer survivors to generating the data needed to incorporate energy balance interventions into clinical practice and ultimately improve cancer outcomes? This report provides potential next steps and solutions derived from the summit.

ASCO SUMMIT RECOMMENDATIONS FOR OBESITY CLINICAL TRIALS IN CANCER SURVIVORS

Large-Scale Trials Testing the Impact of Energy Balance Interventions on Cancer Outcomes

Engaging key stakeholders—providers, payers, and patients and their families—to support energy balance interventions in cancer survivors will require definitive evidence demonstrating that these interventions improve cancer-specific and overall mortality. Although observational evidence has linked obesity and inactivity to increased cancer risk and poor cancer outcomes, without data from randomized trials it is not clear if these associations are causal, how much lifestyle change is needed to change biology sufficiently to affect cancer-specific outcomes, or whether there are certain groups of patients for whom lifestyle change is more or less beneficial with regard to outcomes. Thus, large, prospective, randomized intervention trials are needed to generate such data. Recommendations for the design and implementation of these trials are summarized in [Table 1](#) and detailed as follows:

Table 1. American Society of Clinical Oncology Summit Recommendations for Obesity Clinical Trials in Cancer Survivors

| Recommendation | Description |
|--|--|
| Large-scale randomized trials testing impact of lifestyle change on disease outcomes | |
| Research team | Include multidisciplinary team of researchers with expertise in oncology, clinical trials, behavioral science, weight management, nutrition, and physical activity |
| Target patient populations | Focus on populations with most existing evidence and largest groups of cancer survivors |
| Study design | Ensure adequate power to detect biologically plausible effect size Must take into account improvements in cancer prognosis Must enroll patients with sufficient risk of recurrence |
| End points | Cancer outcomes Comorbidities Feasibility of implementation Economic end points Intermediate biomarkers |
| Concomitant dissemination, translational, and other research | |

Research team. Because of the complexities of developing and implementing large-scale energy balance intervention trials in cancer populations, trials should be designed with a multidisciplinary team of experts in oncology, clinical trials, behavior change, nutrition and/or physical activity, health economics, and disparities research, as well as patient advocates.

Target patient populations. It will be crucial to define the target populations and interventional approaches for large-scale trials in cancer populations based on the strength of the observational and mechanistic evidence linking energy balance factors to outcomes, presence of preliminary data, and likelihood of dissemination in large groups of cancer survivors. For example, evidence to date supports the development of interventional studies in patients with early-stage cancers of the breast,^{13,14,31} colon,^{2-4,32} and prostate.^{4,11,33} It is also important that trials produce evidence that is generalizable, and thus, trial populations should reflect as broad of a patient population as possible, including minorities and those with comorbidities.

Study design. Rates of disease-free and overall survival in the malignancies for which evidence linking energy balance and cancer outcomes is strongest have improved significantly over the past decades. Thus, studies with adequate power to detect energy balance–induced changes in disease end points will require large sample sizes and populations selected not only based on baseline energy balance factors but also based on risk of adverse disease outcomes. For example, for a study to be adequately powered to identify an improvement in disease-free survival in stage I breast cancer, more than 10,000 patients would be required; one third of this number would be required for patients with stage 2 to 3 disease. Large-scale trials should also be designed with attention to the subsequent dissemination of the intervention, in terms of feasibility, cost, and reach. Implementation strategies for emerging data should also include plans to generalize results obtained from one population at higher risk for application to lower risk cohorts.

End points. Given the resources and time needed to perform definitive trials testing the impact of energy balance interventions on cancer outcomes, it will be important that these studies include elements necessary to lead to the incorporation of these interventions into the routine care of patients with cancer as well as to facilitate efficient conduct of future trials in cancer populations. Key end points include:

- Disease-free and overall survival.
- Incidence of and complications resulting from comorbidities such as cardiovascular disease (CVD) and diabetes.
- Financial end points of relevance to third-party payers, such as the per-patient cost of delivering the intervention, cost per life saved, and measures of health services resource use; other economic factors will also be important, such as out-of-pocket costs to patients and costs to health care providers and administrators, as well as cost savings from avoidance of hospitalizations and comorbidities and reductions in sick time and disability claims.³⁴
- Feasibility of dissemination and implementation: Studies will need to establish the feasibility of changing and sustaining behavioral change in large, diverse groups of cancer survivors.

- Intermediate biomarkers: Large-scale studies will need to validate intermediate biomarkers of prognosis to help facilitate and streamline future studies. Inclusion of robust correlative science will be essential to establishing the pathways through which energy balance affects cancer to identify those who benefit from the intervention and establish intermediate end points that can speed discovery. This paradigm has the potential to transform the future of energy balance research in cancer survivors, just as the establishment of the intermediate end points for CVD of hypertension and hyperlipidemia transformed research in CVD. Identification of the patient populations who derive the most benefit from a particular type of intervention will also allow for a personalized approach to lifestyle change in cancer survivors.

Concomitant Dissemination, Translational, and Other Obesity Clinical Trials

Although large-scale trials testing the impact of lifestyle change on cancer outcomes are necessary to define an approach, the evidence generated in these trials alone will not change practice. It must be demonstrated that energy balance interventions can be implemented in oncology practices and in community or home settings with appropriate referral pathways, safety protocols, and feedback loops to the prescribing clinician to facilitate the assessment of ongoing needs and re-referral, if necessary. There are also a number of other research priorities that will need to be addressed to implement energy balance programs successfully among cancer survivors, including:

- Long-term maintenance of behavioral change.
- Use of technology to facilitate referrals to energy balance intervention programs and support short- and longer-term behavioral change.
- Intervention approaches in special populations (eg, elderly, pediatric, minority, and rural populations and those with specific cancer types).
- Translational science to define mechanisms through which energy balance factors affect cancer.

IMPLEMENTATION OF SUMMIT RECOMMENDATIONS

US Example

Advancing a coordinated research agenda of energy balance trials in cancer survivors will require mechanisms to establish research priorities and develop, fund, and implement studies that will fill key gaps in the knowledge needed to establish a role for energy balance interventions in the adjuvant treatment of individuals with early-stage cancers. New partnerships will be needed between diverse groups of investigators to design and implement trials, between public and private funding organizations to allow for the successful conduct of this research, and between the scientific community conducting this research and the providers and patients who will implement these intervention programs in clinical practice.

The ASCO Research Summit on Obesity Clinical Trials in Cancer Survivors focused on overcoming some of the funding and implementation challenges to energy balance research inherent in the US system. It is recognized that some of these issues may be specific to the United States, whereas others, such as the need to secure multiple sources of

funding for the various aspects of these complex, often expensive trials and the need to establish new partnerships between diverse groups of investigators, are likely common in many countries.

Large-scale randomized energy balance trials. A number of large-scale studies have been conducted evaluating the impact of weight loss interventions on outcomes such as the incidence of and complications resulting from diabetes mellitus and CVD. These studies have typically been funded by the National Institutes of Health through program project (P01) or research project cooperative agreement (U01) mechanisms, which cover the cost of all aspects of the study, including patient accrual, data collection, investigators' salaries, collection of study measures, and provision of the lifestyle interventions. In contrast, the NCI has funded its cancer prevention, treatment, and control trials through the National Clinical Trial Network (NCTN; for treatment) and the NCI Community Oncology Research Program (NCORP) research bases system (for cancer prevention and control), peer-reviewed cooperative agreements that provide funds to conduct a portfolio of trials, rather than one grant or contract funding one individual trial.

After a recent restructuring of the NCTN/NCORP system, the NCI issued an official notice (NOT-CA-13-012) announcing a policy to no longer support investigator-initiated phase III clinical trials that could not be completed in a 5-year timeframe through the research project (R01) or P01 mechanisms. Thus, for a large phase III trial to be launched evaluating the impact of an energy balance intervention on cancer outcomes, the study must be conducted through the NCTN/NCORP system. In addition to cost savings, use of the NCTN/NCORP system for the conduct of energy balance trials may have other advantages. Engagement of the oncology community through participation in a randomized weight loss or physical activity trial within the NCI clinical trials system (which includes more than 3,000 sites throughout the country) has the potential to increase familiarity with the intervention approach, resolve problems with delivery, facilitate adoption, and increase the generalizability of the findings. This infrastructure is currently being used to conduct the Men's Eating and Living (MEAL) trial,³⁵ a randomized phase III clinical trial testing the impact of increased vegetable consumption on rates of clinical progression in men with localized prostate cancer, as well as in the Lifestyle Intervention for Ovarian Cancer Enhanced Survival (LIVES),³⁶ a randomized controlled trial designed to evaluate the impact of a diet and exercise intervention on progression-free survival in women with ovarian cancer. Although both trials faced barriers to initial activation, recruitment through the NCTN/NCORP system was subsequently brisk and has allowed enrollment of participants across a diverse group of participating centers.

Use of the NCTN/NCORP system to conduct energy balance trials in cancer survivors also comes with inherent challenges, including the need to engage the support of treatment-focused investigators, find funding for the components of the study not covered under the cooperative group arrangement (eg, intervention development, delivery, oversight, and supplies), and engage the oncology community and patients in studies that can be time consuming. Moreover, these studies may require individuals with specialized expertise (eg, dietitians, exercise physiologists, and clinical psychologists, in addition to oncologists and clinical trial nurses) and resources for monitoring behavior change. These challenges have resulted in delays in the activation of the LIVES and MEAL trials because

of difficulties in gaining endorsement and in securing and maintaining funding for the lifestyle intervention portion of the studies. Funding issues also affected the Lifestyle Intervention Study Adjuvant (LISA) trial,²² a study that was initially designed to test the impact of a weight loss intervention on disease outcomes in postmenopausal women with breast cancer receiving an aromatase inhibitor, but closed to enrollment early when the patent expired for the pharmaceutical company funding the intervention. The Colon Health and Life-Long Exercise Change (CHALLENGE) trial,³⁷ a randomized trial examining the effects of a supervised exercise program on disease-free survival in colon cancer survivors, has experienced similar difficulties. Although the trial was activated in December 2008 and is open in more than 50 centers, only 38% of planned participants have been enrolled to date, in part because of difficulties in identifying centers with adequate expertise in delivering exercise interventions as well as the time commitment required on the part of participants to attend exercise sessions.

Dissemination, translational, and other research studies. In addition to large-scale trials testing the impact of energy balance interventions on cancer outcomes, mechanisms are needed to ensure that essential dissemination, translational, and other research also moves forward in a coordinated fashion. A recent effort from the NCI, the ACS, LIVESTRONG, and the Centers for Disease Control and Prevention presents a model where basic discovery science, fielding of large randomized controlled trials with clinical end points, and implementation science studies can all be conducted simultaneously, with appropriate communication, collaboration, evaluation, and feedback among the teams involved in these efforts.³⁸

In contrast, most energy balance intervention research in cancer survivors to date has followed a more traditional research model, in which a research proposal is formulated by a research team, funded, and implemented, often with little input from medical providers or patients. Positive findings subsequently typically require a different group of advocates to secure third-party payment, educate providers and patients, and ensure access to the new treatment across clinical settings (Fig 1). In the development of new pharmacologic agents, these critical steps are supported by the pharmaceutical company sponsoring the drug under study, but no such entity exists to ensure that positive findings from energy balance trials are implemented in clinical practice. Therefore, the integrated model developed by the NCI, the ACS and others is well suited to these trials in cancer survivors, where successful implementation of weight loss and physical activity programs in oncology clinics will require information regarding the feasibility of implementation of these programs in oncology practices, the cost of providing these services, and the populations most likely to benefit from them.

These models are currently being tested at the ACS, where there are emerging opportunities for the dissemination and implementation of evidence-based energy balance interventions, including the use of e-mail, telephone, and Web-based implementation of interventions for cancer and at-risk populations. The use of dissemination and implementation science methodologies and models will ensure appropriate consideration of the adaptation, pilot testing, acceptability, and evaluation of impact on health behaviors and other clinical outcomes. Future efforts will include plans for scalability and dissemination of interventions, as well as for assessment of cost and cost effectiveness.

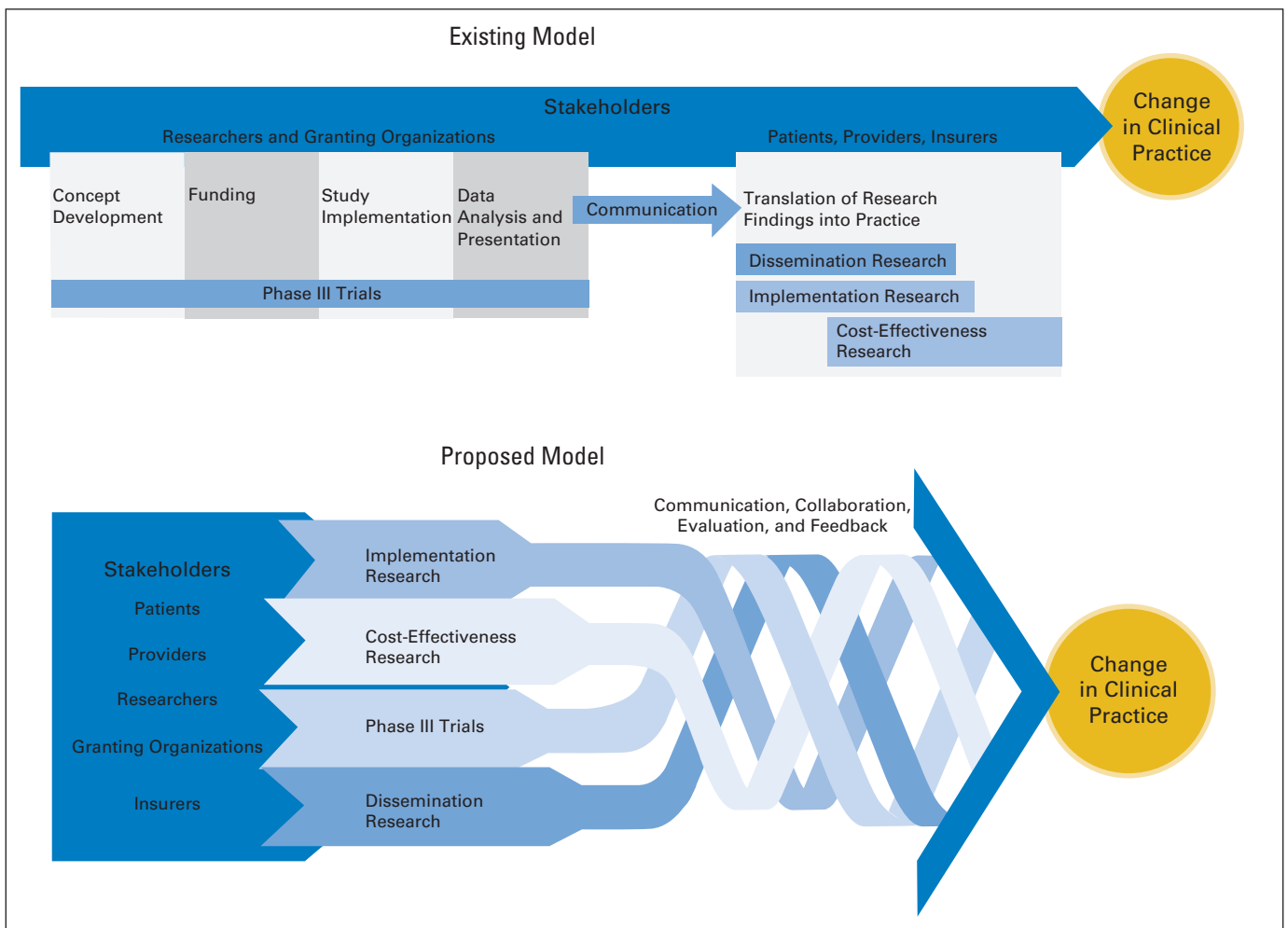


Fig 1. Traditional and integrated models for energy balance interventional research in cancer survivors.

Key Steps in Implementing Summit Recommendations

The key steps in implementing the summit recommendations are summarized in Table 2 and detailed as follows:

Study design. Bringing together the diverse groups of investigators needed to implement large-scale energy balance trials in cancer survivors will require new mechanisms, such as the clinical trials planning meeting, a process developed by the NCI to convene groups of investigators around a particular topic to evaluate the existing evidence, define knowledge gaps, and develop critical elements of studies to test new hypotheses in this area. In addition to building multidisciplinary research teams, moving the field of energy balance trials forward will require the development of a research agenda to prioritize gap areas. This can be accomplished in part through the creation of requests for applications specifically targeting areas where research is needed.

Funding. In the United States, large-scale lifestyle intervention trials require supplemental funds to cover aspects of the study not covered under the cooperative group agreement. Given that the cost of conducting large-scale randomized trials of energy balance interventions in cancer populations often exceeds the capacity of any one organization, partnerships are likely to be needed for research con-

ducted in other countries as well. These partnerships could include different organizations joining together to develop requests for applications or combining resources to cover the cost of large projects. Mechanisms are needed to bring together resources from multiple funding organizations and/or nontraditional sources of funding, such as insurance companies, to supplement the support of studies. Finally, building partnerships with groups conducting similar research in other areas of medicine, such as diabetes or CVD, could allow for resource sharing and the creation of studies that address a broader set of research questions.

Stakeholder engagement. To achieve the ultimate goal of incorporating energy balance interventions into the routine care of patients with cancer, stakeholders will need to be engaged at multiple levels, both for the successful conduct of large-scale trials and, if these trials are successful at improving outcomes, for the implementation of these programs across a wide variety of oncology practices. In the United States, the use of the NCTN/NCORP system to conduct energy balance studies in cancer survivors is an important first step in engaging oncology providers and patients in this research. Other strategies to engage oncology providers include providing education for providers to increase their familiarity with the materials used to encourage lifestyle change and to provide a rationale for these changes in cancer

Table 2. Implementation of Summit Recommendations

| Recommendation | Implementation |
|------------------------|---|
| Study development | Foster transdisciplinary partnerships of investigators Bring stakeholders together through clinical trials planning meetings Guide new research to address critical gaps in knowledge through RFAs targeting specific areas (eg, dissemination of lifestyle interventions, development of lifestyle interventions targeting unique populations) Network with and foster career development of new and early-career investigators |
| Funding | Develop mechanisms to bring together different sources of funding (eg, public and private sources) to support the cost of lifestyle interventions and other costs unique to this area of research Develop new funding partnerships between organizations Create standing funds across organizations for joint projects Jointly fund dream teams Develop collaborative relationships with nontraditional funding partners (eg, insurance companies, CMS, large employers, commercial companies that support fitness or weight loss, advocacy and consumer groups) Develop collaborative projects with groups that study other patient populations with common risk factors (eg, cardiology or endocrinology groups) |
| Stakeholder engagement | Identify key stakeholders for both research and dissemination aspects of lifestyle interventions in cancer survivors and ensure a broad range of perspectives are included in design and conduct of lifestyle intervention trials |
| Providers | Provide education and training sessions at national oncology and primary care meetings and within oncology fellowship training Develop interventions that can be implemented in diverse clinic settings and tested through NCORP practices Integrate lifestyle elements into electronic medical records Provide training for oncology personnel in communication skills for dealing with sensitive topics like weight loss Incorporate lifestyle interventions into survivorship care plans |
| Patients | Involve large advocacy organizations and a diverse group of individual advocates in lifestyle intervention studies Consider convenience, cost, time commitment, and flexibility in intervention design (with integration into routine care appointments and assessments, as possible) Include quality of life and other patient-reported outcomes |

Abbreviations: CMS, Centers for Medicare and Medicaid Services; NCORP, National Cancer Institute Community Oncology Research Program; RFA, request for application.

populations, developing interventions that can easily and cost effectively be implemented into clinical practices, and conducting research to gain an understanding of which types of programs provide the most benefit to specific groups of patients. Patient engagement will also be essential to effective implementation of energy balance interventions. Attention to patient burden, both in terms of time and finances, will be important, as will demonstration of improvement in patient-reported outcomes as a result of energy balance programs.

SUMMARY

Observational evidence has established a relationship between obesity and cancer risk and outcomes. Interventional studies have demonstrated the feasibility and benefits of lifestyle change after cancer diagnosis, and guidelines recommend weight management and regular physical activity in cancer survivors; however, lifestyle interventions are not a routine part of cancer care. The ASCO Research Summit on Advancing Obesity Clinical Trials in Cancer Survivors sought to identify the knowledge gaps that clinical trials addressing energy balance factors in cancer survivors have not answered and to develop a roadmap for the design and implementation of studies with the potential to generate data that could lead to the evidence-based incorporation of weight management and physical activity programs into standard oncology practice. Recommendations highlight the need for large-scale trials evaluating the impact of energy balance interventions on cancer outcomes, as well as the concurrent conduct of studies focused on dissemination and implementation of interventions in diverse

populations of cancer survivors, including answering critical questions about the degree of benefit in key subgroups of survivors. Other considerations include the importance of incorporating economic metrics into energy balance intervention trials, the need to establish intermediate biomarkers, and the importance of integrating traditional and nontraditional funding sources. Establishing lifestyle change after cancer diagnosis as a routine part of cancer care will require a multipronged effort to overcome barriers related to study development, funding, and stakeholder engagement. Given the prevalence of obesity and inactivity in cancer survivors in the United States and elsewhere, energy balance interventions hold the potential to reduce cancer morbidity and mortality in millions of patients, and it is essential that we move forward in determining their role in cancer care with the same care and precision used to test pharmacologic and other interventions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Administrative support: Laura A. Levit
Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Recommendations for Obesity Clinical Trials in Cancer Survivors: American Society of Clinical Oncology Statement

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