Mechanisms in Psychosocial Interventions for Adults Living With Cancer: Opportunity for Integration of Theory, Research, and Practice

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Objective: The diagnosis and treatment of cancer are highly stressful experiences that can profoundly affect emotional and physical well-being. Hundreds of longitudinal investigations that identify risk and protective factors for psychological and physical adjustment in adults living with cancer and numerous randomized controlled psychosocial intervention trials constitute the relevant knowledge base on factors that promote quality of life and health in this group. A critical step for the development of maximally effective interventions is to attend to the mechanisms by which interventions achieve their effects. Our goals in this article are to provide a rationale for theoretical and empirical consideration of mediating processes in intervention research, review existing randomized psychosocial intervention trials for adults diagnosed with cancer that include evaluation of mediators, and offer recommendations for research. *Method:* We draw from the existing conceptual and empirical literature regarding examination of mediating processes and review 16 randomized controlled trials that include evaluations of mediators. *Results:* The current conceptual and empirical literature on evaluating mediators of interventions provides robust rationales and procedures for testing mediators of psychosocial interventions for adults diagnosed with cancer. Promising classes of mediators include alterations in cognitions (i.e., expectancies, illness representations), self-efficacy for using coping strategies and other skills targeted by the intervention, psychological and physical symptoms related to cancer (e.g., mood disturbance, pain), and psychosocial resources (e.g., self-esteem). *Conclusions:* Focused attention to mechanisms underlying the efficacy of interventions can help integrate theory, research, and practice to promote the well-being and health of individuals with cancer.

Keywords: cancer, mechanism, mediation, randomized controlled trial, psychosocial

In the United States, it is estimated that 12 million women and men currently are living with a cancer diagnosis, and 41% will receive a diagnosis during their lifetime (Howlader et al., 2011). A diagnosis of cancer and associated medical treatments can disrupt the lives of individuals and close others in profound ways. In response, researchers have conducted hundreds of longitudinal investigations to illuminate factors that promote and detract from psychological and physical adjustment in individuals living with cancer. Moreover, a wealth of interventions designed to promote positive outcomes exists. Nearly 500 unique studies, 63% of which

involved randomized designs, constituted the evidence base in 2005 on the efficacy of psychosocial interventions for adults diagnosed with cancer (Moyer, Sohl, Knapp-Oliver, & Schneider, 2009). Most often performed with adults in the diagnostic or active medical treatment phases (Jacobsen, Donovan, Swaine, & Watson, 2006; Moyer et al., 2009), this research includes a variety of intervention approaches, often with multiple components (e.g., education regarding cancer and its treatment, provision of emotional support, training in coping skills, cognitive–behavioral therapy, relaxation training), as well as multiple outcomes (e.g., depressive symptoms, cancer-related distress, physical symptoms, fatigue, quality of life). Despite the rapid proliferation of interventions, we know little about how interventions work to reduce distress or promote health. Although ample candidate mechanisms for the effectiveness of psychosocial interventions have been theorized in the general psychology literature (e.g., Craske, 2010), reviews of research on mechanisms of change provide little guidance. As Kazdin (2007) concluded, "It is remarkable that after decades of psychotherapy research, we cannot provide an evidence-based explanation for how or why even our most well studied interventions produce change" (p. 23). Clearly, interventions (e.g., provision of information about radiation therapy), outcomes (e.g., fear of cancer recurrence), and potential mediators (e.g., self-efficacy for managing the cancer experience) of partic-

ular relevance to the cancer and chronic disease context warrant examination.

In this article, we aimed to present evidence for the utility of examining mediators of change in psychosocial interventions to enhance quality of life and health in adults living with a cancer diagnosis. The large bodies of research on contributors to salutary outcomes in individuals with cancer and on interventions designed to influence those outcomes can reciprocally inform each other in that they both have the potential to specify *how* individuals can maintain or recover psychosocial and physical equilibrium in the face of life-threatening disease. Founded in the relevant literatures, the specific goals in this article were to (a) provide an orientation on conceptualization of mediators and mechanisms relevant to this research domain; (b) offer a rationale for studying mediating factors in intervention trials, accompanied by suggestions for selecting and testing mediators; (c) highlight promising, evidence-based candidates for psychosocial and biological mechanisms for the efficacy of recent randomized, controlled trials of psychosocial interventions for cancer; and (d) offer recommendations for future research. We want to remind the reader that our evaluation of trials is *not* informative regarding the overall efficacy of psychosocial interventions; only trials evaluating potential mediators were included in this article.

Conceptualizing Mediators and Mechanisms

A *mediator* (M) is a measured variable that transmits the effect of an independent variable (X) on a dependent variable (Y) and provides an explanation of a causal pathway by which one variable brings about change in another (MacKinnon, 2008). The implied causal chain is from an antecedent variable (e.g., psychosocial intervention) to a more proximal causal (mediating) variable (e.g., reduction in physiological arousal, increase in self-efficacy for relaxation skill) to an outcome (e.g., fear of cancer recurrence). Unlike other types of third variable effects (e.g., moderators, confounds, covariates), mediation assumes that the independent variable (X) precedes and causes the mediator, and the mediator precedes and causes the dependent variable (Y).

Mediators differ from mechanisms in that *mechanisms* are the actual underlying causal processes (i.e., how the change comes about), whereas mediators may or may not reflect the actual processes or events that are responsible for the change. Mediators are the measures obtained in research (i.e., operationalization) with the goal of illuminating underlying mechanisms. For example, randomized controlled trials suggest that an improvement on a relaxation self-efficacy measure mediates the relation between a cognitive–behavioral stress management intervention (vs an attention control) and positive psychosocial outcomes in patients with breast cancer (Antoni et al., 2006). Enhanced self-efficacy is a mediator, but what are the underlying causal mechanisms? Is cognitive change a causal mechanism, or does self-efficacy require behavioral or physiological instantiation in order to produce positive outcomes? Of course, the intervention did not simply instruct people to "have more self-efficacy." Rather, specific components of the intervention most likely led to the change. Although questions remain when one identifies a mediator, a sustained program of replicated research, particularly when accompanied by experimental research to manipulate the putative mediator, can provide strong evidence to support a theorized causal mechanism.

Mediation is distinct from *moderation*, in which the relation between the independent and dependent variables differ at different values of the moderator variable. Unlike mediators, moderators are not intermediate in a causal sequence from X to Y. As an illustration of moderation, Manne, Ostroff, and Winkel (2007) found that cancer-related coping strategies in use prior to the intervention moderated the effects of a couple-focused intervention to decrease distress in women diagnosed with early-stage breast cancer. Mediators also are distinct from *confounds*. A confound is a variable that changes the relation between X and Y because it predicts both variables, but it is not in a causal sequence between them. For example, a statistical relation between social isolation and fatigue could be confounded by chemotherapy-induced inflammation causing both "sickness behaviors" rather than a causal relation between the two variables. In cancer research, potential confounds include such variables as cancer stage, time since diagnosis, family history of cancer, or medical treatments (note that such variables also might be theorized as moderators).

Rationale for Studying Mediators and Mechanisms

Essentially, examining mediators of psychosocial interventions for adults diagnosed with cancer allows researchers to investigate not only *whether* the program achieved the desired effects, but also *how* the program achieved its effects. One good reason for examining mediators within an intervention design is to test theories regarding how individuals adjust to cancer and how psychosocial interventions work. For example, evidence that an expressive disclosure intervention in women with cancer works to reduce bothersome physical symptoms through both a reduction in physiological arousal (Low, Stanton, & Danoff-Burg, 2006) and an affirmation of personal values (Creswell et al., 2007) lends support to functionalist theories of emotion.

A second major reason to examine mediators in psychosocial interventions for cancer survivors is to promote more effective and efficient interventions. Honing multimodal interventions to their maximally effective components can make optimal use of scarce resources. Examination of mediators derived from specific intervention components can aid in identifying effective and ineffective (or iatrogenic) ingredients of interventions. Assuming adequate research designs and sufficient sample sizes, cases in which hypothesized mediators are *not* supported can be practically and theoretically informative (see later discussion of action theory). To illustrate, cancer-related cognitions are a common intervention target. Failure to change those theorized mediators can indicate that program actions were ineffective, measurement of the mediator was inadequate, or the theory of change requires revision.

Alternatively, an intervention might have the expected effect on the proposed mediator, but no significant effect on the outcome of interest, calling into question the theoretical or empirical basis of the causal pathway. For example, an intervention may increase problem-focused coping skills in a group of cancer survivors with high fatigue, but these particular coping skills may not produce a reduction in chronic fatigue. The researcher could benefit from consulting theoretical models of chronic fatigue in cancer survivors and associated empirical evidence (e.g., Bower et al., 2011) to refine the targets of the intervention. It also is possible that the timing of measurement of the mediator and outcome does not

adequately capture when changes occur. Effects on the outcome may emerge at a later date; testing program effects on mediators may increase confidence in late-emerging effects if the supporting theory is strong.

Approaches to Investigating Mediators

Ideally, intervention researchers build tests of mediation into the initial research design. Longitudinal measurement and randomization of participants to conditions provide a crucible for scientific tests of theory. Through establishing that a therapeutic approach influences a mediating variable, which in turn accounts for significant variance in the dependent variable, one can obtain evidence for a causal chain, particularly when temporal ordering can be demonstrated. Ultimately, the strongest test of any proposed mediator is direct experimental manipulation of the mediator itself. Such controlled experimental designs are feasible in some cases through direct instruction or biologic administration (e.g., induction of emotional expression, induction of proinflammatory cytokine activity) but more difficult in other cases (e.g., induction of self-efficacy) in the absence of more elaborated psychosocial intervention.

A vitally important aspect of a mediation approach to psychosocial interventions in cancer is the choice of which mediators to target. Consideration of two types of theory—action theory and conceptual theory—can facilitate selection of mediators (Chen, 1990; MacKinnon, 2008). Action theory is concerned with how aspects of the intervention affect the mediators; it provides the guidance for how the mediator is to be modified. In cancer intervention research, action theory often consists of actions taken by intervention leaders, such as teaching techniques for cognitive reappraisal or relaxation. Action theory requires researchers to consider realistically whether theorized mediators can be changed with available resources and what steps are needed to accomplish change. For example, it is unlikely that resources are available to alter ingrained personality attributes in a brief intervention, but changing negative cognitions may be feasible.

Conceptual theory refers to the mediators that are theorized to be causally related to the outcome. Often conceptual theory is based on a body of theoretical understanding of the predictors of an outcome variable. For example, low coping self-efficacy may be causally related to higher distress in cancer survivors and hence may be targeted for intervention. Action theory and conceptual theory represent the theoretical basis for the path from intervention to the mediator and the mediator to the outcome. For an intervention to reduce cancer-specific anxiety, for example, action theory might suggest that participants keep a record of use of relaxation-inducing imagery prompts and minutes of relaxation practice assigned as homework each week; conceptual theory might postulate reductions in physiological arousal, coping through cancer-related avoidance, and cancer-related intrusive thoughts as mechanisms for decreasing anxiety. Researchers often select a mediator close to the goals of the intervention because it is most likely to change with the intervention (e.g., homework compliance). Care must be taken, however, because simple exposure to an intervention, although important, might not reflect a mechanism by which the intervention changes the outcome. Similarly, a mediator (e.g., negative affect) may be too conceptually or empirically close to

the measure of the outcome (e.g., depression) to be convincing as a cause of it.

In reality, there are many chains of relations in action theory and conceptual theory, all of which would be difficult to measure in a single study. The researcher must make choices about parts of the chain on which to focus. In an ideal world of limitless resources, study participants would be assigned randomly to different conditions, and all possible combinations of program components would be varied across groups (see Strecher et al., 2008, regarding use of fractional factorial designs in tailored interventions for health behavior change). This ideal situation is unlikely; as a result, many studies target more than one mediating variable in the same condition, and a reasonable strategy is to test one mediator at a time and then combine them in a multiple mediator model that can provide a more comprehensive model (MacKinnon, 2008).

Relevant theories and research on how psychological interventions work (e.g., Craske, 2010) can offer guidance in the selection of mediators. Evidence is accruing to specify mediators of change for specific psychological disorders and forms of psychotherapy (e.g., panic disorder, Meuret, Rosenfield, Seidel, Bhaskara, & Hofmann, 2010; mindfulness meditation, Hölzel et al., 2011). Furthermore, therapeutic components (e.g., prevent avoidance, promote emotional awareness, modify cognitive appraisals) hypothesized to be essential in transdiagnostic treatment of emotional disorders are gaining attention (e.g., Wilamowska et al., 2010).

The theoretical and empirical foundations regarding adjustment to chronic disease also offer guidance. For some outcomes (e.g., depression, fatigue, pain, physical health indices), theory and research illuminate potential biological mediators (e.g., Bower et al., 2011; R. R. Edwards, Campbell, Jamison, & Wiech, 2009; Uchino, 2006). Further, an array of presumably malleable cognitive appraisals (e.g., threat potential, goal-related appraisals, illness representations; Lazarus & Folkman, 1984; Leventhal, Halm, Horowitz, Leventhal, & Ozakinci, 2005) and coping and emotion regulation processes (Lazarus & Folkman, 1984; Taylor & Stanton, 2007), as well as facets of the interpersonal context (e.g., Lepore & Revenson, 2007; Taylor, 2011), are linked to adaptive outcomes for individuals with chronic disease (for a review, see Hoyt & Stanton, 2012). As such, these variables constitute promising mediators of interventions.

Steps in Statistical Mediation Analysis

The primary goal in basic mediation analysis is to obtain two statistical tests: (a) a test of the independent variable X (e.g., exposure to an intervention program) on the mediating variable (M), and (b) a test of the relation of M to the outcome (Y) adjusted for X. Both of these tests must be statistically significant to support mediation. For a two-group study in which an intervention condition is compared with a control condition, the X variable is a binary variable coding exposure to an intervention or not. However, multiple intervention or control conditions can also be compared, by coding more than two groups with contrast or dummy codes (see Huntsinger & Luecken, 2004, for an example). The M and Y variables can represent change from baseline to a follow-up assessment. Alternatively, change in M may be measured at earlier waves and used to predict change in Y at a later time point, thereby explicitly modeling the temporal order of change in M and change in Y.

Mediation can by assessed by obtaining an estimate of the mediated effect. The simplest and most general method to estimate the mediated effect is to take the product of the coefficient (a) relating X to M, and the coefficient (b) relating M to Y adjusted for X (ab; see MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Estimates of the standard error of this product are available (MacKinnon, 2008; MacKinnon et al., 2002). The ratio of the mediated effect to the multivariate delta standard error is known as the Sobel test (Sobel, 1982). However, methods to form confidence intervals around the mediated effect estimate, based on the distribution of the product and resampling methods (MacKinnon, Lockwood, & Williams, 2004), have greater statistical power. A statistical test of the mediated effect ab at the .05 level of significance can be obtained by assessing whether zero is in the 95% confidence interval for the mediated effect. Confidence intervals have other superior characteristics to binary significance tests, including providing a range of values for an effect and the combination of an estimate of effect along with a range of possible values. The mediated effect metric is interpreted as the change in the outcome variable between treatment and control conditions through the mediating variable. One useful mediated effect size measure is to divide the mediated effect by the standard deviation of the outcome variable, comparable to a Cohen's d (Cohen, 1988) effect size measure (MacKinnon, 2008). When the mediated effect is significant, and the test of the relation of X to Y adjusted for M is not statistically significant (i.e., failing to reject the null hypothesis of no X-to-Y relation), the pattern is consistent with complete mediation. If the test of the relation of X to Y adjusted for M is also statistically significant, there is evidence for partial mediation.

Of note, this description differs from the commonly used Baron and Kenny's (1986) causal steps approach, which additionally requires a significant test of the X-to-Y relation independent of M (Step 1) and does not explicitly provide an estimate of the mediated effect. Although it may seem counterintuitive, a statistically significant program effect on the outcome is not required for mediation to be present (MacKinnon et al., 2002; see, e.g., Ward et al., 2009, in the review that follows). Kenny (2011) since has stated, "In the opinion of most though not all analysts, Step 1 is not required" (http://davidakenny.net/cm/mediate.htm updated September 25, 2011; retrieved October 20, 2011). Like any other statistical test, the test of the overall relation between X and Y is an estimate of the population relation and is at risk of Type I and Type II errors. Although useful as an organizing approach to evaluating mediation, the Baron and Kenny (1986) approach is underpowered, increasing the risk of Type II error (not detecting a "true" intervention effect) and requiring much larger sample sizes than more recently developed approaches (Fritz & MacKinnon, 2007). Reliance on causal steps approaches may incorrectly lead researchers to neglect examination of mediating variables if the overall relation between the intervention exposure and the dependent variable is not statistically significant. This is a problem because tests of mediation may have more power than the overall test of intervention effectiveness. In some cases, this difference in power is considerable, especially when effect sizes are small (see Fritz & MacKinnon, 2007, for discussion of this phenomenon). Investigation of mediators also is important even when the overall program effect is not statistically significant because the researcher can gain a better understanding of why the program did not have the intended effect on the outcome.

State of the Science: Promising Mediators of Psychosocial Interventions in Cancer

Our aim in this section is to review published psychosocial interventions in adults with cancer that include specific mediational targets for change proposed to be causally related to psychological and physical health. Eligible trials were those that (a) in a randomized controlled design, tested a psychosocial intervention for adults after cancer diagnosis (psychosocial interventions included psychoeducation [i.e., information provision regarding psychosocial issues such as coping skills, communication] and information provision regarding cancer and cancer treatments, support provision, and cognitive and behavioral approaches [e.g., cognitive therapy, expressive disclosure, hypnosis]); and (b) included some minimal test of mediation. In this regard, a rationale for the mediator and its relation to the outcome variable had to be outlined, a temporal precedence between the intervention and the mediator had to be explicit such that a causal effect was plausible, and the analytic approach had to include a test of the relation of the X to M and the relation of M to Y adjusted for X. We do not include in this review health behavior change interventions (e.g., smoking, physical activity, diet), medical treatment decision-making interventions, or pharmacologic interventions for psychological outcomes in cancer patients, although mediators of the efficacy of such interventions are gaining attention (see, e.g., Courneya et al., 2009; Jackson & Aiken, 2006, with regard to cancer prevention and control behaviors; Moyer et al., in press, for a systematic review of mediators of psychosocial and physical activity interventions in cancer).

Eligible trials were generated in three steps. First, with the aid of an electronic resources medical librarian, we (EHT and ALS) conducted a search in PubMed and PsycInfo for articles published from 1980 through September 2011 using combinations of keywords (e.g., mediat*, mechanism, intervention, psych*, cancer, neoplasm). Second, from a review of the resulting 1,668 unique articles, we (EHT and ALS) selected 65 trials that potentially met the inclusion criteria for full-text examination. Of those, EHT and ALS assessed the trials for eligibility on the first criterion. LJL and DPM assessed for eligibility on the second criterion, yielding 14 unique trials (20 articles) that met criteria. Any disagreement was resolved through discussion by the author group. Trials that were considered but not eligible based on the second criterion either did not establish temporal precedence or did not test the M to Y relation controlling for X. Although analyses correlating changes in M with changes in Y across time can provide useful information in their own right, they do not provide sufficient information to test mediation. Trials in which the researchers examined relations of hypothesized predictors to outcomes across the combined intervention and control conditions (e.g., Fawzy et al., 1990) or solely within the intervention condition (e.g., Andersen, Shelby, & Golden-Kreutz, 2007) were not included. Trials in which mediational analyses were planned but not completed because of lack of significant effects of the intervention on outcomes (e.g., Doorenbos, Given, Given, & Verbitsky, 2006) are not included among the trials listed in Table 1. Third, we checked our selection of trials against that of a systematically generated database of relevant randomized controlled trials of psychosocial interventions for cancer patients, for which a review examining mediators also was being conducted (Moyer et al., 2009, in press). The check resulted

Table 1
Mediational Findings in Randomized Controlled Psychosocial Intervention Trials for Adults Diagnosed With Cancer

Study	Sample	Intervention	Mediators	Main effects: Analyses	Outcome variables	Mediational analyses	Mediators: Results
Andersen et al., 2007	$N = 145$ women with breast cancer, postsurgery, preadjuvant therapy	18 sessions over 16 weeks, 1.5 hr per session; group psychointervention (e.g., training in relaxation, assertiveness, coping skills, health behaviors) intensive phase; 8 sessions, 1.5 hr monthly group maintenance (Control: assessment only)	Emotional distress (POMS), immunity (proliferation of T lymphocytes and T-cell subsets)	ANCOVA & MANCOVA	Functional physical health status and symptoms (KPS and SWOG combined)*	Linear path analysis Mediator effect of X to M and M to Y significant. Sobel test	Decreased emotional distress (but not changes in immunity) mediated the relationship between intervention and improved health/reduced physical symptoms.
Thornton et al., 2009[a]	$N = 45$ women with Stage 2 or 3 breast cancer, postsurgery, preadjuvant therapy, reported clinically significant depressive symptoms	18 sessions over 16 weeks, 1.5 hr per session, group psychointervention intensive phase; 8 sessions, 1.5 hr monthly group maintenance (Control: assessment only)	Depressive symptoms (CES-D: Iowa Short Form), depressed mood (POMS: Depressed Mood subscale), fatigue (POMS: Fatigue subscale), quality of life related to pain (SF–36: Bodily Pain subscale), health behaviors (FHQ; 7D-PAR; smoking status)	Mixed-effects modeling	White blood cell count* Neutrophil count* Helper/suppressor ratio*	Regression Bootstrap confidence intervals for the mediated effect	Depressive symptoms, depressed mood, and pain (but not health behaviors) mediated the relationship between intervention and white blood cell count, neutrophil count, and helper/suppressor ratio. Fatigue mediated the relationship between intervention and helper/suppressor ratio only.
Antoni et al., 2006	$N = 199$ women with nonmetastatic breast cancer, 10–12 weeks postsurgery	10 weekly 2-hr sessions, group cognitive–behavioral stress management intervention (Control: educational seminar)	Confidence about being able to relax (MOCS Relaxation subscale) (Note that CBSM did not affect other measured skills.)	Latent growth-curve modeling	Social disruption (subscales of SIP)* Positive states of mind (PSOM)* Benefit finding (Tomich & Helgeson, 2004)* Positive lifestyle change (AuC)* Positive affect (ABS)*	Latent growth-curve modeling Tested whether the path from X to Y became nonsignificant	Confidence about being able to relax mediated the relationship between intervention and all outcomes.
Phillips et al., 2008[b]	$N = 128$ women with nonmetastatic breast cancer, preadjuvant therapy	10 weekly 2-hr sessions, group cognitive–behavioral stress management intervention (Control: educational seminar)	Perceived ability to relax (MOCS Relaxation subscale)	Linear growth modeling	Serum cortisol levels*	Linear growth modeling Test of relation of X to slope in M and test of slope of slope in M to slope in Y	Perceived ability to relax did not mediate the relationship between intervention and reduction in cortisol.

Table 1 (*continued*)

Study	Sample	Intervention	Mediators	Main effects: Analyses	Outcome variables	Mediational analyses	Mediators: Results
Branström et al., 2010[c]	$N = 70$ women and 1 man with cancer diagnoses who were not currently receiving chemotherapy or radiation	8 weekly 2-hr sessions, group mindfulness training course (Control: waitlist control)	Five-Facet Mindfulness Questionnaire (FFMQ)	MANCOVA	Perceived stress (PSS)* Positive states of mind (PSOM)* Anxiety (HADS)* Depression (HADS)* Posttraumatic stress symptoms (IES-R)*	Regression BK reduction in X to Y relation when controlling for M, joint significance test	Self-reported mindfulness mediated the relationship between intervention and perceived stress, positive states of mind, and IES–Avoidance.
Christman & Cain, 2004	$N = 76$ adults with any stage gynecologic, head, neck, or lung cancer, receiving radiation therapy	(a) Concrete objective information (COI) about treatment-related symptoms delivered via audiotape and writing (b) Relaxation instruction (RI) based on progressive muscle relaxation (two audiotapes) (Control: audiotapes with general education about radiation)	Symptom uncertainty (SUS)	ANCOVA	Household activity, recreation and pastime activity, social activity* (all VAS from SIP), emotional distress (POMS)	Regression BK change in R^2 before and after M was added to the regression model of X to Y	Symptom uncertainty partially mediated the relationship between COI and social activity. (Uncertainty not tested as a mediator of RI on social activity).
Creswell et al., 2007[c]	$N = 60$ women with Stage 1 or 2 breast cancer within 20 weeks after completing treatment	Participants wrote four 20-min essays over 3 weeks and were assigned to either (a) emotional expression or (b) benefit-finding condition (Control: fact writing)	Self affirmation, cognitive processing, discovery of meaning (content coded by three judges)	Regression	Cancer-related medical appointments (self-reported),* physical symptoms (AuC)*	Regression BK, joint significance	Self affirmation (but not cognitive processing or discovery of meaning) mediated the effects of both writing conditions on physical symptoms.
Low et al., 2006[c]	$N = 60$ women with stage 1 or 2 breast cancer within 20 weeks after completing treatment	Participants wrote four 20-minute essays over 3 weeks and were assigned to either (a) emotional expression or (b) benefit-finding condition (Control: fact writing)	Heart rate during writing sessions, essay content analysis; positive emotion words, negative emotion words, cognitive processing words (LIWC), postwriting mood (POMS)	Regression	Cancer-related medical appointments (self-reported),* physical symptoms (AuC)*	Regression BK tested X to M and M to Y	Greater within-session heart rate habituation and use of negative emotion words mediated the relationship between the emotional expression condition and physical symptoms. No other significant mediators.

(*table continues*)

Table 1 (*continued*)

Study	Sample	Intervention	Mediators	Main effects: Analyses	Outcome variables	Mediational analyses	Mediators: Results
Cruess et al., 2000[d]	$N = 34$ women with Stage 1 or 2 breast cancer, < 8 weeks postsurgery	10 weekly 2-hr sessions, group cognitive–behavioral stress management intervention (Control: educational seminar)	Benefit finding (BFS)	ANCOVA	Serum cortisol levels* Distress (POMS–abbreviated)	Path model BK tested X to M and M to Y for significance	Increases in benefit finding mediated the relationship between intervention and reduced cortisol.
Goedendorp et al., 2010	$N = 148$ adults with various cancers	Up to 10 sessions (lasting 1 hr) of individual CBT over 6 months (Control: usual care; Condition 2: brief education intervention)	Physical activity (actometer, DOA, QPA)	ANCOVA	Fatigue (CIS Fatigue subscale)*	Regression, bootstrapped confidence interval for the mediated effect	Physical activity did not mediate the relationship between intervention and fatigue.
Hawkins et al., 2010	$N = 370$ women with breast cancer < 2 months diagnosis	(a) Web-based intervention (reactive information, communication, and interactive components), (b) cancer information mentor (10 phone calls over 6 months) or (c) both Web-based intervention and mentor calls (Control: Internet access)	Autonomy (AuC), competence (AuC), relatedness (AuC)	ANCOVA	Quality of life (WHOQOL-BREF)* significant for Group 3 over control condition	Regression Joint significance test	Greater quality of life in Group c over control was mediated by autonomy, competence, and relatedness.
Helgeson et al., 1999	$N = 312$ women with Stage 1, 2, or 3 breast cancer	8 weekly group sessions of (a) 60-min peer discussion, (b) 45-min education, or (c) combination 45-min education & 60-min peer discussion (Control: assessment only)	T2: Self esteem (RSES), body image (AuC), uncertainty (AuC), extent discuss illness (AuC), negative interactions (AuC), negative downward social comparisons (AuC) T3: intrusive thoughts (IES), avoidant thoughts (IES), personal control (AuC), vicarious control (AuC)	ANCOVA	Mental health (MOS SF–36 MCS),* physical health (MOS SF–36 PCS),* positive mood (PANAS),* negative mood (PANAS)* [effects for Groups b and c]	Regression Significance of X to M and M to Y paths and reduction of X to Y path when M is included	T2: Improved self-esteem (for PCS only) and body image mediated the relationship of Groups b and c with PCS. T3: Intrusive thoughts mediated the relationship between Groups b and c with PCS, MCS, and positive mood. No other significant mediators.

Table 1 (*continued*)

Study	Sample	Intervention	Mediators	Main effects: Analyses	Outcome variables	Mediational analyses	Mediators: Results
Johnson et al., 1989	$N = 84$ men with localized prostate cancer who were about to receive radiation treatment for the first time	4 audio tapes with concrete objective descriptions about radiation treatment and side effects (Control: attention control)	Similarity between experience and expectations (AuC), understanding of the experience (AuC)	ANOVA	Disruption in function (SIP recreation and pastime subscale),* negative mood (POMS)	Regression Drop in R^2 for X to Y relation when M is added	Understanding of the experience and perceived similarity between expectation and experience mediated the intervention's effect on functioning.
Manne et al., 2008	$N = 353$ women with primary gynecological cancer	6 individual sessions (1 hr long) and 1 telephone booster session of (a) communication and coping intervention (CCI) or (b) supportive counseling (SC) (Control: usual care)	Positive appraisal, acceptance, planful problem solving, seeking support for emotional reasons, seeking support for instrumental reasons, emotional processing (COPE and EAC items), general emotional expression (EEQ), cancer-specific emotional expression (EAC items), self-esteem (SES)	Intent-to-treat growth curve analyses	Depressive symptoms (BDI)*	Growth curve modeling, z' and the product of coefficients (P) measure Test of the mediated effect	Increases in positive reappraisal, planful problem solving, self-esteem, and expression of intimacy and positive emotions mediated the effect of CCI on depressive symptoms. Positive reappraisal mediated the effect of SC on depressive symptoms. No other significant mediators.
Montgomery et al., 2010	$N = 200$ women with breast cancer scheduled for breast-conserving surgery	15-min hypnosis session (Control: attention control)	Pain expectancy, nausea expectancy, fatigue expectancy (all VAS), presurgical distress (SV–POMS), presurgical emotional upset, presurgical relaxation	Structural equation modeling	Postsurgical pain,* postsurgical nausea,* postsurgical fatigue* (all VAS)	Structural equation modeling Bootstrapped confidence limits for the mediated effect	Change in pain expectancy (but not distress) partially mediated the relationship between hypnosis and postsurgical pain. Presurgical distress (but not nausea expectancy) partially mediated the relationship between hypnosis and postsurgical nausea. Presurgical distress and change in fatigue expectancy each partially mediated the relationship between hypnosis and postsurgical fatigue.

Table 1 (*continued*)

Study	Sample	Intervention	Mediators	Main effects: Analyses	Outcome variables	Mediational analyses	Mediators: Results
Penedo et al., 2004	$N = 92$ men with Stage 1 or 2 prostate cancer treated with radiation or radical prostatectomy	10 weekly 2-hr group sessions of cognitive–behavioral stress management (CBSM) (Control: educational seminar)	Perceived stress-management skills (MOCS)	Regression	Quality of life (FACT-G)*	Regression Sobel test of the mediated effect	Increase in perceived stress-management skills mediated the relationship between intervention and quality of life.
Penedo et al., 2006[e]	$N = 191$ men with Stage 1 or 2 prostate cancer treated with radiation or radical prostatectomy	10 weekly 2-hr group sessions of cognitive behavioral stress management (CBSM) (Control: educational seminar)	Perceived stress-management skills (MOCS)	Regression	Benefit finding (PCS-Cancer)*, quality of life (FACT-G)*	Structural equation modeling Test of X to M and M to Y paths	Increase in perceived stress-management skills mediated the relationship between intervention and both benefit finding and quality of life.
Traeger et al., 2011[e]	$N = 214$ men with Stage 1 or 2 prostate cancer treated with radiation or radical prostatectomy	10 weekly 2-hr group sessions of cognitive behavioral stress management (CBSM) (Control: educational seminar)	Illness cause, illness consequences, personal control, treatment control, illness coherence (IPQ)	Structural equation modeling	Emotional well-being (FACT-G)*	Structural equation modeling Moderator effect of perceived stress in each group with mediated effect in treatment group	For men with high perceived stress pre-intervention, treatment control and illness coherence together mediated intervention effects.
Scheier et al., 2005	$N = 152$ women with stage 0, 1, or 2 breast cancer, age 50 or younger, within 2 months after completion of nonhormonal adjuvant treatment	4 monthly 2-hr sessions, group psychoeducation (and an active nutrition education arm not examined here) (Control: usual care)	Intrusive thoughts (IES–INT) Self-efficacy for dealing with illness and treatment (AuC) Cancer concerns (30 items from PCBC) Self-concept (AuC) Coping (COPE)	MANOVA & multiple regression	Depressive symptoms (10-item CES-D)* Physical functioning (SF-36: PCS)* Mental health functioning (SF-36: MCS)	Regression Sobel test of significance of mediated effect	Final model: Improvements in intrusive thoughts, self-concept, and self-efficacy for managing cancer-related issues mediated the relationship between intervention and depressive symptoms. Reduction of concerns about cancer recurrence and mortality mediated the relationship between intervention and physical functioning. No other significant mediators.

Table 1 (*continued*)

Study	Sample	Intervention	Mediators	Main effects: Analyses	Outcome variables	Mediational analyses	Mediators: Results
Ward et al., 2008	$N = 150$ adults with pain from metastatic cancer	Single session, individual educational intervention (RIDcancerPAIN) lasting 20–60 minutes with one follow-up phone call (Control: pain education booklet and nurse responded to questions)	Attitudinal barriers to pain management (BQ-II), coping/medication use (PMI)	ANCOVA	Pain severity (BPI, TPQM),* pain interference with life (BPI), overall quality of life (QLI-CV)	ANCOVA Joint significance test	Reduction in attitudinal barriers to pain management mediated the effect of intervention on pain severity.
Ward et al., 2009	$N = 124$ patients with cancer reporting moderate to severe pain and significant other pairs	(a) Single session, solo educational intervention (RIDcancer PAIN+) lasting 20–60 min with one follow-up phone call or (b) same procedures with dyad (Dyad RIDcancerPAIN+) (Control: usual care)	Attitudinal barriers to pain management (BQ–II)	ANCOVA	Pain severity (BPI, AuC), pain interference with life (BPI), global quality of life (G-QOL), negative mood (QLQ–C30), pain relief (single item)	ANCOVA Joint significance test	Reduction in attitudinal barriers to pain mediated the effects of solo and dyad interventions on pain severity, relief, and interference, negative mood, global quality of life.

Note. POMS = Profile of Mood States; KPS = Karnofsky Performance Status; SWOG = Symptom listing used by the Southwest Oncology Collaborative Group; IES–R = Impact of Event Scale–Revised; CES–D = Center for Epidemiologic Studies Depression Scale; MOS SF–36 = Medical Outcome Study Short Form Health Survey; PSOM = Positive States of Mind; FHQ = Food Habits Questionnaire; 7D-PAR = 7-Day Physical Activity Recall; MOCS = Measure of Current Status; SIP = Sickness Impact Profile; AuC = author-constructed scale; ABS = Affect Balance Scale; BFS = Benefit Finding Scale; FFMQ = Five Facet Mindfulness Questionnaire; PSS = Perceived Stress Scale; HADS = Hospital Anxiety and Depression Scale; LIWC = Linguistic Inquiry and Word Count; SUS = Symptom Uncertainty Scale; VAS = Visual Analog Scale; SET = Symptom Experience Tool; CIS = Checklist of Individual Strength; DOA = Daily Observed Activity; QPA = Questionnaire Physical Activity; WHOQOL–BREF = World Health Organization Quality of Life; SF–36 PCS = Physical Component Summary; SF–36 MCS = Mental Component Summary; PANAS = Positive and Negative Affect Scale; EAC = Emotional Approach Coping; EEQ = Emotional Expression Questionnaire; SES = Self-Esteem Scale; BDI = Beck Depression Inventory; FACT–G = Functional Assessment of Cancer Therapy-General; PCS–C = Positive Contributions Scale–Cancer; IPQ = Illness Perceptions Questionnaire; PCBC = Profile of Concerns about Breast Cancer; TOI = Trial Outcome Index; SSQ–6 = Social Support Questionnaire; BQ II = Barriers Questionnaire; TPQM = Total Pain Quality Management item; PMI = Pain Management Index; QLI–CV = Quality of Life Index–Cancer Version; QLQ-30 = Quality of Life Questionnaire. Goedendorp et al. (2010) also included an intervention arm to encourage physical activity, and Scheier et al. (2005) included a nutrition education arm. BK = Baron & Kenny, 1996; Joint Significance = test of relation of X to M and M to Y, adjusted for X; Sobel test = test of mediated effect divided by its standard error. ANOVA = analysis of variance; ANCOVA = analysis of covariance; MANOVA = multivariate analysis of variance.
[a] Primary findings reported in Andersen et al. (2007). [b] Primary findings reported in Antoni et al. (2006). [c] Primary findings reported in Stanton et al. (2002). [d] Primary findings reported in Antoni et al. (2001). [e] Primary findings reported in Penedo et al. (2004).
* Significant main effects of intervention on outcome measure.

in two additional trials that met eligibility criteria, for a total of 16 separate trials (21 articles).

Characterization of Trials

Table 1 contains a description of 16 randomized controlled trials of psychosocial interventions for adults diagnosed with cancer that contained at least minimal criteria for testing mediation. Examination of the table yields several observations regarding the nature of the trials. First, it is apparent that the number of trials that include tests for mediators is very small relative to the number of trials published (Moyer et al., 2009). Two caveats temper this observation. First, although we attempted to be comprehensive in the identification of eligible trials, detection of whether researchers conducted tests of mediation can be difficult; rather than being stated in the abstract or hypothesized in the introduction, tests for mediation often are mentioned in other sections of the article. Second, it is quite possible that researchers planned to (e.g., Doorenbos et al., 2006) or did perform tests of mediation in additional trials, but did not publish those tests, particularly if they did not yield significant findings. Nonetheless, the conclusion seems reasonable that the substantial majority of researchers do not build examination of mediators into randomized controlled trials of psychosocial interventions for adults with cancer.

Second, seven of 16 trials involve women diagnosed with breast cancer, although samples with prostate, gynecological, and mixed cancers are represented. The relative focus on women with breast cancer is reflective of the larger body of psychosocial intervention trials in cancer (Andersen, 2002), which is sensible in light of the fact that this group represents a sizeable proportion of adults diagnosed with cancer in the United States. Some evidence exists that the mediators might act in common across patient genders and specific cancers. An increase in perceived stress management skills (and particularly relaxation skill) mediates the effects of cognitive–behavioral stress management (CBSM) on psychosocial outcomes in both men with prostate cancer (Penedo et al., 2004, 2006) and women with breast cancer (Antoni et al., 2006). Examination of mediators across psychosocial trials for various cancers is needed, as guided by theories positing gender-specific, cancer-specific, or cross-cutting mechanisms for interventions.

Again mirroring the general literature on psychosocial interventions in cancer (Moyer et al., 2009), a third observation is that the 16 trials involve multiple interventions and outcomes; proposed mediators of interventions are similarly diverse. Educational (information provision, psychoeducation) and cognitive–behavioral interventions are most frequent, although systematic relaxation, mindfulness meditation, expressive disclosure, communication-focused approaches, hypnosis, and other interventions are included. The diverse outcomes can be categorized broadly into domains of psychosocial adjustment (e.g., depressive symptoms, quality of life, positive affect, social disruption), self-reported physical health indicators (e.g., physical symptoms, physical functioning, pain), and biological indicators (e.g., immune and neuroendocrine function). The range of mediators includes variables targeted by the intervention (i.e., action theory) or theoretically or empirically linked to the outcome of interest (i.e., conceptual theory).

Mediators of Psychosocial Intervention Effects in Adults Diagnosed With Cancer

Although findings are not entirely consistent and the pool of trials is relatively small, several classes of mediators are promising pathways between psychosocial interventions for adults diagnosed with cancer and psychological and physical health outcomes.

Cognitive expectancies and illness representations. As postulated in theories of self-regulation (Carver & Scheier, 1998; Leventhal, 1970) and stress and coping (e.g., Lazarus & Folkman, 1984) and supported by longitudinal research in adjustment to cancer (see e.g., Stanton & Revenson, 2011), cognitive expectancies and illness representations are central contributors to psychosocial outcomes during chronic illness. Hence, cognitive variables are frequent targets for change in the 16 trials, with generally positive results.

Administered prior to and during radiation therapy for cancer, brief interventions to provide concrete, objective treatment-related information (Christman & Cain, 2004; Johnson, Lauver, & Nail, 1989) affect disruptions in activities in part through bolstering understanding of the experience, lessening uncertainty about symptoms, and decreasing the perceived discrepancy between treatment-related expectancies and experience. Hypnotic suggestions for relaxation, positive imagery, and diminution of postsurgical symptoms can reduce those symptoms through improvement in response expectancies (e.g., expectation of postsurgical pain; Montgomery et al., 2010). Further, an educational intervention directed toward providing credible information to replace misconceptions about cancer pain (i.e., cause, time line, consequences, cure, control representations regarding cancer pain) can reduce attitudinal barriers to pain management, which in turn predict improvement in pain severity and other outcomes (Ward et al., 2008, 2009).

These trials demonstrate that brief (e.g., 15-min, 90-min) interventions administered in person or via audiorecording carry their effects on activity disruption and cancer treatment-related symptoms in part through altering cancer-related expectancies and illness representations. It should be noted that follow-up assessments of dependent variables in these trials did not exceed 3 months following medical treatment completion. A more intensive 20-hr CBSM intervention with prostate cancer patients (Traeger et al., 2011) produced positive effects on cancer-related emotional well-being at 2 weeks after the 10-week intervention. Increases in perceived treatment efficacy and illness coherence (i.e., understanding of the cancer experience) together mediated effects of CBSM on improved emotional well-being, partially buffering the negative effects of high perceived stress on well-being (note that illness representations of perceived cause, personal control over cancer outcomes, and perceived consequences of cancer were not significant mediators).

Self-efficacy for coping and other skills targeted by the intervention. Several trials indicate that participants' increasing use of particular coping processes or other skills targeted by the intervention and participants' increasing confidence (i.e., self-efficacy) that they can use such skills mediate psychosocial interventions' effects on outcomes (see Table 1). Specifically, group mindfulness training improves psychological status by increasing perceived mindfulness skills (Branström, Kvillemo, Brandberg, & Moskowitz, 2010). CBSM that includes relaxation training carries

its effects on psychosocial outcomes (e.g., on quality of life, benefit finding, and positive affect, but not on serum cortisol; Phillips et al., 2008) at least in part through increasing participants' confidence in their ability to relax at will and to use other stress management skills (Antoni et al., 2006; Penedo et al., 2004, 2006). An increase in confidence for managing cancer-related issues mediates the effect of a psychoeducational intervention on depressive symptoms (Scheier et al., 2005). An increase in perceived skills in meeting the psychological needs of health-related autonomy, health care competence, and relatedness mediates the effects of a combined multifaceted Internet- and telephone-delivered intervention on quality of life after the first 6 weeks of intervention (Hawkins et al., 2010). An intervention designed to improve coping and support-recruitment skills (Manne et al., 2008) produces its effects on depressive symptoms primarily via an increase in self-reported coping with the most stressful aspect of the cancer experience through problem solving and positive reappraisal (and self-esteem, as will be discussed later; cf. Scheier et al., 2005, on coping processes). In that trial (Manne et al., 2008), nondirective supportive counseling was (partially) mediated only via an increase in coping with cancer through positive reappraisal, suggesting that skills-based interventions might affect a broader range of mediators than does a nondirective approach.

The findings of Manne et al. (2008) provide some support for the self-reported use of particular coping strategies as mediators. It should be noted, however, that other coping strategies did not evidence significant mediation, and coping strategies were not significant mediators in a psychoeducational trial (Scheier et al., 2005). Theoretically, use of adaptive coping strategies is likely to diminish once they are effective in addressing the stressor (Lazarus & Folkman, 1984). Precise timing of assessment would be required to detect an increase in coping as a mediator. In contrast, once established through intervention, confidence in one's ability to manage the cancer experience might be likely to persist over time and hence be more amenable to measurement. Indeed, self-efficacy for coping and for using other skills targeted by the intervention emerged as a significant mediator not only in the trials reported here, but also in adults diagnosed with other diseases or health problems (HIV, Chesney, Chambers, Taylor, Johnson, & Folkman, 2003; pain, Keefe et al., 2004).

An important observation qualifying these findings is that none of the trials observed actual coping behaviors as mediators, but rather assessed self-efficacy for performing the behaviors or changes in self-reports of the coping processes. For example, indicators of mediators were participants' perceived confidence in using the skill in question (e.g., perceived ability to use muscle relaxation techniques to reduce tension, Antoni et al., 2006) or changes in the self-reported skill (e.g., nonjudgmental awareness of experience, Branström et al., 2010; coping through problem solving, Manne et al., 2008) rather than participants' actual behavioral facility (e.g., arousal reduction, problem solving). Although there is evidence for a connection between the report of self-efficacy for a behavior and successful performance of the behavior (e.g., Beaudoin & Desrichard, 2011; Gwaltney, Metrik, Kahler, & Shiffman, 2009), the question that deserves attention is whether possessing high self-efficacy in and of itself or behavioral instantiation of the specific skills targeted by an intervention is an influential mediator of psychosocial interventions for individuals diagnosed with cancer.

Two studies (Creswell et al., 2007; Low et al., 2006) in Table 1 from one trial (Stanton et al., 2002) might be described as experimental inductions of the specific skills of processing and expressing emotions and of finding benefit in the cancer experience. Stanton et al. (2002) compared experimental induction of written cancer-related emotional processing and expression (EXP) or benefit finding (BEN) with a control condition in which women wrote about the facts of their cancer experience. Main effects of the interventions emerged at 3-month follow-up on self-reported physical symptoms and medical appointments for cancer-related morbidities, suggesting that both cancer-related emotional processing and expression and finding benefit in the cancer experience influence health outcomes. (Also note that an increase in self-reported cancer-related benefit finding [but not a decline in mood disturbance] significantly mediated the effect of CBSM on a reduction in serum cortisol in breast cancer patients; Cruess et al., 2000). In an attempt to elucidate the mechanisms underlying these effects, Low et al. (2006) found that within-session heart rate habituation and greater use of negative emotion words in essays mediated the effect of EXP on the reduction in physical symptoms over 3 months. A second study demonstrated that higher frequency of self-affirmation (i.e., positive reflection on a valued self-domain) mediated the effects of both EXP and BEN on reducing physical symptoms (Creswell et al., 2007).

Psychological and physical symptoms as mediators. Five trials demonstrate that palliation of general or cancer-related psychological symptoms mediates the effect of psychosocial interventions on physical and psychological health outcomes. A hypnotic induction prior to breast-conserving surgery revealed a decline in distress as a mediator on postsurgical nausea and fatigue (but not pain; Montgomery et al., 2010). A reduction in cancer-related intrusive feelings and thoughts mediated the effects of psychoeducational interventions on depressive symptoms and other psychological outcomes in two trials (Helgeson, Cohen, Schulz, & Yasko, 1999; Scheier et al., 2005). In a cognitive-behavioral intervention incorporating several techniques (e.g., relaxation, coping skills education) for nonmetastatic breast cancer patients (Andersen, Farrar, et al., 2007), a reduction in mood disturbance (but not improvement in immunity) at 4 months mediated the effect of the intervention on health status (i.e., composite of functional health status and nurse-rated symptoms or signs) at 12 months. In a secondary analysis of women with elevated depressive symptoms, a reduction in those symptoms (but not health behavior change) at 8 months mediated the effect of the intervention on markers of inflammation (e.g., white blood cell count) at 12 months (Thornton, Andersen, Schuler, & Carson, 2009). A reduction in self-reports of pain also was a significant mediator in that trial.

Dispositional psychosocial resources as mediators. Some lengthier (i.e., 6–14 hr) interventions have targeted presumably more stable psychosocial resources, such as self-esteem and body image, as mediators of effects on psychological outcomes. Three trials (Helgeson et al., 1999; Manne et al., 2008; Scheier et al., 2005) demonstrated that an increase in self-esteem or self-concept with regard to one's body or attractiveness mediates the effects of coping skills or psychoeducational interventions on depressive symptoms or health-related quality of life.

Unsupported mediators. Initial findings provide no evidence that changes in health-promoting behaviors mediates the

effects of psychosocial interventions. Two cognitive–behavioral intervention trials did not reveal health behaviors (e.g., physical activity, diet) as significant mediators on fatigue (Goedendorp et al., 2010) or inflammatory markers (Thornton et al., 2009). However, neither trial focused on changing health behaviors as a central component of the intervention.

Recommendations for Future Research

The impressive range of theoretical approaches, mediators, and outcome measures in the studies we reviewed confirms that many investigators are attempting to integrate theory, research, and practice by addressing how psychosocial interventions for cancer patients work. We also noted a variety of approaches to investigating mediation. Although all of the studies provide a valuable contribution toward the goal of understanding mechanisms of intervention effects, in many cases additional useful information could have been obtained had more accurate or powerful approaches to testing mediation been applied. Several studies included suboptimal tests for mediation, in part owing to the reliance on the causal steps method (Baron & Kenny, 1986), which has been supplanted in recent years by more accurate and more powerful methods. One common misconception was that a statistically significant overall intervention effect on the outcome is required in order to pursue mediation analyses, as originally suggested by Baron and Kenny (1986). Although the test of the overall intervention effect is the primary test of any intervention trial, analyses of mediation can provide useful information even in the absence of a significant direct effect of the intervention. Of the 16 trials, one study that failed to find an overall intervention effect took the additional step of evaluating mediators (Ward et al., 2009).

Another common misconception was the belief that a decrease in the statistical significance (or variance accounted for) of the X-to-Y relation after inclusion of the mediator in the equation is sufficient to conclude mediation. Although consistent with mediation, there can be reasons for such a decrease that would not support mediation (e.g., by chance). Further, the amount of the decline may not be statistically significant, the determination of which requires a test of the significance of the mediated effect. In the following, we highlight "best practices" in mediation for intervention research.

Specification of Theory

One important characteristic of exemplary studies is the clear specification of theory for how the intervention would achieve effects on outcome variables by describing both the conceptual theory for which mediators are causally related to the outcome and the action theory for how the intervention affects selected mediators. For example, Johnson et al. (1989) employed stress and coping theory (Lazarus & Folkman, 1984) and self-regulation theory (Leventhal, 1970) to support hypotheses about the causal relationship between mediators and outcome. An important aspect of the specification of the action and conceptual theory is the identification of variables that may confound observed relations in a study. If these confounding variables are omitted, then observed mediated effects may be caused by the omitted influences and not those hypothesized on the basis of theory. Specification of possible confounding variables is one of the most challenging aspects of

mediating variable research because randomization supports causal interpretation of intervention effects on mediators and outcomes, but it does not lead to causal interpretation of relations of the mediators to the outcome. The value of the mediator is not randomly assigned.

Temporal Precedence of X to M to Y

Mediation assumes a temporal precedence in which X precedes M, and M precedes Y. The studies we reviewed were generally explicit in theory relating each variable to the others, but few explicitly addressed corresponding theory for *when* mediators and outcomes would change in response to the intervention, or the temporal relations among the intervention, mediator, and outcome. Although there may be logistic challenges, a measurement protocol that uses theory to dictate when measures are obtained is preferable to measurement intervals based on convenience. Johnson et al. (1989) provide a good example of a conceptual approach to timing the assessment of the mediator (similarity of expectation and experience, understanding of experience) relative to the content of the intervention.

All of the studies had baseline and at least one follow-up measure in order to assess change in intervention and control conditions for both mediators and outcomes. In this way, intervention-induced change in the mediator can be related to change in the outcome. However, the temporal precedence of the mediator to the outcome is less clear when the mediator and outcome are measured at the same time. Such contemporaneous relations are important and can provide some evidence that the mediator is related to the outcome. But an ideal study would obtain at least three repeated measures to assess whether changes in the mediator between earlier waves predicts change in the outcome at later waves. For example, Antoni et al. (2006) used three waves of data and fit growth curve models to assess mediation, thereby modeling change in these variables, but the relation of change in the mediator to change in the outcome was not assessed. Phillips et al. (2008) used latent growth modeling to evaluate perceived ability to relax as a mediator of the effects of a stress management intervention on serum cortisol. Four or more waves can further clarify preintervention trends and the timing of linear and nonlinear changes in the mediator and outcome. In addition to latent growth curve models, alternative longitudinal mediation models such as autoregressive and latent change score models are available to help clarify the relations among variables (see Cheong, MacKinnon, & Khoo, 2003; Cole & Maxwell, 2003; Fritz & MacKinnon, 2011; MacKinnon, 2008; Maxwell & Cole, 2007). Latent growth and change score models are ideal when there is growth over time in measures studied, and they provide a framework to model a wide variety of linear and nonlinear change over time. Autoregressive models, which allow for detailed examination of different mediated effects over time, are most suitable when there is not growth over time in measures (MacKinnon, 2008).

Use of Methods With Increased Statistical Power

Recent statistical advances suggest methods for mediation that have more power and more accurate Type I errors than the causal steps method (Baron & Kenny, 1986). Many studies we reviewed used a test based on the assumption that the distribution of the

mediated effect is normal (Sobel, 1982), but this test can be underpowered because the assumption is inaccurate (see MacKinnon et al., 2002, 2004). Ideal tests of significance account for the nonnormal distribution of the estimate of the mediated effect by using the distribution of the product or bootstrapping methods instead of the normal distribution (MacKinnon et al., 2004).

One straightforward method for testing mediation is to test jointly whether there is a significant relation of X to M and whether there is a significant relation of M to Y, adjusted for X. These two tests, known as the *joint significance test* (MacKinnon et al., 2002), have good power and accurate Type I error rates in simulation studies. Hawkins et al. (2010) provide an example of the joint significance test for mediation. Joint significance tests can be difficult to apply in more complicated models, however, such as models in which the total mediated effect through multiple mediators is assessed.

A more general test of mediation, which is useful for a simple or complex mediation model, is to estimate the indirect effect and generate confidence limits for it using one of two methods that more accurately accommodate its distribution. First, because the product of two normal variables is not normally distributed, statistical analysis using the distribution of the product of the a and b coefficients provides more accurate confidence limits and statistical tests than traditional tests of significance (MacKinnon et al., 2004). The second method uses bootstrapping to form the confidence limits. The bootstrapping method is more general and applies to any mediated effect model, including more complex models that include longitudinal and multilevel data. The use of bootstrapping is exemplified by Montgomery et al. (2010) in their test of mediators of a hypnosis intervention on side effects after breast surgery. These methods have the most power to detect mediated effects as well as to provide accurate confidence intervals.

Consideration of Multiple Mediators

It is likely that multiple mediators are present in intervention research; including a modeling approach that combines multiple mediators is ideal. For example, Andersen, Shelby, et al. (2007) evaluated emotional distress and immunity as mediators of an intervention effect on health status in a path analysis model. It is good practice to evaluate each putative mediator in a separate model, but additional information can be gained by combining mediators into a single multiple mediator model. Although this adds a layer of complexity, statistical methods exist for evaluating multiple mediators by estimating a comprehensive path analysis model that simultaneously estimates all relations in a hypothesized multiple mediator model including mediated effects through different mediators (Bollen, 1987; MacKinnon, 2008). Multiple mediators may also exist in a sequence or chain of relations such that the intervention changes one mediator, which changes another mediator, which then affects an outcome (Taylor, MacKinnon, & Tein, 2008). Theory and empirical research can help guide these complex multiple mediator models that reflect chains of relations among variables in a research study. Path analysis and structural equation modeling are the methodological areas where more information on these comprehensive mediation models can be obtained (Bollen, 1989).

Consideration of Moderators

Although not a focus of this review, there may be subgroups of individuals who respond differentially to intervention effects. Moderator variables may be static characteristics of study participants such as sex and age, or they may be variables that can change such as stress perceptions or baseline measures of mediator and outcome variables. These moderator effects may have different mediated effects such that the process of intervention change in one group may differ from intervention change in another group (for example, see Traeger et al., 2011). Although models that combine moderation and mediation (J. R. Edwards & Lambert, 2007; Fairchild & MacKinnon, 2009; Morgan-Lopez & MacKinnon, 2006; Preacher, Rucker, & Hayes, 2007) can be quite complex, they more accurately describe the real effects of interventions (MacKinnon, 2011).

Recent Developments in Mediation Analysis

The most recent developments in mediation analysis focus on the evidence necessary for causal claims (MacKinnon, 2008). With randomization of participants to intervention and control groups, causal estimates of the program effect on the mediator and the program effect on the outcome are obtained. However, the effect of the mediator on the outcome variable is not a causal effect unless certain assumptions are made because the mediator is not directly randomized. In particular, omitted variables may exist that predict the mediator and the outcome such that the observed relation between the mediator and outcome is not causal but rather occurs because both variables are related to an unmeasured confounder.

Several new methods outline the criteria for identifying mediation and provide methods to assess the sensitivity of results to omitted confounding variables (Imai, Keele, & Tingley, 2010; VanderWeele, 2010; VanderWeele & Vansteelandt, 2009). For example, these sensitivity analyses make it is possible to ascertain the size of the relation of a confounder to mediating and outcome variables that is necessary to make an observed effect become zero. Other recent developments outline experimental methods to investigate mediated relations in a program of research (Imai, Tingley, & Yamamoto, in press; MacKinnon & Pirlott, 2009; Ten Have et al., 2007). For example, the use of designs to block or enhance action of a mediating variable provides randomized evidence consistent with theoretical mediating processes. Generally, a multifaceted approach consisting of action theory and conceptual theory to improve interventions systematically, replication and extension studies, qualitative data, and clinical judgment are necessary for the identification of mediating processes and underlying mechanisms.

Conclusions

Mounting interest in how psychosocial interventions work to improve quality of life and health for individuals diagnosed with cancer and development of relevant quantitative methods have catalyzed investigation of mediators of such interventions. Taken together, findings of the 16 trials that met eligibility criteria suggest that psychosocial interventions in adults diagnosed with cancer produce benefit at least in part through effectively altering

cancer-related expectancies and illness representations, self-efficacy for using coping strategies and other skills targeted by the intervention, psychological and physical symptoms (e.g., mood disturbance, pain) related to cancer, and dispositional psychosocial resources (e.g., self-esteem).

Several points from these studies can inform future research. First, the trials demonstrate that it is possible to put hypothesized mechanisms of therapeutic interventions to direct test. Second, such tests hold promise for illuminating fundamental mechanisms that cut across effective interventions. Enhancement of self-efficacy for managing aspects of the cancer experience might constitute one such mechanism. Valuable next steps will entail specifying intervention components that best promote self-efficacy (e.g., Ashford, Edmunds, & French, 2010) and illuminating the link between self-efficacy and successful performance of acquired skills. As another example, physiological and psychological (e.g., learning to tolerate cancer-related emotions) habituation at least partially underlies effects of relaxation (Antoni et al., 2006), expressive disclosure (Low et al., 2006), and mindfulness (Hölzel et al., 2011; note that if simple exposure and habituation to cancer-related content were at play, then the Stanton et al. 2002 control condition itself should produce benefit, and it did not). Third, addition of behavioral and biological indicators of proposed mediators (e.g., behavioral and physiological indicators of the ability to relax) would supplement self-report measures (e.g., relaxation self-efficacy) to aid in identification of underlying mechanisms. Fourth, some potential mediators of psychosocial interventions have received very little empirical attention, including physiological processes (e.g., reduction in inflammation or sympathetic arousal), health behaviors, and interpersonal processes (e.g., gain in emotional support). Finally, the observation that so few published trials include tests of mediation leads us to speculate that many mediational analyses remain in the proverbial file drawer. Firm theoretical and empirical grounding of hypothesized mediators, comprehensive reporting that includes the magnitude of mediated effects as well as hypothesized but unsupported mediators, and direct experimental manipulation of postulated mediators will produce stronger evidence of key mediators of specific psychosocial interventions for adults diagnosed with cancer.

Although we identified several promising classes of mediators, the relatively small group of relevant trials and their diversity with regard to interventions, outcomes, and proposed mediators support our observation that much remains to be learned. For interventions still in the design phase, we encourage consideration of measurable and modifiable mediators prior to implementation. Along with research to identify predictors of quality of life and health in cancer survivors, action theories and conceptual theories can provide essential grounding for selecting, testing, and interpreting findings regarding mediators. Considerable additional work often is required, however, including specification of contributors to the mediator through additional longitudinal and experimental research. Deriving from theory and empirical evidence (e.g., Bower et al., 2011; Broadbent, Ellis, Thomas, Gamble, & Petrie, 2009; Chesney et al., 2003; Graves, 2003), one would expect that distinct mediators might exist for particular interventions and specific outcomes. Identification of cross-cutting, fundamental mechanisms of psychosocial interventions also deserves attention (e.g., Carey, 2011; DeRubeis, Siegle, & Hollon, 2008; Hölzel et al., 2011; Wilamowska et al., 2010).

We suggest that there is too little cross-talk among theorists, researchers who conduct experimental and longitudinal predictive investigations, and investigators who conduct clinical trials, resulting in missed opportunities to make full use of available knowledge to promote positive outcomes in individuals with cancer and their interpersonal milieu. Theories and investigations of risk and protective factors for adjustment to cancer, experimental manipulations of putative mechanisms, and randomized, controlled trials of psychosocial interventions that include tests of mechanisms can be reciprocally enhancing. Although much progress has been made in developing methods for investigating mediators of intervention effects, in practice mediation analyses can be quite complex. Complicating issues include the specification of action theory and conceptual theory, specification of moderators of effects, theory for temporal change in mediators and outcomes, consideration of confounds, and application of state-of-the-art statistical techniques. Despite these challenges, it is our hope that the present call for careful evaluation of mediating variables can help integrate theory, research, and practice by focusing attention on modifiable risk and protective factors to influence quality of life and health in individuals who face a cancer diagnosis and their loved ones.

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