Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2011 October ; 20(10): 2078–2084. doi:
10.1158/1055-9965.EPI-11-0605.

Design and conduct of intervention-based research among cancer survivors

Kathleen Y. Wolin and Graham A. Colditz

Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine and Alvin J. Siteman Cancer Center, St Louis, MO

Abstract

Intervention trials in cancer survivors play an important and growing role in complementing the wealth of knowledge obtained from observational studies about how lifestyle can improve clinical, physiological and psychological outcomes. As the number of intervention trials grows, attention to study design and reporting is essential to establishing a high-quality data pool from which to make evidence-based recommendations and guidelines. We highlight several key issues important to the design and interpretation of intervention trials in cancer survivors. Intervention dose and duration both matter in trials of cancer survivors, yet few trials have evaluated different intervention doses and few intervention trials with multi-year follow-up exist. Finally, there is a need for interventions both of longer duration and those that take a practical trials approach and reflect clinical practice to speed implementation within practice and improve outcomes for cancer survivors.

Keywords

intervention; randomized trial; cancer survivor

Introduction

Both randomized intervention trials and observational studies serve important functions in advancing our understanding of the role of lifestyle in the cancer survivorship experience. Observational studies have provided important evidence that lifestyle can improve the quality and quantity of life in cancer survivors and are discussed in detail in Oeffinger et al (reference information TBD) in this special issue. Randomized trials are expensive and less frequently implemented, but, when conducted well, add key insights on causation in narrowly defined populations. Clinical medicine has historically been dismissive of observational findings (1) despite several recent key reports demonstrating comparable results between well conducted observational and randomized trials (2-4). However, the ability of intervention-based research to answer the myriad of questions facing oncology clinicians and cancer survivors may be limited. Here, we focus on key issues in study design in cancer survivorship research highlighting the relative strengths and limitations of intervention research. We organize our discussion using broad categories of how such research is typically described (i.e., exposure, outcome, population, implementation), recognizing that these components are often inextricably linked and choices in one inevitably influence the others. We focus on intervention trials of exercise in survivors as an informative example, drawing on other survivor intervention modalities as needed.

Exposure/intervention

Intervention trials offer the advantage of a tightly controlled exposure, often with measureable adherence. However, in some cases, this becomes a disadvantage. Intervention trials cannot easily evaluate dose-response. Similarly, they cannot answer the question of what dose of a behavior is necessary to create clinically meaningful change in the outcome. Often, when a study fails to achieve the desired result, the discussion notes that the intervention dose may not have been large enough (or delivered for long enough) to change the endpoint. In their study of strength training to preserve bone in breast cancer survivors, Winters-Stone et al failed to see a significant effect of the intervention on hip bone density, despite finding one at the spine (5). They note that a greater bone loading may be necessary to preserve bone density at the hip in postmenopausal women. This example highlights the way that observational and intervention research must work together to advance our understanding of lifestyle in cancer survivorship. Using exposure doses identified in observational research as significantly associated with changing the desired outcome, be it quality of life or survival, intervention trials are more likely, though certainly not guaranteed, to achieve success. However, if a significant result is found, it provides the strongest evidence that the dose used is causally associated with the outcome and makes a strong case for developing future intervention messages for that intervention dose. Despite the importance of dose in medication intervention trials in cancer treatment, reporting of detailed dose information in lifestyle intervention trials lags. In their review of exercise trials in cancer survivors, Speck et al noted that nearly 30% of studies did not specify the intensity of physical activity in the intervention (6).

Intervention dose and duration both matter in trials of cancer survivors. For example, Ferrer et al reported that the dose targeted by the intervention predicted efficacy in exercise trials of quality of life endpoints, particularly when examining studies of longer duration (7). Intervention duration can pose challenges in studies assessing multiple endpoints. For example, Winters-Stone et al note that exercise studies of bone mineral density should last a year or longer, but to date only three studies have done so (5). They also note, studies of longer duration tend to experience higher rates of attrition, which poses additional challenges in establishing an intervention effect. As a result, intervention trials, to leverage the “gold standard” aspect of the randomized trial design, are only able to evaluate one intervention dose and duration. To explore actual dose, the trial must rely on analyses that parallel those in observational studies, but likely with a narrow range. Thus, if participants in an exercise trial are randomized to an intervention dose of 30 minutes of moderate intensity activity per day and the trial fails to see an effect because the true dose needed to change endpoint risk is 60 minutes per day, the randomized trial might be interpreted as showing exercise isn’t effective. Further limiting the design and interpretation of the trial is that few participants will have exceeded the intervention dose sufficiently to explore the ideal dose. In contrast, observational studies can explore a range of exercise doses, as has been done in the Nurses’ Health Study by Holmes et al (8) and Meyerhardt et al (9, 10). The observational study and intervention trial need to be used in tandem – with the observational study pointing to what intervention dose (or doses if the observational data suggests different doses may yield differentially strong effects, but some doses may be less attainable) should be evaluated in the intervention trial.

Adherence poses numerous challenges in intervention research as researchers must balance the need for measureable adherence with the flexibility study participants desire to continue engaging with the intervention. The long-term adherence to behavior change is particularly important for cancer survivorship studies of physiological endpoints, as in bone density mentioned above, but also for studies of recurrence, survival and co-morbid conditions (e.g., cardiovascular disease). As study duration lengthens, adherence and retention challenges

often become greater. Studies that engage participants remotely or at home for some or all of the intervention may promote higher long-term adherence to the behavior change (11). However, to date, these studies have generally relied on self-report of behavior adherence, which is known to have error for many lifestyle factors including diet and physical activity (12-14). Studies have shown that interventions can induce learning effects in behavioral self-reporting independent of real change in behavior (15). Post-hoc analyses can evaluate adherence as a predictor of the outcome, but by doing so, the analysis loses the strengths of a randomized trial and it becomes an observational analysis. Of particular concern is that the disease causes the behavior change. In survival trials this is worsened by recurrence and other complications that alter ability to exercise, decrease appetite, or otherwise reduce adherence. To maximize the value of the randomized trial, greater attention to intervention adherence in the cohorts created by intervention trials' adherence levels would allow for a more refined understanding of the intervention effect. Follow-up after the active intervention is completed requires rigorous epidemiologic methods for maintaining high follow-up rates and endpoint confirmation. To date, few trials (16) have conducted long-term follow up of participants after the active intervention period. This, again, highlights the complimentary roles that the two study designs can play, a notion that is increasingly gaining traction, even in drug studies (17).

The timing of the intervention in relation to disease and the outcome likely plays an important role in the associations seen. The carcinogenic process can include substantial lag time from when exposure matters for an outcome, as seen for smoking and colon cancer risk (18). However, trials don't easily have the ability to evaluate the effect of exposure/intervention timing on the outcome as that is set by the study protocol and eligibility criteria. Intervention length also becomes a challenge in cancer survivors, often similar to the challenges faced in cancer prevention studies (19). Lifestyle interventions lasting six months or less are common. In their review of exercise studies among cancer survivors, Speck et al report that only 40% of studies published through November 2009 lasted greater than three months (6). Pekmezi and Demark-Wahnefried noted that there is a trend toward studies of longer duration in more recently published studies (11), and report that in studies of weight management in survivors published between November 2007 and June 2010, duration ranged from six months to two years. The challenge with such interventions is that the maintenance of the behavior change isn't typically evaluated, yet is often necessary for the lifestyle change to impact outcomes. An intervention of this length may also not be long enough to change some physiologic endpoints. As noted before, an exercise intervention of three or six months is likely not long enough to alter bone density (5). In this regard, observational studies have the potential to provide important clues if they can establish that participants have been engaging in a behavior consistently over months or years through repeated exposure assessment. This again points to the importance of linking the intervention design, including exposure dose and intervention length to the biology of the primary endpoint and highlights the limitations that can arise when using intervention trials to examine secondary endpoints.

Defining which component of an intervention drives changes in the outcome can also be challenging in intervention trials. The Women's Intervention Nutrition Study, a randomized intervention trial of dietary fat reduction in women with breast cancer (20), resulted in a significant reduction in recurrence. However, the intervention, in addition to reducing dietary fat intake, also resulted in a significant decrease in body weight in the intervention versus control arms. As both diet and weight loss have been shown in observational studies to reduce recurrence, the WINS trial could not be said to definitively show that dietary fat reduction reduced breast cancer recurrence. The subsequent Women's Healthy Eating and Living (WHEL) study randomized women with breast cancer to a dietary intervention targeting increased fruit, vegetable, and fiber and decreased fat intake and found no effect on

recurrence or survival (21). Similarly, when a yoga intervention is shown to improve quality of life (22), the effect could be due to any number of the components of yoga – including movement and meditation. Multi-component interventions are common – Speck et al (6) found that a quarter of exercise studies in cancer survivors included other components and Pekmezi and Demark-Wahnefried (11) similarly found multi-components in recent lifestyle interventions in survivors. Post-hoc analyses can often explore questions of the component driving the outcome, for example, distinguishing those who exercised more or less, or controlling for weight change can provide some insight into the exercise effect, but this becomes an observational, not trial analysis. The use of multi-component interventions in trials provides a unique set of interpretation challenges. In designing such studies, the investigators likely seek to maximize the benefit participants might obtain by participating in more than one type of behavior change, but as we've highlighted, interpreting the results, positive or negative, can then pose challenges. Multi-arm trials can help in some situations, such as trials that include an exercise only, a diet only and an exercise plus diet intervention arm to compare with the control or usual care group.

Trials are an excellent setting for exploring safety questions in cancer survivors as was done in the Physical Activity and Lymphedema (PAL) trial which rebuked the previously held assumption that women with or at risk for lymphedema could not engage in strength training exercises (23, 24). However, for trials to be able to answer safety questions well, the data needs to be systematically collected. Trials where contact time is differential between arms are particularly subject to concerns that the intervention arm receives more care and thus has more opportunity to report adverse events. Furthermore, given that cancer survivors often have a high prevalence of co-morbidities and chronic disease risk factors (e.g., obesity, diabetes), adverse events of some kinds (e.g., myocardial infarction) are to be expected simply owing to their age and lifestyle. As noted previously (6, 25), those survivors with intervention induced side effects may not be well enough to complete outcome assessments and thus, loss to follow-up is an important study quality parameter in cancer survivor studies. In studies of exercise in survivors, 88% of studies reviewed for adverse events had a loss to follow-up rate under 20% (6).

Finally, intervention quality matters. In a review of exercise studies targeting cancer fatigue, Brown et al found a mean quality score of 6.8 (out of 11 using the Physiotherapy Evidence Database scale (PEDro) (26). In reviewing studies of resistance training in cancer survivors, De Backer et al reported a median quality score of 4 out of 10 using a modified PEDro scale (27). One of the most common failings in the study ratings was low adherence and loss to follow-up or failure to report data on either. Well conducted studies and those relying on a theory of behavior change have been shown to be more efficacious at employing exercise to manage cancer related fatigue (26). However, use of theory is often underutilized or underreported. In an analysis of exercise studies targeting cancer related fatigue, Brown et al found only 10 of 44 studies included a theoretical basis for the intervention (26). In reviewing the theories of motivation used to inform physical activity studies in cancer survivors, Pinto and Ciccolo note that only a subgroup of the interventions included in the Speck et al (6) review were based on theory (28). Thus, while the key components of a quality intervention have been identified, they are not systematically included in survivor interventions.

Outcomes

An increasingly diverse number of outcomes are included in cancer survivorship studies ranging from psychological and physical function to symptoms and side effects and, finally, recurrence and overall survival. Intervention trials are typically powered on a single endpoint but assess myriad others. In their review of exercise studies among cancer

survivors, Speck et al identified 14 different outcome domains, some which, such as “psychosocial”, “physiological” and “quality of life” included numerous distinctly assessed outcomes. As noted above, the interventions may be able to measure the endpoints but may not have the appropriate intervention dose or timing to impact change in the outcome.

Endpoints may also vary from those considered clinically relevant, such as side effects of treatment, to those considered patient-centered, such as quality of life. In exercise studies, Speck et al found there is less high quality data on the psychosocial outcomes (e.g., mood, body image, weight concerns) than the quality of life, despite both being patient reported (6). Clinical endpoints may be collected as part of routine care, but the patient-centered outcomes are not. Patients on therapeutic treatment trials may have more uniform work up for endpoints than observed in similar patients receiving routine follow-up after intensive therapy has ceased. This creates challenges for uniform classification of nonfatal endpoints in lifestyle studies.

Understanding how these endpoints change and integrating the research and clinical care can only serve to improve our understanding of the challenges facing survivors and the opportunities to identify causes and pathways to improvement. While change in physiological endpoints may have implications for clinical disease management, that doesn't always translate into more high quality intervention studies targeting those outcomes. In the Speck et al review of exercise, no more than three high quality studies had reported on a single physiological outcome (6). As has been noted elsewhere (29), interventions that test changes in physiological endpoints, such as serum biomarkers, can help identify the mechanisms by which lifestyle changes alter risk of recurrence or mortality. Much the same way that cancer centers have tracked mortality over time using tumor registries, cancer centers, such as H. Lee Moffitt are moving to routinely collect quality of life data on all cancer patients across the treatment and follow-up periods (30) (P. Jacobsen, personal communication). Efforts like these have the potential to yield important research data in addition to improving the quality of patient care. A particular advantage of this systematic approach is that the data collected reflect the quality of life of the whole population of cancer center patients, not just the subset who enroll in research studies, reducing volunteer bias.

An added concern when interpreting outcomes in the survival setting is the definition of the endpoint being reported. This issue has recently been raised as a concern in cancer drug trials (31). For example, a recent San Antonio breast conference session on obesity and survival included several studies, but each appeared to have chosen a different endpoint focus: lymph node changes, local recurrence, disease free survival, disease specific mortality, and total mortality. A similar approach to endpoint reporting is often seen in prostate cancer (32). Integrating findings with such divergent reporting is both difficult and open to publication bias. From the patient perspective is mortality the most important endpoint, or disease specific mortality? It appears clinicians focus on disease specific mortality – reflecting their disease treatment focus, yet patients often die from complications of lifestyle (smoking and obesity) with coronary heart disease and diabetes driving mortality, not the underlying malignancy (33). Clearer a priori definition of endpoints and priority among endpoints will help move the science of survivorship forward faster.

Finally, loss to follow-up in intervention trials remains an ongoing challenge, but one that is particularly relevant to survivors. Studies conducted in the US are further challenged by the lack readily accessible national tumor or death registries as are found in many European countries. The best approach to managing loss to follow-up is to build strong systems to prevent loss to follow-up into the study from the beginning. Approaches found to be successful in prospective cohort studies (34), such as the use of incentives, and face-to-face

follow-up, will likely also help interventions in cancer survivors. The use of technology to engage with and track participants can also facilitate this. However, as cancer survivors move within a system of disconnected care, that they are no longer visiting their oncologist may not mean they no longer seek medical care. Engaging with a survivors' entire care team may facilitate higher follow-up. As noted by Ware et al (35), in behavioral intervention studies, many of the options for handling loss to followup at the analysis phase result in biased analyses and thus, the best approach is to invest study resources in loss prevention.

Design and dissemination

Lifestyle intervention trials in cancer survivors can contain enormous heterogeneity that makes issuing simple evidence-based guidelines challenging. Exercise, diet and weight management trials include samples ranging from newly diagnosed patients and those undergoing treatment to long-term survivors more than five years since diagnosis (6, 11). Thus, issuing a single simple message that applies to a large segment of the cancer survivor population can be challenging. While the US Physical Activity Guidelines for Americans (36) provide a single set of guidelines on aerobic, strength and flexibility training for most US adults, the American College of Sports Medicine Guidelines for cancer survivors separate recommendations by diagnosis and within diagnosis, further based on additional treatment or medical characteristics (37). Intervention trials in cancer survivors to date have largely been efficacy studies, which are valuable for evaluating safety questions, such as in PAL (23, 24), but pose challenges when questions of effectiveness and generalizability inevitably arise. The investigators are currently investigating the broad dissemination of the trial (R21CA152451). While PAL showed that supervised resistance training over 16 weeks was safe and did not cause or exacerbate lymphedema in breast cancer survivors, the study does not demonstrate the safety of strength training overall in that it did not evaluate unsupervised resistance training or resistance training in gynecologic cancer patients experiencing lower limb lymphedema. As such, Schmitz et al have cautioned not to extrapolate study findings too broadly. However, we have argued (38) that the success of smoking cessation programs in childhood cancer survivors (39) and head and neck cancer survivors (40) points to the ability to successfully engage cancer survivors in smoking cessation and that these programs should be implemented more broadly across disease groups. These examples provide bookends for the challenges faced when defining an intervention study population at the beginning and in deciding about the possible marginal value of the evidence for informing the evidence base and broader dissemination and implementation into routine clinical care. While we would ideally have at least one high quality randomized controlled trial for each behavior, the practicalities of gathering such data will likely preclude it. As shown in Table 1, the sheer number of studies required (and time and funds necessary to conduct them), leaves the current population of over 12 million cancer survivors without advice on how to adopt a healthy lifestyle. As a result, we have called for more focus on under what circumstances clinicians and the survivorship community can extrapolate data to address the desire of survivors to improve their lifestyle in a safe and effective manner (38). Further challenging the ability of clinicians and researchers to make decisions about extrapolation and implementation are the gaps in reporting key features of trials. In reviewing exercise trials, Speck et al report that only 24% of intervention studies provided an adequate description of the study population including diagnosis, treatment, race/ethnicity, gender and sociodemographic variables (6).

In contrast with drug treatment trials that often narrowly define a study population by numerous disease subtypes, co-morbidities and behavioral risk factors, lifestyle intervention studies are often broader in their recruitment criteria. While this improves the generalizability (41-43), it can also serve as a barrier to uptake by clinicians accustomed to a narrowly defined set of study eligibility criteria. Other factors common to intervention trials

in cancer survivors also limit uptake, including the high costs of implementing the evidence-base (and the lack of cost data in most trials), the lack of population diversity in trials ranging from few minorities to populations clustered around academic medical centers. Trials in rural cancer patients are emerging but come with necessary differences in their approach to the intervention – often relying on non-face to face contact approaches and unsupervised interventions. In such settings, investigators rely on self-reported measures of intervention adherence or outcomes, though remote wireless devices could bridge this gap. Self-report reduces the costs associated with the intervention, but can be considered a limitation in systematic reviews. Such reviews may better define methods to adjust for bias in self-report when synthesizing data using regression approaches to estimate the expected magnitude of benefit in the broader patient population.

Dissemination and implementation science provides an opportunity for thinking about these issues during intervention study design, through approaches like RE-AIM (44) and when evaluating the evidence-base to make programmatic or policy recommendations (38). Thus, calls have been made more broadly for a focus on practical clinical trials, which reflect routine clinical care and a focus on future implementation in study design (42). This approach has been taken in other clinical areas, as was done with the Practice-based Opportunity for Promotion of Weight Reduction (POWER) trials sponsored by NHLBI (45, 46), which focused on the effectiveness of interventions in routine clinical practice. The survivorship community must balance the need for effectiveness research with the limited amount of efficacy data currently available for many interventions and outcomes to generate recommendations that are both effective and safe.

Concluding remarks

Despite increasing interest in using intervention trials to assess the role of lifestyle in reducing risk of recurrence and mortality in cancer survivors, conducting these trials poses numerous challenges (47). The sample sizes required to evaluate disease-free survival are large and obtaining the necessary adherence to the intervention can be challenging. Layered on the challenges of operating a well-conducted trial are those posed by the current funding environment in the US, where most large initiatives are funded by NIH and limited to ROI mechanisms lasting no more than five years. As noted by others, to conduct a trial of disease free survival requires recruiting a larger sample to account for a short follow-up time, or limiting the study population to individuals at higher risk for the primary endpoint (47). As a result, other approaches to making evidence-based guideline and program implementation decisions such as cross-design synthesis will be necessary. While the ideal would be to have randomized trial data for each lifestyle intervention in each cancer patient population (in some cases further stratified by clinical indicators) to evaluate physiological, psychological, quality of life and disease-free survival endpoints, the feasibility of doing so, particularly in a resource-limited funding environment is small. Thus, we see a need to begin identifying ways in which the clinical and research communities can draw from other studies, be they observational or intervention trials in other populations (e.g., weight loss in the general population) to speed translation of research to improve outcomes for cancer patients.

Acknowledgments

Supported by the Barnes Jewish Hospital Foundation and NCI U54-155496, A multilevel approach to energy balance and cancer across the life course.

References

1. Chalmers TC, Celano P, Sacks HS, Smith H Jr. Bias in treatment assignment in controlled clinical trials. *N Engl J Med*. 1983; 309:1358–61. [PubMed: 6633598]

2. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000; 342:1887–92. [PubMed: 10861325]
3. Benson K, Hartz AJ. A Comparison of Observational Studies and Randomized, Controlled Trials. *N Engl J Med*. 2000; 342:1878–86. [PubMed: 10861324]
4. Institute of Medicine of the National Academies of Science. [1/4/2011] 100 Initial Priority Topics for Comparative Effectiveness Research. <http://www.iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.pdf>. cited; Available from: <http://www.iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/Stand%20Alone%20List%20of%20100%20CER%20Priorities%20-%20for%20web.pdf>
5. Winters-Stone KM, Dobek J, Nail L, Bennett JA, Leo MC, Naik A, et al. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. *Breast Cancer Res Treat*. 2011; 127:447–56. [PubMed: 21424279]
6. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*. 2010
7. Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. *Ann Behav Med*. 2011; 41:32–47. [PubMed: 20931309]
8. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005; 293:2479–86. [PubMed: 15914748]
9. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, et al. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol*. 2006; 24:3527–34. [PubMed: 16822844]
10. Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol*. 2006; 24:3535–41. [PubMed: 16822843]
11. Pekmezci DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. *Acta Oncol*. 2011; 50:167–78. [PubMed: 21091401]
12. Bonnefoy M, Kostka T, Patricot MC, Berthouze SE, Lacour JR. Lack of correlation between 6-month fluctuations in habitual physical activity and testosterone concentrations in elderly subjects. *J Sports Med Phys Fitness*. 2001; 41:78–82. [PubMed: 11317152]
13. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. *Am J Epidemiol*. 2001; 154:1089–99. [PubMed: 11744511]
14. Wolin KY, Heil DP, Askew S, Matthews CE, Bennett GG. Validation of the International Physical Activity Questionnaire-Short among Blacks. *Journal of physical activity & health*. 2008; 5:746–60. [PubMed: 18820348]
15. Espeland MA, Kumanyika S, Wilson AC, Wilcox S, Chao D, Bahnson J, et al. Lifestyle interventions influence relative errors in self-reported diet intake of sodium and potassium. *Ann Epidemiol*. 2001; 11:85–93. [PubMed: 11164124]
16. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet*. 2010; 376:1741–50. [PubMed: 20970847]
17. Rimm EB, Stampfer MJ. Folate and cardiovascular disease: one size does not fit all. *Lancet*. 2011; 378:544–6. [PubMed: 21803413]
18. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:725–31. [PubMed: 11440957]
19. Colditz GA, Taylor PR. Prevention trials: their place in how we understand the value of prevention strategies. *Annu Rev Public Health*. 2010; 31:105–20. [PubMed: 20070190]
20. Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J Natl Cancer Inst*. 2006; 98:1767–76. [PubMed: 17179478]

21. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, Flatt SW, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA*. 2007; 298:289–98. [PubMed: 17635889]
22. Lin KY, Hu YT, Chang KJ, Lin HF, Tsauo JY. Effects of yoga on psychological health, quality of life, and physical health of patients with cancer: a meta-analysis. *Evid Based Complement Alternat Med*. 2011; 2011 659876.
23. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, et al. Weight lifting in women with breast-cancer-related lymphedema. *New England Journal of Medicine*. 2009; 361:664–73. [PubMed: 19675330]
24. Schmitz KH, Ahmed RL, Troxel AB, Cheville A, Lewis-Grant L, Smith R, et al. Weight lifting for women at risk for breast cancer-related lymphedema: a randomized trial. *JAMA*. 2010; 304:2699–705. [PubMed: 21148134]
25. Mock V, Pickett M, Ropka ME, Muscari Lin E, Stewart KJ, Rhodes VA, et al. Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Pract*. 2001; 9:119–27. [PubMed: 11879296]
26. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2011; 20:123–33. [PubMed: 21051654]
27. De Backer IC, Schep G, Backx FJ, Vreugdenhil G, Kuipers H. Resistance training in cancer survivors: a systematic review. *International Journal of Sports Medicine*. 2009; 30:703–12. [PubMed: 19585401]
28. Pinto BM, Ciccolo JT. Physical activity motivation and cancer survivorship. Recent results in cancer research *Fortschritte der Krebsforschung Progres dans les recherches sur le cancer*. 2011; 186:367–87. [PubMed: 21113773]
29. Irwin ML, Mayne ST. Impact of nutrition and exercise on cancer survival. *Cancer J*. 2008; 14:435–41. [PubMed: 19060611]
30. Dalton, WS.; Fenstermacher, D.; Jacobsen, P.; de la Parte, LD.; Yeatman, T. Community-Based Personalized Health Care. *Personalized Health Care: Community Studies*. cited June 28, 2011; Available from: <http://www.hhs.gov/myhealthcare/news/community.html#cmunty7>
31. D'Agostino RB Sr. Changing end points in breast-cancer drug approval - The Avastin story. *N Engl J Med*. 2011 in press.
32. Boorjian SA, Karnes RJ, Viterbo R, Rangel LJ, Bergstralh EJ, Horwitz EM, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. *Cancer*. 2011
33. Patnaik JL, Byers T, Diguseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res*. 2011; 13:R64. [PubMed: 21689398]
34. Booker CL, Harding S, Benzeval M. A systematic review of the effect of retention methods in population-based cohort studies. *BMC Public Health*. 2011; 11:249. [PubMed: 21504610]
35. Ware JH. Interpreting incomplete data in studies of diet and weight loss. *The New England journal of medicine*. 2003; 348:2136–7. [PubMed: 12761370]
36. Physical Activity Guidelines Advisory Committee Report, 2008. Washington, DC: U.S Department of Health and Human Services; 2008. Physical Activity Guidelines Advisory Committee.
37. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine and science in sports and exercise*. 2010; 42:1409–26. [PubMed: 20559064]
38. Wolin KY, Colditz GA, Proctor EK. Maximizing benefits for effective cancer survivorship programming: Defining a dissemination and implementation plan. *The oncologist*. 2011 in press.
39. Emmons KM, Puleo E, Park E, Gritz ER, Butterfield RM, Weeks JC, et al. Peer-delivered smoking counseling for childhood cancer survivors increases rate of cessation: the partnership for health study. *J Clin Oncol*. 2005; 23:6516–23. [PubMed: 16116148]

40. Gritz ER, Carr CR, Rapkin D, Abemayor E, Chang LJ, Wong WK, et al. Predictors of long-term smoking cessation in head and neck cancer patients. *Cancer Epidemiol Biomarkers Prev.* 1993; 2:261–70. [PubMed: 8318879]
41. Green LW, Glasgow RE. Evaluating the relevance, generalization, and applicability of research: issues in external validation and translation methodology. *Eval Health Prof.* 2006; 29:126–53. [PubMed: 16510882]
42. Kessler R, Glasgow RE. A proposal to speed translation of healthcare research into practice dramatic change is needed. *Am J Prev Med.* 2011; 40:637–44. [PubMed: 21565657]
43. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group *BMJ.* 1998; 317:465–8.
44. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* 1999; 89:1322–7. [PubMed: 10474547]
45. Greaney ML, Quintiliani LM, Warner ET, King DK, Emmons KM, Colditz GA, et al. Weight management among patients at community health centers: The “Be Fit, Be Well” study. *Obesity and Weight Management.* 2009; 5:222–8.
46. Yeh HC, Clark JM, Emmons KE, Moore RH, Bennett GG, Warner ET, et al. Independent but coordinated trials: insights from the practice-based Opportunities for Weight Reduction Trials Collaborative Research Group. *Clin Trials.* 2010; 7:322–32. [PubMed: 20573639]
47. Ballard-Barbash R, Hunsberger S, Alciati MH, Blair SN, Goodwin PJ, McTiernan A, et al. Physical activity, weight control, and breast cancer risk and survival: clinical trial rationale and design considerations. *J Natl Cancer Inst.* 2009; 101:630–43. [PubMed: 19401543]

Table 1
Extent of evidence necessary to have high quality trial data on interventions within cancer groups*

	Complementary and alternative medicine	Physical activity	Smoking cessation	Weight management	Multiple-risk factor interventions
Breast	X**	x		x	x
Colorectal		x		x	
Endometrial				x	
Esophageal					
Gastric					
Leukemia		x			
Lung			x		
Lymphoma		x			
Ovarian					
Pediatric		x	x	x	
Prostate		x		x	

* Does not account for number of possible endpoints or outcomes (for a partial list, beyond mortality and recurrence, of possible endpoints see Speck 2010 (6)), separated by intervention during or after active treatment, separated by tumor subtype, or separated by treatment regimen, all of which would magnify the amount of evidence needed exponentially.

** X indicates currently have high quality data for at least intervention targeting one outcome within this disease group