Biobehavioral Outcomes Following Psychological Interventions for Cancer Patients

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Psychological interventions for adult cancer patients have primarily focused on reducing stress and enhancing quality of life. However, there has been expanded focus on biobehavioral outcomes—health behaviors, compliance, biologic responses, and disease outcomes—consistent with the Biobehavioral Model of cancer stress and disease course. The author reviewed this expanded focus in quasi-experimental and experimental studies of psychological interventions, provided methodologic detail, summarized findings, and highlighted novel contributions. A final section discussed methodologic issues, research directions, and challenges for the coming decade.

Cancer remains a significant national problem, with over 1 million Americans diagnosed each year. The adjustment process for cancer survivors may be burdensome and lengthy, and deteriorations in quality of life are underscored if they also have adverse health effects. A previous review noted the significant quality-of-life gains that can be achieved with psychological interventions (Andersen, 1992), a conclusion echoed here. In this review, I look more broadly and include biobehavioral responses and disease outcomes as areas important for intervention efforts. Although there are proportionately fewer studies that have included the latter, multimodal interventions and assessment of psychological, behavioral, and biologic mechanisms are the pathways for future research.

The Biobehavioral Model of cancer stress and disease course (Andersen, Kiecolt-Glaser, & Glaser, 1994) provides the organizational framework for the discussion. Represented in Figure 1, the model includes psychological (e.g., stress and quality of life), behavioral (e.g., health behaviors and compliance), and biologic (e.g., neuroendocrine and immune) components and specifies the pathways by which health outcomes (e.g., disease endpoints—recurrence, disease free interval) might be affected. A complete discussion of the model is available elsewhere (Andersen et al., 1994), as only brief summaries are provided prior to each section.

Studies conducted since 1992 with adult cancer patients are reviewed; selected investigations prior to that period are included because of their importance, novelty, or absence from the earlier article focusing on quality of life (Andersen, 1992). Each compo-

nent of the model is considered as an outcome following psychological interventions. Prior to each, I review descriptive findings and highlight prominent correlational investigations. For all experimental studies, accrual and retention rates and patient characteristics are provided, as these areas are in need of methodologic attention, as discussed later in the article. Although tedious at times, specific techniques of interventions are provided to enable the reader to distinguish among those with similar labels. Quasi-experimental designs are included for emerging areas. With few exceptions, all studies included psychological outcomes, but in the first section, I focus on studies with only these endpoints.

Stress and Quality-of-Life Outcomes

Severe, acute stress occurs at the time of cancer diagnosis (Maunsell, Brisson, & Deschenes, 1992; McBride, Clipp, Peterson, Lipkus, & Demark-Wahnefried, 2000); however even after lengthy, difficult treatments have ended, individuals may still report disruptions in major life areas and, for some, chronic stress (Cordova et al., 1995). If not remediated, acute or chronic stress may contribute to emotional distress, life disruptions, and, in turn, to a stable, lower quality of life (see Figure 1). Cancer survivors report continuing problems with emotional distress, fatigue, reduced energy, and loss of stamina (Broeckel, Jacobsen, Balducci, Horton, & Lyman, 2000; Michael, Kaqwachi, Berkman, Holmes, & Colditz, 2000). Permanent sequelae from cancer treatments have the potential to impact intimate relationships, social support, and even heighten emotional distress (Ey, Compas, Epping-Jordan, & Worsham, 1998; Ganz et al., 1996; Hagedoorn et al., 2000; Spencer et al., 1999; Stegina et al., 2001). Finally, a cancer history can also result in financial difficulties, jeopardize insurance coverage, and narrow employment options, as one fifth of cancer survivors report these chronic, stressful, economic difficulties (Hewitt, Breen, & Devesa, 1999). In sum, when left untreated, stress and lowered quality of life conspire to produce a difficult trajectory on the road to cancer survivorship (Gotay & Muraoka, 1998; Green et al., 2000).
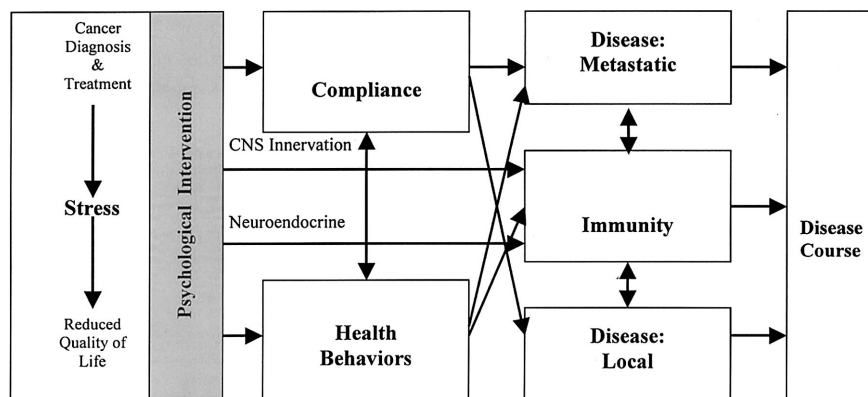
Figure 1. The biobehavioral model of the psychological (stress and quality of life), behavioral (compliance and health behaviors), and biologic pathways from cancer stressors to disease course. Psychological interventions may moderate the effect of adverse psychologic, behavioral, or biologic responses on disease outcomes. CNS = central nervous system. Adapted from "A Biobehavioral Model of Cancer Stress and Disease Course," by B. L. Andersen, J. K. Kiecolt-Glaser, and R. Glaser, 1994; *American Psychologist,* p. 390. Copyright 1994 by the American Psychological Association. Adapted with permission.

Experimental Designs

Pretest–posttest control group designs. Larsson and Starrin (1992) compared the effectiveness of relaxation training for breast cancer patients undergoing radiotherapy with no treatment. Accrual rate was not provided; 64 consecutive breast cancer outpatients were randomized, and there was only 3% attrition. Disease characteristics of the sample were not provided. Those in the intervention condition were given 15 min of instruction, an audiotape, and encouragement to practice. Analyses revealed significant differential improvements for the relaxation group on measures of daily hassles (Kanner, Coyne, Schaefer, & Lazarus, 1981), mood (Andrews & Withey, 1976), and appraisal of radiation therapy as less threatening (Larsson, 1987). There were no significant effects on measures of daily uplifts (Kanner et al., 1981), other treatment appraisal aspects (e.g., treatment as challenging; Larsson, 1987), or cognitive coping strategies (Larsson, 1989).

Marchioro et al. (1996) compared individual cognitive psychotherapy and added family counseling with no treatment for women with breast cancer. The intervention included weekly 50 min therapy sessions, focused on changing dysfunctional coping behaviors and depressive thoughts, and included bimonthly family (partner and/or close relatives) counseling sessions; the total number of therapy hours was not provided. The accrual rate was 90%, and 36 women (stage characteristics not provided) were randomized within age strata. Assessments were conducted prior to surgery and at 1-, 3-, 6-, and 9-month follow-up; attrition was not reported. Repeated measures analysis of variance (ANOVAs) revealed significant effects, with the intervention group reporting fewer depressive symptoms (Beck Depression Inventory; Beck, Ward, Mendelsohn, Mock, & Erbaugh, 1961) and higher quality of life (Function Living Index for Cancer [FLIC]; Schipper, Clinch, McMurray, & Levitt, 1984).

Rutter, Iconomou, and Quine (1996) conducted a novel study. An abbreviated time-series design was used to test physician communication training as a strategy to reduce patient distress. Patients were treated by physicians prior to or following their communication training. One hour and 15 min training and a handbook on improving the structure and style of their patient interactions were provided. On the basis of work by Ley (1988), training included cognitive aids to understanding (e.g., simplification, repetition) and emotional aspects (e.g., conveying warmth, listening, giving feedback). Trained physicians also provided patient information booklets describing adjuvant treatments to encourage patient participation and perceived control. Accrual rate was 80%, and 36 patients participated; the majority had solid tumors, with 64% having advanced disease. All patients were assessed pre and post their physician consultation for adjuvant therapy. A consecutive series of 18 control patients was seen by three physicians prior to their training. Then physician training was completed, and data were gathered from the next 18 patients of the same physicians. A mixed-model ANOVA revealed a significant effect for time, with all patients reporting reductions in anxiety (State–Trait Anxiety Inventory [STAI]; Spielberger, Gorsuch, & Lushene, 1970). Of more importance, analyses revealed a significant interaction, with patients seen following physician training reporting fewer depressive symptoms (Beck & Beck, 1972) and higher levels of satisfaction and personal control. On experimenter measures, the physicians were evaluated as more cognitively skilled following their training than before.

McQuellon et al. (1998) compared a brief orientation for patients new to a medical oncology clinic with no treatment (no orientation) for a heterogeneous sample of cancer patients. The 15–20-min tour by a master's-level psychologist included reception, phlebotomy, nursing, and chemotherapy areas, written materials on clinic hours and procedures, and a question-and-answer session. The accrual rate was 65%, and 180 patients were randomized with 83% retained for the postintervention (1 week) assessment. Repeated measures ANOVAs revealed significant effects, with intervention patients reporting lower state anxiety (STAI), less mood disturbance (Profile of Mood States [POMS]; McNair, Lorr, & Droppleman, 1971), and fewer depressive symptoms (Center for Epidemiologic Studies measure of Depression [CES–

D]; Burnam, Wells, Leake, & Landsverk, 1988). On experimenter-derived measures, intervention patients reported significantly more knowledge of clinic procedures, greater confidence in their physicians, higher levels of satisfaction, and higher levels of hope regarding their illness.

Fukui et al. (2000) attempted to replicate the Fawzy and colleagues study (Fawzy, Cousins, et al., 1990) with Japanese breast cancer patients. Women with Stage II or III disease, 65 years of age or less, and without a psychiatric history were eligible, and 50 women were accrued (33%), with 92% of the sample retained. Participants were significantly older ($M = 53$ years) than nonparticipants ($M = 50$ years). Consistent with Fawzy (Fawzy, Cousins, et al., 1990), intervention components included health education, coping-skills training, stress management with progressive muscle relaxation and audio tapes, and group support; patients met for 1.5 hours weekly for 6 weeks (9 therapy hr). The POMS, anxiety and depression measures (Hospital Anxiety and Depression Scale; HAD; Zigmond & Snaith, 1983), and the Mental Adjustment to Cancer scale (M. Watson, Greer, Young, Inayat, & Burgess, 1988) were administered at pre- and posttreatment and at 6-month follow-up, but analyses revealed no significant Group × Time interactions.

Antoni et al. (2001) reported on the effects of cognitive–behavioral stress management (CBSM) group intervention for women with breast cancer. Accrual rates were not available as women were self-referred, responding to mailings and postings. Those with a psychiatric history were excluded, and 136 women with in situ disease or Stage I or II breast cancer were randomized to 10 weekly group sessions of CBSM (20 therapy hr) or a control condition of abbreviated CBSM instruction (6 hr). The intervention included didactic and experiential exercises of making positive social comparisons for coping, using social support, emotional expression, assertion training, and progressive muscle relaxation. The control condition received this information in a 6-hr instructional format. With a 74% retention rate, analyses were completed with postintervention and 3- and 9-month follow-ups. Analyses revealed no significant Group × Time interactions on the distress measures (i.e., POMS: CES–D; Comstock & Helsing, 1976, or the Impact of Event Scale [IES]; Horowitz, Wilner, & Alvarez, 1979). In contrast, the analyses suggested significant, differential gains for the intervention subjects in an experimenter-derived measure of patients' self reports of benefits from cancer. Post hoc analyses tested the effects of an individual difference variable, optimism, moderating the effects of the intervention on the benefits measure. The greatest change in positive benefits was reported by the women in the intervention condition who were low in optimism.

Allen et al. (in press) reported outcomes for a randomized study of a cognitive–behavioral problem-solving intervention compared with no-treatment controls for young women (age < 50 years; $N =$ 164) with Stages I–IIIA breast cancer. Treatment was conducted individually, with Sessions 1 and 6 in person and Sessions 2–5 on the telephone. The control participants ($n = 77$) received only the regular assessments. The intervention, including problem orientation, problem definition, generation of alternatives, decision making, and solution implementation and verification stages, was taught in the first session with the remaining sessions for clarification and maintenance. Women were also provided with written information on body image, sexuality, family relationships, interaction with medical providers, and survivorship concerns. Total

intervention time was not provided, although it was at least 4 hr excluding the telephone calls. Women were accrued from three locations/hospitals during a 3-year period with the overall accrual rate being 90%; women were randomized within hospital site and presence or absence of significant-other strata. Pretreatment and 4- and 8-month follow-ups were conducted; by 8 months, there was 9% attrition. Analyses indicated significant group differences in favor of the intervention at 4 months on the SF-36 mental health scale (Ware, Snow, Kosinski, & Gandek, 1993) and on an experimenter measure of unmet needs for assistance; there were no differences at 8-months, however. Null effects were found at both follow-ups for the remaining measures: Cancer Rehabilitation Evaluation System (Schag, Heinrich, Aadland, & Ganz, 1990), the IES, and the Social Problem-Solving Inventory (D'Zurilla & Nezu, 1990). Post hoc analyses suggested that the intervention was effective only for women entering the study with a moderate level of problem-solving ability, whereas outcomes were actually negative for women with either low or high problem-solving skills at the initial assessment.

Factorial designs. McArdle et al. (1996) conducted a 2 × 2 design to compare the effects of supportive nursing care with support from a cancer patient volunteer on reducing distress for breast cancer patients. The four conditions were nurse support only, support from a cancer patient volunteer only, combined nurse and volunteer support, and no treatment (routine care). Nurse support, provided by a nurse practitioner, consisted of delivery of preoperative medical information (20–30 min) and follow-up postoperative visits as needed. In contrast, those receiving volunteer support were visited postsurgery and provided written materials (content not provided). Volunteers were trained in transactional analysis theory; however, it is unclear how this training influenced the content or methods of volunteer support. Accrual rate was 100% ($N = 272$), as patients were enrolled without informed consent. Information on disease stage was not provided, but nodal status and treatment information suggested that approximately 50% had Stage I breast cancer. Assessments occurred at the first postoperative visit and then at 3-, 6-, and 12-month follow-ups, although follow-up data were collapsed for the analyses. Group comparisons indicated significant improvements for the nurse support condition only on self-report measures of general health (General Health Questionnaire; Goldberg, 1979) and depressive symptoms, although there were no group differences on anxiety symptoms ((HAD). Unfortunately, distress for the two groups treated by volunteers was equivalent to, if not worse than, that of the no-treatment group.

Helgeson, Cohen, Schulz, and Yasko (1999) conducted a 2 × 2 factorial design comparing the effects of education with peer discussion for women with breast cancer. The four conditions were education only (ED), peer discussion only (PD), education plus peer discussion (ED/PD), or no treatment. All intervention conditions, facilitated by an oncology nurse and social worker, met for 8 consecutive weeks, although duration of therapy time differed across conditions with 6 hr for ED, 11 hr for PD, and 17 hr for ED/PD. The ED intervention provided information about the disease and treatment with strategies for managing treatment morbidity (e.g., nutrition, exercise, body image) and facilitating control and provided relaxation training and an audiotape; the group meetings were lectures only and group discussion was discouraged. Unlike ED, PD encouraged expression of positive and neg-

ative feelings among the patients, and workbooks were provided to record feelings and thoughts during the week. The accrual rate was 70%, and 312 women with Stage I (25%), II (69%), or III (6%) breast cancer were randomized; attrition by 2 years was in the range of 10%. Validity check data indicated that women in the ED and ED/PD groups acquired more information about breast cancer and its treatment than women in the PD and control groups. Also, women in the PD condition were more likely to have maintained contact with other group members than were women in the other conditions.

Repeated measures ANOVAs of posttreatment data revealed a main effect for education, with significantly better physical aspects of quality of life (SF-36) at posttreatment and at follow-up and additional significant effects of positive affect at follow-up (Watson, Clark, & Tellegen, 1988). There was no main effect for peer support or for interactions of the factors at posttreatment or follow-up. Additional analyses suggested the education condition resulted in higher levels of self-esteem, lower illness uncertainty, and more discussions about the illness, whereas the women in the peer discussion groups reported more negative interactions with family members. Finally, women in the education conditions reported significantly higher levels of control and fewer intrusive thoughts, whereas women in the peer conditions reported significantly more avoidant thoughts. Post hoc analyses of these data examined individual differences in social support (Helgeson, Cohen, Schulz, & Yasko, 2000). The level of partner support interacted with intervention condition; women with low levels of support responded positively to both interventions, whereas women with high levels of support were unaffected by the education but adversely affected by the peer support groups. Parallel outcomes were found with an experimenter derived measure of oncologist informational support.

Finally, long-term follow-up data revealed similar outcomes (Helgeson, Cohen, Schulz, & Yasko, 2001). Two sets of one-way analyses were provided: Contrasting all intervention conditions collapsed versus the control and each intervention condition versus the control, with both analyses collapsed across five assessments, from posttreatment (2 weeks following the intervention to 3 years posttreatment. (Thus, this article incorporates data from Helgeson et al., 2000 with data from Years 1–3.) Group differences lessened with time. Comparison of intervention (all groups) with control revealed significantly higher scores on the Vitality, Social Functioning, and Bodily Pain scales of the SF-36. Only the ED group showed significant differences from the control condition, with significantly higher scores for the ED group on the SF-36 scales of Vitality, Bodily Pain, and Physical Functioning.

Summary

Intervention participants have been, predominantly, women with breast cancer. Only two studies included heterogeneous samples (McQuellon et al., 1998; Rutter et al., 1996), although significant effects emerged even with their small sample sizes (e.g., $N = 36$ in Rutter et al., 1996). The samples from the United States remained primarily Caucasian, with minorities underrepresented among participants and/or overrepresented among refusers (e.g., McQuellon et al., 1998), with the exception of Antoni et al. (2001), which had a sample that was 26% minority. An important indication of the universality of these issues is the international repre-

sentation, with studies from the United Kingdom (McArdle et al., 1996; Moorey, Greer, Bliss, & Law, 1998), Sweden (Larsson & Starrin, 1992), Italy (Marchioro et al., 1996), Greece (Rutter et al., 1996), and Japan (Fukui et al., 2000). This characteristic is also mirrored in the studies of other responses and outcomes; I note non-U.S. study participants in the studies to follow.

Drawing general conclusions about the efficacy of "psychological interventions" is made difficult by their heterogeneity. They appear to include "all of the above," including relaxation training alone (Larsson & Starrin, 1992), individual (Allen et al., in press; Marchioro et al., 1996), group (Antoni et al., 2001), cognitive–behavioral therapy (CBT) replication efforts (Fukui et al., 2000), clinic orientation (McQuellon et al., 1998), disease/treatment educational interventions (Helgeson et al., 2000; McArdle et al., 1996), and indirect efforts to impact patients' adjustment through physician training (Rutter et al., 1996). Two factorial designs tested different strategies of using peer support, either in a group format (Helgeson et al., 1999) or with individual counselors (McArdle et al., 1996), but both interventions had null effects for peer support and, in fact, some negative outcomes when compared with educational interventions. Researchers have used a no-treatment comparison condition, with the exception of Antoni et al.'s (2001) abbreviated treatment.

Investigations began during the earliest days of the cancer experience (e.g., first clinic visits). Stress is then at its highest, but for the majority of patients it will dissipate rapidly (e.g., Antoni et al., 2001), making intervention effects difficult to detect. When patients are accrued months after cancer therapy has ended, effects are similarly difficult to achieve (e.g. Fukui et al., 2000). However, it has been found that, in general, interventions produce significant reductions in distress (see also Sheard & Maguire, 1999, for a meta-analysis and discussion) at posttreatment. Effects, however, may be transitory, as intervention and control conditions may be equivalent at follow-up. This implies that repeated measure designs require more power to detect late effects, as distress continues to decline for all patients and group differences are smaller. Power can be further challenged with attrition, as the causes (e.g., death, disease progression, noncompliance, dropout) are varied and rates can be high.

Compliance

The Biobehavioral Model suggests compliance as one behavioral route to impact disease outcomes (see Figure 1). Compliance might be improved directly, such as with a patient education component so that patients have greater knowledge and ability to be compliant. Or compliance might be influenced indirectly, as when psychological interventions improve patient moods and emotions or reduce the occurrence or severity of treatment side effects (e.g., nausea or vomiting) so that patients are more accepting or tolerant of treatment regimens, particularly those with added toxicity (Redd, Montgomery, & DuHamel, 2001). Compliance with chemo- and radiotherapy is reviewed.

A search of the literature revealed no studies of the factors governing treatment refusals, premature terminations, or receipt of fewer radiation sessions than prescribed, even though these circumstances do, indeed, occur (Vokes et al., 2000). This is surprising, as regimens for some disease sites (e.g., vulva, head/neck, or lung cancers) deliver high doses, combine radiotherapy with che-

motherapy, and/or incur considerable toxicity (e.g., skin reactions including burning, pain; Huang, Wilkie, Schubert, & Ting, 2000). Refusal of therapy, which directly impacts control of local or distant control of the disease, has been reported (Vokes et al., 2000).

Chemotherapy noncompliance can similarly hasten recurrence or death. The Budman et al. (1998) data provided a clear demonstration of the effects of lowering the prescribed dosage of chemotherapy. They reported that women who received a high- or moderate-dose intensity[1] of a standard chemotherapy regimen (i.e., cyclophosphamide, doxorubicin, and 5-fluorouracil) for Stage II breast cancer had a 77%–79% likelihood of 5-year survival versus only a 66% likelihood of 5-year survival for women receiving a low-dose intensity. Similar data were reported earlier (e.g., Bonadonna & Valagussa, 1981). Despite the thousands of cancer patients entered in chemotherapy trials (and the hundreds of thousands treated off protocol) each year, there are few reports of the interaction of quality-of-life variables and the acceptability or compliance with cancer therapies. Some Phase I or II[2] chemotherapy studies have examined these variables, but sample sizes have been equivalent or even smaller than the number of variables studied (e.g.,. 79 patients in Macquart-Moulin et al., 2000; 19 patients in Swain et al., 1996). Surprisingly, investigators have concluded that toxicity is "tolerable" or "manageable," even when 50% or more of the patients reported moderate to severe disruption in their personal relationships and work-related problems (Swain et al., 1996). For early-phase trials, data on compliance would seem of paramount importance as these variables—disruption of social function, work-related difficulties, significant emotional distress—are the same ones correlated with lower dosages received (Lebovitz et al., 1990; McDonough, Boyd, Varvares, & Maves, 1996) as well as with refusal (Levin, Mermelstein, & Rigberg, 1999).

Despite its importance to disease outcomes (see Figure 1), there has been minimal investigation of compliance with cancer therapies. The notable exception was an important study by J. L. Richardson et al. (1987). A 2 × 2 randomized block design was conducted comparing medication shaping with a home visit to enhance supportive medication (allopurinol) and chemotherapy (prednisone) for hematologic malignancies. Accrual rate from an inner-city medical center was 80%, with 92 patients randomized. Importantly, the sample was composed of unemployed (56%), minority (86%), and low-income individuals with hematologic malignancies: multiple myeloma, leukemia, lymphoma, or Hodgkin's disease. There was heterogeneity of disease severity, with 57% having "high" or "moderate" disease severity and 43% having indolent disease. In addition to the target drugs, patients may have had multiple other chemotherapies, with 31% of the regimens rated as "easy" and 69% as "complex." Patients were assigned in randomized blocks to one of four conditions: education–shaping ($n = 26$), education–home visit ($n = 18$), education–shaping–home visit ($n = 25$), or no-treatment control ($n = 23$). Intervention patients in all three conditions were provided with disease and treatment information that emphasized patient responsibilities to be compliant. The shaping intervention was conducted during hospitalization and shifted from nurse administered medication to patient initiated requests for medication under nurse supervision. The home visit was by a project nurse, and she or he assisted the patients with developing a *cue* system for

pill taking (e.g., a reminder posted next to the coffee pot). Patients were followed for 3- and 6-month assessments, and self-reports of compliance were supplemented with serum samples for analysis of the target drugs and their metabolites.

Analyses indicated no significant differences between the intervention groups, but when intervention groups were collapsed, there were significant intervention versus control findings. Intervention patients were more compliant with allopurinol (50% vs. 23% for control), though there were no compliance group differences for prednisone (approximately 35% compliance). On the experimenter derived attitudinal measures, the groups did not significantly differ in their ratings of illness uncertainty, although intervention patients reported significantly higher levels of satisfaction with medical care and knowledge of their disease than the control patients. Finally, there was differential compliance with clinic visits, as the intervention patients returned for significantly more of their follow-up visits (approximately 85%) compared with the control patients (61%). Post hoc analyses examined variables predictive of compliance (J. L. Richardson, Marks, & Levine, 1988). Satisfaction with treatment was predictive of appointment keeping, though not predictive of medication compliance. Also, compliance with appointments decreased as difficulty in tolerating side effects (e.g., hair loss, nausea, anorexia) and interference of the side effects with daily activities increased.

Although the Richardson et al. (1987) study is dated, a similar comprehensive effort has yet to be conducted. The study has multiple strengths, including accrual of a sociodemographically underrepresented sample; relevant interventions for complex, self-administered chemotherapies for medical oncology patients; a broadband assessment of compliance (e.g., self-reports, serum values, appointment keeping); and an examination of psychological, attitudinal, and toxicity variables as additional predictors of compliance. The null effects from the treatment conditions were likely limited by two factors: the inclusion of an important educational component that might have leveled group differences and the small sample sizes. Nevertheless, it was an important demon-

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[1] The term *dose intensity* is defined as the amount of drug delivered to a patient per unit time. It is expressed as a ratio of milligrams delivered per meter squared per week ($mg/m^2/week$), regardless of the schedule. Calculating dose intensity provides a mathematical strategy for making comparisons among patients, drugs, and/or intensities of chemotherapy regimens in clinical trials.

[2] Clinical trials are usually classified into four phases (Evans & Ildstad, 2001). Phase 1 trials are the earliest stage and are used to study a new treatment (oftentimes a drug) to determine the toxicity and maximum safe dose. These trials are typically small, with fewer than 100 participants. Phase 2 trials are to provide preliminary data on whether a treatment has efficacy and safety for the patient population for which the treatment is being developed. Phase 3 trials are designed to show how well the new treatment works. Comparison is made with a control (or reference) arm and possibly variants of the new treatment. Another approach to classifying phases of clinical trial research is that of Piantadosi (1997), who defined the four phases as (a) early-development studies (testing the treatment mechanism); (b) middle-development studies (testing treatment tolerability); (c) comparative trials, providing firm evidence of safety and efficacy; and (d) late-development studies (extended safety and provision of additional information about risks and benefits.

stration project and it provides data for generating hypotheses and selecting methods for future efforts.

Health Behaviors

The biobehavioral model suggests the importance of heath behaviors (see Figure 1), and interest in these variables has expanded (see Pinto, Eakin, & Maruyama, 2000, for a review). There are many manifestations of negative health behaviors. For example, distressed individuals often have appetite disturbances or dietary changes such as eating meals of lower nutritional value (Grunberg & Straub, 1992). If eating habits change because of treatment (e.g., food restriction with nausea or taste aversions from chemotherapy; Broeckel et al., 2000; Jacobsen et al., 1995), vulnerability may be heightened. In contrast, some cancer patients, particularly breast cancer patients receiving adjuvant chemotherapy, are at risk for weight gain (Camoriano, Loprinizi, & Ingle, 1990), perhaps because of changed metabolic requirements (Denmark-Wahnefried et al., 1997). Although cancer patients might be strongly counseled to change their negative health behaviors—such as to stop smoking—this comes when they may be least able to quit, as cigarette smoking and caffeine use can increase with stress (Miller, Cohen, & Herbert, 1999). Positive health behaviors—such as regular physical exercise—may be abandoned when patients feel they have neither the time nor the energy to change as they undergo or recover from treatments. These complex circumstances are posed when conducting health behavior interventions. Although others might be chosen, diet, exercise, and smoking interventions are reviewed, as each have quality-of-life and health-outcome rationales with selected cancer groups.

Diet

Nordevang, Callmer, Marmur, and Holm (1992) randomized Swedish women with Stage I or II breast cancer to individualized dietary counseling versus control (no treatment) conditions. Intervention participants met individually with a nutritionist on 9–11 occasions during a 2-year period. Components included general nutrition information and strategies for reducing fat intake to 20%–25% of energy intake, increasing fiber, and altering shopping and cooking practices. Also, intervention participants and family members could attend bimonthly group meetings to sample low-fat foods, discuss difficulties with dietary changes, and take cooking classes. Accrual rates were not reported; 240 women were randomized. However, by posttreatment there was significant differential attrition (52% of the intervention and 89% of the control participants). Analyses revealed improvements for both groups, although the intervention group had significantly larger reductions in total intake of fat, meat products, eggs, and sugars.

Chlebowski et al. (1993) provided data from the Women's Intervention Nutrition Study collaborative trial. With an accrual rate of 55%, 290 women with breast cancer (Stages I–III) from seven medical centers were randomized to dietary intervention or no-treatment (counseled for nutritional adequacy only) conditions. Focused on lowering fat intake, dietitians provided individual counseling, beginning with four 1-hr, individual, biweekly sessions and tapering to quarterly sessions during the 2-year intervention (15 total therapy hr). Although not provided, attrition appeared to be 68%. As early as 3 months into the intervention,

percentage of fat calories, total fat, and body weights were significantly lower for the intervention participants, and these differences were maintained at the 2-year assessment.

Pierce et al. (1997) conducted a smaller scale investigation but also achieved positive outcomes. Accrual rate was not reported, but 93 women treated within the previous 4 years for Stage I–III breast cancer were randomized between intervention and control (only general dietary recommendations to increase fiber intake) conditions. The intervention was provided by telephone for an unspecified number of contacts and included efforts to increase fruit, vegetable, and fiber intake and lower fat intake. There was 76% retention. By the 6- and 12-month assessments, vegetable, fruit, and fiber servings per day had significantly increased and fat calories had significantly decreased for the intervention in contrast to the control participants. Analyses of biomarkers (e.g., increases in beta carotene) were also in the predicted direction.

Kristal, Shattuck, Bowen, Sponzo, and Nixon (1997) used health professional volunteers from the American Cancer Society to deliver a dietary intervention to community women recently treated for breast cancer. The intervention focused on lowering dietary fat to 15% of total energy through nutrition education and information on eating patterns, dietary change skills, and behavioral skills in 6 1-hr weekly individual sessions and then 10 monthly group sessions for social support and maintenance of change (16 total hr). The volunteer staff included dieticians (40%), nurses, and related health professionals. Women at risk for weight gain (i.e., cancer patients who were 105% or more of ideal body weight) were accrued at the rate of 49%. One hundred forty-four women were randomized, although by 12 months there was approximately 25% attrition. Analyses indicated that intervention participants consumed significantly less fat and more carbohydrates, and weights were significantly lower; there were no group differences in total energy, protein, or alcohol intakes. Outcome did not covary with the profession of the volunteer (i.e., dieticians vs. others).

Exercise

Inpatient interventions: Bone marrow transplant (BMT). B. A. Cunningham et al. (1986) conducted an important early study with patients undergoing BMT for leukemia. Experimental conditions were physical therapy five times per week, physical therapy three times per week, or control (no treatment). The context of this study is important to note. Pretransplant therapy consisted of 2 days of cyclophosphamide followed by whole-body irradiation and the beginning of total parenteral nutritional support. During hospitalization, ambulation was restricted by the sterile environment (laminar air flow). Beginning at hospital admission and ending on the 35th day posttransplant, the exercise program was resistive and consisted of 15 repetitions of curls, leg raises, sit ups, and related exercises. Sessions were 30 min. Forty patients were eligible and randomized, but 10 (25%) patients were not evaluable (5 dropouts and 5 removed from the study because of medical complications). Measures included assessment of arm muscle area, arm fat area, weight, caloric and protein intakes, as well as creatinine, 3-methylhistidine excretion, and nitrogen balance to quantitate muscle protein turnover. Analyses of group differences were not significant, but the group means suggested a sparing effect of exercise on skeletal muscle protein status.

Dimeo and colleagues (Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Stieglitz, Novelli-Fisher, Fetscher, & Keul, 1999) conducted two randomized studies of the effects of aerobic exercise on health outcomes and treatment morbidity for patients undergoing high-dose chemotherapy for stem cell transplantation in Germany. As the Cunningham et al. (1986) investigation, the study was notable for its comprehensive outcome assessment and the challenging clinical context. Accrual rate was 90%, and 72 patients were randomized to daily aerobic exercise or control (no treatment). The exercise was in-hospital-bed "biking" with an ergometer for 1-min intervals for a total of 30 min, reaching an intensity of 50% of cardiac reserve. As physical performance declined, pedaling speed was readjusted daily to achieve the target heart rate. Prior to the transplantation, all patients had received one to four chemotherapy cycles of etoposide, ifosfamide, and cisplatinum, with or without epirubicine, which was followed by granulocyte colony-stimulating factor. High-dose chemotherapy with etoposide, ifosfamide, and carboplatin was followed by autologous peripheral blood stem-cell transplantation. Analyses revealed that physical performance for all patients significantly declined during the hospitalization, as anticipated, but the decline was 27% greater in the control group. Notably, hematologic indexes were more positive for the aerobic group, with a significantly shorter duration of neutropenia and thrombopenia and fewer platelet transfusions performed. Regarding toxicities, the incidence of diarrhea was significantly lower as was the severity of pain for the training group. Only for the cardiac indices, stress test and VO2 max (i.e., maximal oxygen consumption), no group differences were found. Finally, the duration of hospitalization was significantly shorter for the training group (14 vs. 16 days).

Using a similar paradigm, Dimeo et al. (1999) reported fatigue and emotional distress outcomes. Again, in-bed biking was the exercise intervention, with 63 German patients with solid tumors or lymphomas randomized to intervention (exercise) or control (no intervention) conditions. Chemotherapy and stem-cell regimens were similar. Posttreatment assessment was completed on day of discharge; attrition rate was 7%. Analyses revealed significant differential improvements, with the intervention group reporting significant reductions in anger and anxiety, whereas the control group showed no improvements and also increases in fatigue and decreases in vigor (POMS). On the Symptom Check List–90 (SCL-90; Derogatis, 1977), the intervention group reported significant reductions on anxiety symptoms (i.e., obsessive–compulsive and interpersonal sensitivity scales), whereas the control group showed no reductions and a significant increase on the somatization scale.

Outpatient interventions. Following their pilot work (MacVicar & Winningham, 1986), MacVicar, Winningham, and Nickel (1989) were the first to test exercise as a strategy to improve functional status in cancer patients. Forty-five women about to begin adjuvant chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil [CMF] or CMF plus vincristine and prednisone) for Stage II breast cancer were randomized within age and functional capacity strata to exercise, placebo (mild stretching and flexibility exercises), or control (no treatment–usual care) conditions. Accrual rate was not reported. Intervention women exercised on stationary bicycles for 20–30 min (to a level of 60%–85% of their highest heart rate attained during pretesting), three times per week, for a 10-week period. Analyses indicated a significant improvement in functional status (VO2 max) for the intervention participants in contrast to control groups.

Other outcomes were published separately. They reported significant intervention effects with reductions in nausea (50% for the intervention group, 7% for the placebo, and 17% for the control group) and lower somatization scores on the SCL-90 (Winningham & MacVicar, 1988). Also, weight and skin-fold measures (suprailliac crest, anterior thigh, and triceps) indicated modest weight gain for both exercise and control groups (0.82–2.0 kg). Follow-up analyses, however, suggested that weight gain for the control group consisted of fat gain and loss of lean body tissue, with the converse effect for the exercise group (Winningham, MacVicar, Bondoc, Anderson, & Minton, 1989).

Mock et al. (1997) conducted a randomized study of a walking program (Winningham, Glass, & MacVicar, 1987) offered to Stage I or II breast cancer patients. Accrual rate was 75%, and 50 women treated with surgery and chemotherapy and awaiting radiation therapy were randomized. Women in the intervention arm were instructed to walk 20–35 min per day and self-monitor pulse rates and subjective experiences with diaries. Telephone or personal contact follow-ups by nurses occurred during radiation therapy to improve adherence; similar contacts were made with control (usual care) participants regarding patients' general health. The intervention extended for the duration of radiation therapy, approximately 6 weeks. Significant intervention effects were found across outcomes, with increases in exercise self-reports; decreases in anxiety symptoms, sleep disturbance, and fatigue as assessed with visual analogue scales; and improvements on a 12-min-walk test (McGavin, Gupta, & McHardy, 1976).

Segal et al. (2001) conducted a randomized investigation with breast cancer patients comparing self-directed exercise, supervised exercise, and a control. Accrual rate was 33%; 123 women with Stage I or II breast cancer awaiting adjuvant therapy were randomized within type of adjuvant therapy strata. Women in the two intervention conditions met with an exercise specialist to receive feedback on their fitness test, be given instructions for monitoring exercise intensity and diary recording of sessions, be taught stretching exercises, and be provided with a walking program to use. Specific instructions given to the self-directed group were to practice at home five times per week for 26 weeks; they were also called every 2 weeks by the specialist to check on progress. Specific instructions for the supervised group were to attend three exercise sessions per week at the cancer center, during which the specialist led warm-up, walking, and cool-down exercises; they were also instructed to practice two other times per week. The control was usual care, which provided the group information on the benefits of exercise and encouragement to do so from their medical oncologist. There was 20% attrition by the Week 26 assessment. Repeated measures analyses revealed significant Group $\times$ Time effects on the Physical Functioning scale of the SF-36; follow-up comparisons indicated better physical functioning for the self-directed group compared with the control group. However, findings were not significant for the remaining scales of the SF-36, the Functional Assessment of Cancer Therapy Scale—General measure (FACT-G; Cella et al., 1993) and the Breast Quality-of-Life scale (FACT-B; Brady et al., 1997), or for physical status measures, including aerobic capacity and body weight.

Smoking

Gritz et al. (1993) conducted a smoking cessation intervention with long-term smokers, head and neck cancer patients, at high risk for recurrence and death. Accrual rate was 84%; 186 patients with squamous cell carcinomas of the oral cavity, pharynx, or larynx were randomized. Both the intervention and control conditions were delivered during postsurgery outpatient clinic visits with more than 100 participating physicians in the community. To enhance experimental control, standardization of the usual care control condition was attempted by providing information on the risks of continued smoking and benefits of cessation, followed by strong physician advice to quit. The intervention patients received usual care advice plus discussion of the person's readiness to quit, provision of three informational booklets on smoking cessation, and the physician's expressions of confidence in the patient's ability to quit. The latter strategies were reiterated in booster sessions conducted during six monthly appointments. Self-report data and urine samples for cotinine assays were collected. Attrition by the 12-month follow-up was 39%; reasons for data lost included progressive disease or death (51%), dropout (22%), or lost to follow-up (19%) and typify follow-up difficulties with this sample. Across groups, the rate of continuous abstinence during 12 months was high, 60%, and among the remaining smokers, consumption dropped by 50% (12/cigarettes/day). Although all analyses revealed null effects, the reader is referred to the report, as it provides an excellent discussion of design challenges in field study and clinical implications.

Wewers and colleagues conducted three smaller sample studies using individual nurse delivered interventions with postoperative cancer patients. In the first report (Wewers, Bowen, Stanislaw, & Desimone, 1994), cardiovascular ($n = 22$), oncology ($n = 30$), and general surgery ($n = 28$) patients ($N = 80$) were randomized (89% accrual) to intervention or control (usual care) conditions. Of the cancer patients, 25 (78%) had head/neck cancer. Beginning with postoperative Day 2, intervention patients received three 20 min daily visits, and on discharge, they were telephoned weekly for 5 weeks by a nurse. The intervention provided discussion of smoking habits, the health benefits of not smoking, and the development of smoking alternatives, progressive muscle-relaxation training, and maintenance strategies. Collapsing across medical diagnoses, there were no significant differences between conditions; trends in the data suggested greater effectiveness for the cardiovascular and oncology patients. Self-report abstinence rates (confirmed by cotinine) at 6 weeks were 65% for the intervention and 50% for the control condition.

The second study (Stanislaw & Wewers, 1994) randomized 26 postoperative cancer patients with solid tumors to the same intervention condition or to usual care. Six-week abstinence rates (cotinine confirmed) were 75% for the intervention and 40% for usual care. The third report (Griebel, Wewers, & Baker, 1998) included a briefer intervention. With an accrual rate of 45%, 28 solid tumor cancer patients were randomized. During hospitalization, intervention patients received one 20-min session with weekly telephone follow-ups for 5 weeks. Analyses indicated no significant differences between groups in abstinence (21% intervention vs. 14% control, confirmed by cotinine), but data trends suggested that intervention subjects were smoking fewer cigarettes.

Summary

Health behavior interventions are included in the biobehavioral model as they have implications for affect regulation and, perhaps, disease progression (see Figure 1) for selected disease sites. An empirical case can be made for both dietary and exercise interventions for breast cancer patients, with data suggesting that obesity at diagnosis, increased fat intake, and weight gain during follow-up are related to recurrence and poorer survival (Holm et al., 1993; Saxe, Rock, Wicha, & Schottenfeld, 1999; Willett, 1999; Zhang, Folsom, Sellers, Kushi, & Potter, 1995).

Accrual to the dietary studies, when reported, was roughly 50%, and retention varied from 30% to 76%. Standard, cost-effective (10–20 total hr, some delivered by telephone) dietary interventions were provided, and one had an elaborate and effective maintenance program (Chlebowski et al., 1993). Whereas dietary assessments were state-of-the-art, there appeared to be no psychological–behavioral assessment component, which might have been useful to establish broadband effects as well as to examine important individual differences. The small-sample single-site trials indicated that fat intake can be significantly reduced and/or fiber intake increased (Nordevang et al., 1992; Pierce et al., 1997), with the larger, collaborative efforts also producing changes (Chlebowski et al., 1993; Kristal et al., 1997). Even though there are only four studies, the effects appear robust, as they have been achieved with heterogeneous modes of delivery (e.g., individual, telephone) and therapists (e.g., dieticians, volunteers).

For exercise, the results are also quite positive. The Dimeo studies (Dimeo et al., 1997, 1999) showed impressive psychological and health benefits in the difficult context of BMT. These results are encouraging and suggest important health outcomes (e.g., improved clinical measures, shorter hospital stays) for patients undergoing this high morbidity and mortality treatment. In the outpatient setting, breast cancer patients have been the primary participants, as would be expected, with interventions occurring during chemo- and radiotherapy treatments. Although both treatments produce debilitation and fatigue, the interventions achieved positive affective, somatic, and functional status outcomes. Follow-ups have not been of sufficient time to test for differential disease outcomes following either dietary or exercise interventions. However, second-generation trials incorporating both interventions may be an important next step for research with breast cancer patients (Stoll, 1996).

In contrast, smoking cessation has been difficult to achieve beyond the high, postoperative base rate (50%–60%). The clinical group often targeted for such efforts—head and neck cancer patients—represent individuals who, on average, come to their diagnosis with heavy smoking and alcohol use histories and constrained economic circumstances. Subsequently, they undergo radical surgeries, rigorous chemotherapy, or combination radio–chemotherapy regimens. Brief education-focused efforts appear insufficient to increase quit rates beyond the base rate, and future research may need to include other components (e.g., nicotine replacement; Emmons et al., 2000). In addition to the respiratory problems associated with continuing to smoke, the high rates of depression (e.g., Baile, Gibertini, Scott, & Endicott, 1992) and nutritional problems associated with continued alcohol consumption and/or malnutrition (Zemel, Maves, Mickelson, & Kaplan, 1991) have been documented for many head and neck cancer

patients. These psychological and behavioral difficulties also correlated with lower survival rates, as for example, they predict higher rates of infection and pneumonia leading to death (Hussain et al., 1991), and continued smoking may hasten recurrence (Stevens, Gardner, Parkin, & Johnson, 1983) and death (Browman et al., 1993). In sum, there are multiple, health behavior intervention targets for this needy cancer group, and broadband research efforts are needed in addition to those focused on smoking cessation.

Finally, health behaviors change is also important because of the interaction with biological responses (see Figure 1). For example, nutritional improvements can enhance immune responses, reduce rates of infection, and improve mortality (Galban et al., 2000). Exercise may have positive consequences for both the immune (Nieman & Pedersen, 1999; Woods, Davis, Smith, & Nieman, 1999) and endocrine systems (Smith & Weidemann, 1990), and the Dimeo data (Dimeo et al., 1997) showed improved hematologic indexes, lowered toxicities, and shortened hospital stays. Regarding smoking, a variety of data now suggest that lower levels of natural killer (NK) cell activity are found with smoking (Yovel et al., 2000), the interaction of smoking and depression (Jung & Irwin, 1999), and with depressed mood and other symptoms of depression, such as poor sleep quality (Savard et al., 1999). These data can be juxtaposed with other data indicating that even a month-long abstinence from smoking can reduce cortisol levels and increase NK cell cytotoxity (Miliska, Stunkard, Gilbert, Jensen, & Martinko, 1995). Taken together, there is compelling evidence to focus intervention efforts on changing health behaviors in selected cancer groups.

Biologic Responses

The Biobehavioral Model suggests that stress triggers important biological effects involving the autonomic, endocrine, and immune systems (see arrows from stress to immunity in Figure 1). Stress may be routed to the immune system by the central nervous system by means of activation of the sympathetic nervous system (e.g., Felten, Ackerman, Wiegand, & Felten, 1987) or through neuroendocrine-immune pathways (i.e., the release of steroid hormones, glucocorticoids). The endocrine axes which have been the best characterized are the hypothalamic–pituitary–thyroid axis, the hypothalamic–growth hormone axis, and the hypothalamic–pituitary–adrenal (HPA) axis, although it is the latter that has received the greatest attention in the human stress literature. The few neuroendocrine studies with cancer patients have suggested that they may exhibit the same dysregulation of the HPA axis that is observed in depressed patients (i.e., hypersecretion of adrenocorticotropic hormone and cortisol, adrenal and pituitary hypertrophy; Evans et al., 1986; Joffe, Rubinow, Denicoff, Maher, & Sindelar, 1986; McDaniel, Musselman, Porter, Reed, & Nemeroff, 1995). Also, hormones released under stress (e.g., catecholamines, cortisol, prolactin, and growth hormone) have been implicated in immune modulation (see Maier, Watkins, & Fleshner, 1994, for a discussion; Rabin, Cohen, Ganguli, Lysle, & Cunnick, 1989; Sabharwal et al., 1992). Epinephrine and norepinephrine, for example, regulate lymphocyte levels that can, in turn, alter immune responses such as cellular migration, lymphocyte proliferation, antibody secretion, and cell lysis (Madden & Livnat, 1991). In vitro work has shown that the addition of catecholamines to human

whole blood produced a suppression of interleukin (IL)-12 production yet an increase in IL-10 production (Elenkov, Papanicolaou, Wilder, & Chrosusos, 1996). This cytokine shift (i.e., suppression of IL-12 yet enhancement of IL-10) causes a T-helper (Th) cell shift from Th1 cells involved with cell-mediated inflammatory reactions to Th2 cells that produce cytokines promoting humoral responses, such as encouraging antibody production. Thus, a stress-related, lower Th1 response might increase susceptibility to infectious pathogens requiring a cellular response (Clerici et al., 1997). Also, Th1 responses may be more important to antitumor immune responses (e.g., Brunda et al., 1993).

Prior to considering stress effects on immunity in cancer patients, it is important to consider the role of immune responses in host resistance against cancer progression (see arrow from immunity to disease course in Figure 1). Although the role of immunity in cancer is debated, research has addressed three avenues of influence. The first area examines the capability of the immune system to detect cancer cells and the characteristics of cancer cells that allow their detection (i.e., antigenic processes). Research has centered on the identification of antigens that are selectively expressed by cancer cells and that serve as a basis for their rejection by immune effectors. Classes of antigens identified include mutated oncogenes (p53, Ras), aberrantly expressed fetal and embryonic antigens (e.g., CEA), and tissue-specific antigens (e.g., tyrosinase, mucin; Rosenberg, 2000).

The second area examines the capability of the immune system to mount an effective response to particular cancer cells or the cellular characteristics of the cancer cells (i.e., immunogenicity). The NK cell cytotoxic response has been widely explored (Brittenden, Heys, Ross, & Eremin, 1996), as has the generation of lymphokine-activated killer cells with the administration of recombinant cytokines such as IL-2 and the interferons (IFN; Rosenberg et al., 1993; Walter et al., 1998). Other mechanisms are the actions of cytotoxic T cells and antibody-producing B cells. The lytic (killing) activity of antitumor T cells is of obvious importance to the eradication of malignant cells, but high-affinity antibodies with specificity for tumor antigens might also play an important role. These could directly interfere with tumor growth by means of the induction of apoptotic mechanisms (cell death) or the triggering of complement-mediated lysis and antibody-mediated cellular cytotoxity (Cragg, French, & Glennie, 1999).

The third area examines the role of the immune system in the eradication of newly formed cancer cells. Low NK cell activity correlates with cancer onset (Imai, Matsuyama, Miyake, Suga, & Nakachi, 2000). Once diagnosed, NK cell activity is associated with local recurrence (Brittenden et al., 1996) and distant metastases (Malygin et al., 1993; Pross & Lotzov'a, 1993; Yamaguchi, Takashima, Funakoshi, Kawami, & Toge, 1994). Moreover, survival time without metastasis correlates with NK cell activity (Whiteside & Herberman, 1989). Finally, immunotherapeutic interventions based on these findings have developed rapidly within the past decade. Examples include therapy with recombinant cytokines (IL-2 and IFN-α), monoclonal antibodies (anti-HER2/neu), and peptide vaccines (gp100 protein). This research is contemporary and cutting-edge cancer immunology. Consider these immune effector mechanisms when reviewing the measures intervention investigators have chosen.

Correlational studies have been conducted with endocrine and immune outcomes. Turner-Cobb, Sephton, Koopman, Blake-

Mortimer, and Spiegel (2000) provided data on social support and salivary cortisol in women diagnosed with recurrent breast cancer. Women provided four salivary cortisol samples (i.e., 8 a.m. and 12, 5, and 9 p.m.) for 3 consecutive days. A significant negative correlation (-.17–.19) between the grand mean of the cortisol assessments and three of the four subscales of the Inter-personal Support Evaluation List (Cohen, Mermelstein, Kamarck, & Hoberman, 1985) was found, yet there was no relationship with a measure of social network size (-.07; Yale Social Support Index; Seeman & Berkman, 1988). A reanalysis was also reported (Sephton, Saplosky, Kraemer, & Spiegel, 2000); rather than averaging the four cortisol assessments, the slope of a patient's four values was examined. A typical profile would be for cortisol values to decline steadily from the morning peak to the evening assessment. Using a Cox proportional model, they showed patients with the more typical declining pattern had better survival (60%) versus those individuals whose slopes had patterns of slower declines, abnormally timed peaks, or increasing levels during the day (77%).

Correlational immune studies have reported consistent relationships between measures of stress and immune outcomes, both quantitative (e.g., cell count) and functional (e.g., NK cell lysis). Tjemsland, Soreide, Matre, and Malt (1997) studied Norwegian women diagnosed with breast cancer awaiting their surgical treatment. Preoperative depressive symptoms correlated with postoperative lymphocyte, total T cell, and T4 counts, with higher depression scores related to lower counts. Andersen et al. (1998) examined the relationship between stress and several aspects of the cellular immune response in women with breast cancer following surgery. All completed a measure of traumatic stress about the cancer experience (IES). Multiple regression models, controlling for age, stage of disease, and length of time since surgery, found significant, down-regulating effects for stress, replicated within (across effector to target cell ratios or concentrations) and between assays: NK cell lysis, the response of NK cells to recombinant interferon gamma (rIFN-γ), and T cell responses including proliferative responses to concanavalin A (ConA), phytohemagglutinin, and a T3 monoclonal antibody. In combination, these studies provided suggestive evidence of the adverse effects of stress on endocrine (i.e., cortisol) and immune responses. The premise of the following studies is that interventions may enhance biologic indicators (i.e., reduce stress hormone levels and increase immune responses).

Quasi-Experimental

Immune. Lekander, Furst, Rotstein, Hursti, and Fredrikson (1997) used a static group-comparison design to examine the effects of progressive muscle relaxation during chemotherapy for Swedish women with Stages I–IV of ovarian cancer. Intervention subjects were provided with instruction (1.5 therapy hr) and audiotapes. Two inpatient units, with 22 total patients, were randomized, one unit assigned to the intervention group ($n = 12$) and the other to the control ($n = 10$). Analyses revealed no differences between groups either on anxiety symptoms or on enumerative cell counts, NK cell lysis, or blastogenesis (ConA).

Experimental

Endocrine. Cruess et al. (2000) conducted a small-sample study examining the effect of CBSM for women with Stage I or II

breast cancer. The intervention consisted of 10 weekly group meetings of 120 min (20 therapy hrs) including cognitive restructuring, coping skills, assertiveness and anger management training, social support, and relaxation training (combination of progressive muscle, meditation, breathing, and guided imagery). Thirty-four women, self referred and part of a larger clinical trial, were randomized to the intervention or wait-list control. Analysis of covariance analyses indicated a significant reduction in cortisol and significant increases in an experimenter-derived measure of positive benefits from cancer for the intervention group. There were no changes in emotional distress (POMS).

Immune. Elsesser, van Berkel, Sartory, Biermann-Gocke, and Ohl (1994) conducted a small randomized study comparing anxiety management training with a wait-list control for a heterogeneous sample of German cancer patients. The treatment consisted of instruction in progressive muscle-relaxation training and cognitive restructuring for anxiety provoking cognitions and was administered in eight individual sessions during a 6-week period. In the predominantly female sample, (85%) of 20 patients had Stage I cancer, but they represented six different disease sites. The sample was recruited from existing self-help groups that had completed their medical therapy. Analyses indicated significant reductions in both state and, surprisingly, trait anxiety (STAI). However, there were no significant differences on measures of depression, quality of life, or cell counts.

Larson et al. (Larson, Duberstein, Talbot, Caldwell, & Moynihan, 2000) reported on a randomized study comparing an intervention to reduce presurgical anxiety with a no-treatment (standard care) control for breast cancer patients (Stages I–IV). The intervention consisted of two 90-min (3 therapy hr) sessions including information on common somatic and psychological reactions to stress, problem-solving strategies, support, and progressive muscle-relaxation training with audiotapes. The accrual rate was not provided; however 41 women were randomized. Assessments included psychological measures of depressive symptoms, traumatic stress, quality of life, optimism, and NK cell lysis and IFNγ production. Attrition was substantial (47%), and repeated measures ANOVAs revealed no significant group differences for either the psychological or the immunologic measures.

Endocrine and immune. Gruber et al. (1993) reported a small-sample randomized study comparing "enhanced" relaxation with a wait-list control in women with Stage I breast cancer. Progressive muscle relaxation was enhanced with guided imagery exercises and electromyographic biofeedback, administered in 9 consecutive weekly sessions, followed by monthly sessions for 3 months. Accrual was not described; 13 women were randomized. Psychological measures were not significant, but significantly higher cell counts and blastogenesis (ConA) and significantly lower levels of cortisol were found for the intervention group. There were no group differences on NK cell counts or the antibody (IgA and IgM) assays.

M. A. Richardson et al. (1997) compared two group treatments, support and imagery–relaxation, with a no-treatment control for Stage I–III breast cancer patients. The support intervention focused on reducing stress, minimizing feelings of isolation, and enhancing self-esteem with 6 weekly sessions (duration not specified). The imagery intervention, also six sessions, provided instructions in relaxation, imaging ability, and breathing, with the use of images to enhance healing and stimulate immune function. Accrual rate

was 30%, and 47 women were randomized. There were no significant differences between groups in mood (POMS), quality of life (FACT-B; Brady et al., 1997), or any biologic variable (i.e., NK cell lysis, IL-1, IL-2, IFNγ and beta endorphins). The only group differences were found for coping (Ways of Coping; Dunkel-Schetter, Feinstein, Taylor, & Falke, 1992), which indicated that both intervention groups sought more support from others than did women in the control group. Also, women in the imagery group used positive coping strategies, whereas women in the support group reported distancing themselves from the stressor.

Van der Pompe, Duivenoorden, Antoni, Visser, and Heijnen (1997) compared experiential–existential group psychotherapy with a wait-list control for Dutch breast cancer patients. The treatment was described as dynamic and included expression of emotions through self-disclosure, body-awareness exercises and relaxation, social support, and conflict resolution skills. Accrual was not described. Women ($N = 31$) with Stage II, III, or recurrent breast cancer were randomized; however with attrition (26%), data were analyzed from 23 participants. Regression analyses indicated no intervention effect on the endocrine or immune outcomes, and some immune findings were in the opposite direction (e.g., higher posttreatment NK percentage scores for the wait-list group).

Summary

At the time of the prior review, experimental data on stress and immunity in cancer patients came from a single study, Fawzy and colleagues (Fawzy, Cousins, et al., 1990; Fawzy, Kemeny, et al. 1990). Specifically, Stage I or II melanoma patients were randomized to a structured, short-term (10 sessions) group-support intervention or control (no intervention). Significant psychological and coping outcomes for the intervention subjects were evident by 6 months posttreatment, as were significant increases in NK cell numbers and IFNα-augmented NK cell activity.

In the intervening years, some consistencies have emerged. First, contrasting individuals who differ in their level of stressor distress, one finds that higher stress is correlated with higher endocrine (cortisol) and lower immune responses (Andersen et al., 1998; Sachs et al., 1995; Vitaliano et al., 1998). However, data from experimental studies have been less positive; null findings predominate, with the exception of the cortisol data in the Cruess report (Cruess et al., 2000). Collectively, these studies illustrate the difficulties inherent in intervention research and the added challenge of including biologic measures. Generalization is limited because of the selectivity of the samples and the often high attrition. Data analyses were hampered by small sample sizes (e.g., Ns from 13 to 47), likely resulting in large within-group variability and/or insufficient power. Nevertheless, these reports are resources for investigators wishing to meet the methodologic challenges faced in these pioneering efforts.

Regarding endocrine and immune measures, the ones used thus far are common to the stress and psychoneuroimmunology literatures (e.g., Miller & Cohen, 2001; Zorrilla et al., 2001), although many have no particular relevance to cancer, per se. The case can be made for selective ones, such as cortisol (as it is known to be immune down regulating), NK cell lysis, or NK cell responses to cytokines. These assays are familiar and easy to perform. However, they have drawbacks, as they are nonspecific and there are not enough data to show that changes in nonspecific immune responses are paralleled by changes in specific immune responses. For example, NK cell function may improve with an intervention. However, if there are still no tumor-specific T lymphocytes or antibodies to fight the tumor(s), the relevant disease outcomes will not improve.

One of the best ways to prove the hypothesis that psychological interventions effect cancer outcomes by way of the immune system is to evaluate tumor-specific immune responses, such as with specific tumor antigens or other surrogates of tumor-specific responses, as discussed earlier. Examples of antigens include melanoma antigen for melanomas; growth factor receptor HER-2/neu for breast and ovarian cancers; epithelial mucin for breast, pancreas, colon, prostate, lung, and ovarian tumors; CEA for colon cancer; prostate specific antigen and prostatic acidic phosphatase for prostate cancer; oncogene products such as Ras and p53 for a variety of tumors; human papilloma virus type 16 antigens E6 and E7 for cervical cancer; and others (Finn, 2001). Although these assays are not as easy to perform by generalists, they can be routine in cancer immunology laboratories.

Disease Outcomes

There is considerable interest in linking psychological interventions to disease course (see Figure 1). In the prior review, there were four intervention studies reporting disease outcomes, but none had been designed a priori to do so. The most comprehensive was the Fawzy and colleagues (Fawzy, Cousins, et al., 1990; Fawzy, Kemeny, et al. 1990) study noted above. They reported differences in survival, with 29% of controls but only 9% of experimental subjects dying after a 6-year follow-up (Fawzy et al., 1993). J. L. Richardson, Zarnegar, Bisno, and Levine (1990) also reported higher survival rates for intervention patients beyond the gains achieved with improved treatment compliance. Two other studies provided data from patients with a poor prognosis. Spiegel and colleagues (Spiegel & Bloom, 1983; Spiegel, Bloom, & Yalom, 1981) randomized women to a supportive–expressive therapy intervention or no treatment, and a 10-year follow-up (Spiegel, Bloom, Kraemer, & Gottheil, 1989) indicated a significant survival time difference, 18.9 months for the control subjects and 36.6 months for the intervention subjects. Reanalysis of data suggests that the control group may have had more progressive disease, as they had more bony ($p = .07$) and lung metastases ($p = .09$) and received more radical treatment (i.e., adrenalectomy, $p = .08$; Kogon, Biswas, Pearl, Carson, & Spiegel, 1997). In contrast, Linn, Linn, and Harris (1982) found no survival advantage despite favorable quality-of-life outcomes for male cancer patients offered a supportive death and dying intervention. It is in this context, I consider the investigations of the past decade.

Quasi-Experimental

Gellert, Maxwell, and Siegel (1993) reported outcomes from a nonequivalent control group (case control) design used with women with breast cancer. The intervention was described as a weekly meeting of 90 min offering individual counseling, patient peer support, family therapy, relaxation, positive imagery, and meditation. Participants were 34 breast cancer patients with Stage I (38%), Stage II or III (50%), or distant (12%) disease; accrual and retention rates were not reported. For each intervention par-

ticipant, three comparison patients ($n = 102$) with similar dates of diagnosis and disease stage were identified from a cancer registry. After 10 years of follow-up and a 59% death rate, analyses indicated no survival benefit for the intervention group.

Ilnyckyj, Farber, Cheang, and Weinerman (1994) conducted a modified randomized study examining the extent of therapist involvement versus no treatment with a heterogeneous group of Canadian cancer patients. Three intervention groups varied in terms of the involvement of a social worker leader: leader for 6 months, leader for 3 months followed by member-led only, and member-led only groups were compared with a no-treatment group. The social work leaders were "not instructed in any specific techniques, but were encouraged to give information and (to) be supportive" (p. 93). Accrual rate was 32%, and 127 patients were randomized. Overall attrition was 43%, but later, differential attrition in the member-led group (66%) necessitated that an additional 21 nonrandomized patients be assigned to that group. Analyses revealed no significant differences on psychological outcomes (state–trait anxiety, depression symptoms, and health locus of control). Conducting survival analyses according to intent to treat, the follow-up period was 11 years, during which time 81 deaths (66%) occurred. As expected, disease stage and performance status predicted survival, but there was no differential survival between intervention groups or between intervention and control conditions.

Ratcliffe, Dawson, and Walker (1995) conducted a study comparing two treatments, relaxation therapy with or without hypnosis for patients with Hodgkin's disease or non-Hodgkin's lymphoma ($N = 63$) residing in the United Kingdom. As the report is brief, several methodology details are not reported, including information on accrual, attrition, intervention descriptions, and outcome data for the psychological measures. Patients were assigned to the relaxation with hypnosis group ($n = 36$) or the relaxation only group ($n = 27$). After 5 years of follow-up, 27 (43%) of the patients had died. Univariate analyses indicated no significant differences in survival, with 39% of the relaxation plus hypnosis patients and 48% of the relaxation patients dying. Because of the absence of a control condition, the base rate for survival among these patients is unknown.

Shrock, Palmer, and Taylor (1999) reported outcomes from a nonequivalent control group (case control) design used with two samples: Stage I breast and Stage I prostate cancer patients. The intervention was community based and consisted of six 2-hr (12 therapy hr) Simonton-framed (Simonton, Matthew-Simonton, & Creighton, 1978) psychoeducational classes. Content included information on the effect of attitudes and beliefs on health, relaxation and imagery training, nutrition, exercise, stress management, self-esteem and spirituality, problem solving, creation of a personal health plan, and goal setting. Intervention subjects (21 breast, 29 prostate) were identified from intervention attendance rosters indicating their attendance to at least five of the six sessions. Comparison patients (74 breast and 65 prostate) who had not attended any sessions were similarly identified. Patients in both groups were matched on date of diagnosis, stage, age, ethnicity, and referring hospital. For the analyses, follow-up intervals ranged from 4 to 7 years; however the death rate was very low. Analyses indicated no significant differences in the rate of recurrence (i.e., 12% vs. 14% for prostate, 14% vs. 11% for breast) or death from cancer (i.e., 7% vs. 9% for prostate, 0% vs. 5% for breast) between the intervention

and control groups, respectively. Cox regression analyses suggested a higher rate of survival for the intervention group; however this was accounted for by a higher rate of death from noncancer causes for each site in the control groups.

Experimental

Cunningham and colleagues (A. J. Cunningham et al., 1998; Edmonds, Lockwood, & Cunningham, 1999) reported outcomes for a randomized study of a psychological intervention versus an information-only control for Canadian women with metastatic breast cancer. Designed as a replication of the Spiegel study (Spiegel et al., 1981), the intervention incorporated supportive–expressive elements but also cognitive techniques (e.g., thought monitoring, goal setting, mental imaging, homework exercises) and relaxation training. Treatment was conducted in a group format of 35 weekly 2-hr sessions (70 therapy hr). An additional weekend-long session was also offered for coping-skills training with accompanying written materials. The control subjects received the written materials, relaxation-training audiotapes, and periodic telephone calls during the months to offer support and assist in study retention. Accrual rate was 27%, and 66 women were randomized within age and extent of disease strata; attrition was approximately 30%. Data on compliance with the intervention indicated that the intervention subjects, on average, attended 63% of the intervention sessions and completed 40% of the homework assignments. Analyses indicated no differential improvements or reductions in distress (POMS), quality of life (FLIC), mental adjustment to cancer (Watson, Greer, et al., 1988), or social support (Broadhead, Gehlback, DeGruy, & Kaplan, 1988). With 5 years of follow-up and 80% of the sample dying, Kaplan-Meier survival plots revealed no significant differences between the groups.

Edelman and colleagues (Edelman, Bell, & Kidman, 1999; Edelman & Kidman, 1999; Edelman, Lemon, Bell, & Kidman, 1999) compared CBT versus no treatment for Australian women with metastatic breast cancer. The CBT intervention consisted of 12 sessions of 2 hr each (24 therapy hr), offered in a group format, and included identifying and challenging maladaptive cognitions, problem solving and goal setting, assertive communication, relaxation training, homework, and group support. Accrual rate was 61%, and 121 women were randomized by blocks of 10. Twenty-nine patients (24%) dropped out, half of whom died of their disease; dropouts reported significantly higher levels of emotional distress, lower levels of self-esteem, more advanced disease, and lower performance status. Analyses indicated significant improvements for the intervention group in terms of lower emotional distress (POMS) and higher self-esteem (Coopersmith, 1981) at the posttreatment assessment; however differences were absent at the 3- and 6-month follow-ups. There were no changes on the performance status evaluations. After 2 years of follow-up, 70% of the sample was deceased. Using a Cox regression model, researchers found that only disease variables predicted survival, whereas study arm did not.

Kuchler et al. (1999) compared individual and inpatient (pre- and postsurgery) counseling with no treatment (standard care) for a heterogeneous group of German gastrointestinal patients ($N = 271$). The intervention participants ($n = 136$) received individualized therapy, usually conducted at the bedside, which included

conducting a psychological history, providing coping information, giving support, and providing a discharge session focused on transitions to recovery; one of two psychotherapists delivered the intervention. Control patients ($n = 135$) received routine hospital support services. Accrual rate was 85%; attrition was not reported. There were no sociodemographic, prognostic, or medical treatment and recovery differences between the groups. After 2 years of follow-up, 60% of the sample was deceased. A Cox proportional hazards model was conducted and a significant difference in survival was found (hazard ratio of 0.612), even after adjusting for extent and site of disease. Specifically, 49% of the experimental and 67% of the control patients had died; a difference of at least 15% between groups is the accepted standard in cancer treatment clinical trials (see later discussion). Follow-up analyses found that most of the differences in favor of the experimental group occurred in females rather than males (percentage of females in the samples was approximately 60%) and tended to occur in patients diagnosed with stomach, pancreatic, liver, or colorectal cancer rather esophageal cancer.

Goodwin et al. (2001) reported outcomes for a randomized study of a supportive–expressive group intervention compared with no treatment for Canadian women ($N = 235$) with metastatic breast cancer. Spiegel was a consultant for the design and implementation of the intervention ($n = 158$), but the intervention also incorporated information about breast cancer sessions and relaxation training. Treatment was conducted in a group format of weekly 90-min sessions, with requests to the participants of a year commitment (70 therapy hours). Also, a monthly 90-min session was offered to family and friends. The control participants ($n = 77$) only received the regular assessments. Women were accrued from seven regional cancer centers during a 4-year period with the overall accrual rate being 43%; 235 women were randomized within presence/absence of visceral disease strata. Attrition for follow-up data was 30% in the intervention condition and 35% in the control condition. Compliance data indicated that intervention participants attended 67% of the sessions, with the most common reasons for absence being ill health and medical appointments. There were initial significant group differences on prognostic variables (i.e., age at diagnosis, extent of nodal disease, ER/PR (estrogen/progesterone), receptor status, and receipt of adjuvant chemotherapy) and differences approaching significance (i.e., .06–.09) on the emotional distress (i.e., Depression, Anxiety, and Depression) subscales of the POMS. Thus, intervention women were younger at diagnosis, had more extensive disease and more treatment, and had greater distress; control women had a higher incidence of negative receptor status.

Data were gathered at the initial appointment, 4, 8, and 12 months, although the latter three assessments were collapsed for all analyses. Analyses using t tests, typically with change scores, were conducted. Analyses considering only follow-up data indicated significant group differences on the POMS, but inclusion of the initial values negated the effects. Measure of pain and experience of pain and suffering were assessed using a 10 cm visual analogue scale. Baseline scores were low with a significant increase in pain for all participants with time. There were no initial group differences; posttreatment only data indicated a significantly smaller increase in pain for the intervention group compared with the control (0.4 vs. 1.3, respectively, on a 10-point scale). Post hoc analyses with the POMS and pain measures were conducted by

splitting the groups on the initial values for the measure (i.e., high vs. low) and then using change scores to examine posttreatment outcomes. In all cases, the data were interpreted as indicating improvements for the high distress or pain intervention patients only, with no group differences for the low distress or pain groups. These analyses are, however, difficult to interpret. The division of the groups on the outcome variable (rather than a different, but relevant, variable) introduces the possibility of regression to the mean being an influential factor, particularly with the use of change score analyses and the initial higher levels of distress on the POMS for the intervention participants. After 85% of the study participants were deceased, a Cox model indicated no significant difference between groups in survival rates. A Kaplan–Meier analysis indicated approximately 18 months postrandomization as the survival time for both groups. The analyses were repeated by entering prognostic disease variables prior to the group variable, an important analysis as the groups were significantly different on the majority of the prognostic variables. However, only ER/PR status, the one variable for which the initial differences were in favor of the intervention group, predicted survival, and the addition of the group variable was again nonsignificant.

Summary

There have been several efforts to examine disease outcomes in recent years. The quasi-experimental studies included breast cancer (Gellert et al., 1993; Shrock et al., 1999), prostate cancer (Shrock et al., 1999), or were heterogeneous (DeVries et al., 1997; Ilnyckyj et al., 1994; Ratcliff, Dawson, & Walker, 1995), with sample sizes ranging from 35 to 136 and follow-up intervals ranging from 4 to 10 years. All studies reported null effects. Of the four experimental studies, three accrued women with recurrent breast cancer (A. J. Cunningham et al., 1998; Edelman, Lemon, et al., 1999; Goodwin et al., 2001), and the fourth accrued gastrointestinal cancer patients (Kuchler et al., 1999). Sample sizes ranged from 66 to 235 and follow-up was from 2 to 11 years. Three studies reported psychological data, with positive psychological gains (Edelman, Lemon, et al., 1999), modest gains (Goodwin et al., 2001) and null effects (A. J. Cunningham et al., 1998). The Kucher group reported impressive positive survival effects, but interestingly, the studies reporting null effects garnered substantial attention in the media and research literatures (e.g., Spiegel, 2001). These studies are a challenge to conduct, as selective study samples, high rates of attrition, and weak or nonexistent intervention effects makes testing disease endpoint hypotheses all the more difficult.

In testing for disease outcomes, there are two common, but different, strategies. Although specifically relevant for these outcomes, I detail them here as they have relevance for other biobehavioral outcomes, and investigators may be generally unfamiliar with them. The first is to conduct analyses according to *intention to treat*, which means inclusion of data from all subjects who were randomized, including those participants whose data are incomplete (as with noncompliance) or missing. This strategy includes all participants randomized, even those receiving only part of or none of the intervention. The second analysis model is to include only *evaluable patients*, defined as those who are treated according to the allocated trial arm and who complete the required follow-up (e.g., 5 years of follow-up is often used in cancer treatment clinical

trials). This necessitates that the investigator define prior to the start of the trial a minimally effective dose of the intervention as well as the minimal period of follow-up during which power is achieved to test for intervention effects. If, of course, a disease endpoint is the outcome, the length of required follow-up can easily be estimated. Even for other outcomes, there are now sufficient biobehavioral data that these endpoints could also be estimated.

Once the analytic strategy is determined, there are two disease outcome metrics. One is comparison of group differences in proportions at a given endpoint (e.g., recurrence, death). In such an analysis, a 15%–20% difference in the proportion of patients remaining disease free is a standard in cancer treatment clinical trials to indicate that one therapy results in a clinically important improvement over another. As overall patient mortality is closely related to the time of intermediate events, such as recurrence, the latter is a common endpoint in many trials. The second metric is group comparisons on median times (e.g., disease-free interval) to an endpoint. Here a doubling of time to an endpoint is a standard in clinical trials to indicate that one therapy results in a clinically important improvement over another. For either to be tested, sufficient time and/or events need to have occurred. In some of the above studies, tests have been premature (e.g., after only a rate of 16% recurrence in the breast sample in Shrock et al., 1999). Investigators must wait until at least 50% of the sample has experienced the event (or if time is the relevant endpoint, follow-up intervals appropriate to the estimated survival rate with time) so that the analysis has the greatest likelihood of being reliable.

Strategies and Directions for Future Research

Research Design

The summaries above provide outcome-specific commentaries for methodologic issues and areas of needed emphasis. Here I discuss cross-cutting issues. First, I offer the observation that whereas some studies are testing therapies framed within theory (e.g., cognitive–behavioral model of Beck, Rush, Shaw, & Emery, 1979) in Antoni et al. (2001) and/or of known empirical efficacy (e.g., dietary interventions in Chlebowski et al., 1993), this is not the case for many others. For example, education—broadly defined—has efficacy in reducing distress (e.g., McQuellon et al., 1998). However, it is too seldom that researchers articulate the theoretical case for their specific intervention components and the mechanisms by which a specific outcome are to be achieved (see Helgeson et al., 2001, for an exception). In short, interventions need to be empirically, if not theoretically, based if one is to understand the mechanisms for achieving biobehavioral gains.

To state the obvious, intervention studies face considerable manpower, logistic, collaborative, and funding challenges. This review suggests that when under-piloted, -manned, -organized, or -powered, there are methodologic and/or statistical problems, not the least of which is accrual and retention. Appropriate description and data must be provided for both. There is no gold standard for accrual. Regardless of its range, it must be accompanied by a rigorous statistical analysis (and not one limited by low power due to a small sample size) to rule out biases that might be correlated with outcome. Similarly, investigators struggle to maintain partic-

ipant retention. Again, comparison with retained subjects and information on causes of dropout is important. Some are under control of the investigator (e.g., lack of participant interest, poor staff training resulting in low accrual) and can be eliminated, whereas others are not under one's control (e.g., physician turnover, changes in institutional policies for study accrual) yet need to be anticipated in power analyses.

One strategy used in cancer treatment trials to achieve timely accrual goals (other than multi-institution trials) is to accrue a heterogeneous sample but then to randomize within strata. The variables chosen for stratification are ones that may potentially covary with the outcome or that are of interest but whose power is insufficient to test them a priori. For example, in breast cancer treatment clinical trials, strata can include numbers of nodes positive, estrogen receptor status, menopausal status, or others; such variables are of importance to learn differential treatment efficacy with patient subgroups. Ignoring such variables relies on lady luck and/or a large sample to reduce the likelihood of inequality and confounding. Few investigators have used this procedure, though there are exceptions: MacVicar et al. (1989) used functional capacity strata and age for an exercise intervention, and A. J. Cunningham et al. (1998) used presence of visceral metastases strata to test for survival. Indeed, stratification on disease or prognostic variables becomes more important as study outcomes shift from the psychological–behavioral to the biologic–disease endpoints. However, all investigators might consider stratification and related strategies to increase—but control—heterogeneity of study samples and generate hypotheses for future efforts.

Patient Variables

I have noted three classes of variables—sociodemographics, premorbid status, and individual differences—as important for description and, perhaps, manipulation in experimental studies (Andersen, 1992). I echo those recommendations here. Considering the first class, it would appear that study samples are less heterogeneous, as the young (e.g., 20–40 years), old (e.g., 65+ years), non-White, male, and those with fewer years of education or lower incomes remain understudied. All of these groups represent one sort of accrual challenge or another, yet the burden of cancer for the elderly, African Americans, men, and the poor remains in this millennium (Bradley, Given, & Roberts, 2002; National Cancer Institute, 2000) just as before (e.g., Baquet, Horm, Gibbs, & Greenwald, 1991). Without increasing diversity, the field is at risk of characterizing intervention outcomes for only middle age, middle class, women with cancer.

Concerning premorbid status, I refer to both physical and mental health conditions that predate the onset of cancer. Most investigators screen out individuals with one or both conditions in a likely attempt to decrease heterogeneity, but this may adversely affect the likelihood of finding intervention effects, as either condition adds to the risk for adjustment difficulties (e.g., Satariano, 1992; Wells et al., 1989). In some studies, intervention effects were weak to nonexistent. Post hoc analyses often revealed intervention effects with subgroups (e.g., interventions are more effective with high distress rather than low distress patients; Antoni et al., 2001; or those with low levels rather than high levels of support; Helgeson et al., 2000).

Some researchers with descriptive, longitudinal data sets are attempting to characterize the posttreatment trajectory for individuals with differential levels of distress at diagnosis, and additional reports would be informative. Data from Epping-Jordan et al. (1999), for example, suggested that upward of 80% of patients report low distress as they cope with cancer treatments and recover. Thus, researchers might consider including, rather than excluding, those with premorbid conditions, particularly depressive or anxiety disorders, as well as including only those with moderate to high levels of distress. These procedures would enhance power and thereby reduce sample sizes.

There are at least two salient directions for research on individual differences. One avenue includes identifying psychological factors (aside from premorbid or overall stress levels) that place patients at risk for poorer psychological and behavioral outcomes. Some have proposed models for predicting risk (e.g., Andersen, 1994), and other testable conceptualizations are needed. Examples of psychological variables include social–cognitive factors, including attributions (e.g., control in Astin et al., 1999; self-blame in Glinder & Compas, 1999), social comparison processes (Stanton, Danoff-Burg, Snider, Cameron, & Kirk, 1999), differential use of coping strategies (e.g., emotion focused disengagement in Epping-Jordan et al., 1999; Livneh, 2000), and outcome-specific individual differences (e.g., sexual self-schema for sexual morbidity in Yurek, Farrar, & Andersen, 2000).

A related direction is the consideration of positive, in contrast to negative, dispositional or situational factors. This primarily includes individual-difference factors such as optimism (see Allison, Guichard, & Gilain, 2000; Epping-Jordan et al., 1999, for examples), but positive coping (Andrykowski et al., 1996) and meaning and perspective taking (Antoni et al., 2001) are other examples. Positive factors take on added relevance if studies oversample the moderately to severely distressed, as these factors covary, but do not necessarily overlap, with distress.

Cancer Variables

Investigators have become more alert to fully describing disease characteristics (e.g., site, stage, time since diagnosis, treatments received) of study samples, although continued vigilance is in order by both investigators and journal editors evaluating research methods. Adequate description will take on greater importance as the heterogeneity of samples increases.

The larger issue regarding cancer variables is the pattern of patient selection that has evolved; that is, across studies the samples are homogeneous, with an oversampling of women and primarily, women with breast cancer. The magnitude of the breast cancer problem, the large numbers of available participants that facilitates rapid accrual, a research design decision to increase homogeneity to enhance power, and, of course, differential funding opportunities in breast cancer research contribute to this outcome. These are important, positive circumstances, yet if not balanced by equally important needs, the generalizability of the findings to both research and clinical contexts will be constrained.

Therapists and Therapeutic Techniques

Aside from peers, interventions were conducted by a range of professionals (e.g., psychologist, psychiatrist, nurse, social worker) who performed similar tasks (e.g., relaxation, cognitive–behavioral interventions); the data do not show any differential outcomes between professionals. Regarding peers, the factorial designs suggest that peers may not be effective in a support only context (Helgesen et al., 1999; McArdle et al., 1996). Moreover, the Helgeson data (Helgesen et al., 1999) suggest that peers had a negative effect on women beginning the study with high levels of support. Alternatively, peers or volunteers may be quite effective when delivering a content-specific treatment, such as dietary counseling (e.g., Kristal et al., 1997).

The novel interventions reviewed here were the brief, cost-effective, physician communication-training intervention of Rutter et al. (1996) and the clinic orientation of McQuellon et al. (1998). Although considerably more intensive, the individual intervention of Kuchler et al. (1999) was novel in its delivery in the in-patient setting and impressive with the positive survival outcomes. The brief interventions produced positive, immediate outcomes on measures of anxiety and depression. These interventions, as well as relaxation therapy alone (Larsson & Starrin, 1992), are the type of efforts that could be implemented widely to all cancer patients (see Dreher, 1997, for a discussion). Further, with adequate training and supervision, peers or volunteers could be successfully used as the "therapists." With a triage model, intensive (and expensive) efforts, such as group or individual interventions, could be provided selectively to moderate to high risk–high distress patients.

The majority of the interventions testing for psychological–behavioral, biologic, and disease outcomes were multimodal and included components consisting of stress reduction (progressive muscle-relaxation training), disease and treatment information, cognitive–behavioral coping strategies, and social support, as was previously the case (Andersen, 1992). Intervention studies, particularly ones testing multiple component therapies, should include validity checks to ensure that each components has its expected effect (e.g., an education intervention tests participants knowledge of a relevant topic). Similarly, intervention process measures can provide data for post hoc hypotheses regarding which components were instrumental in achieving specific biobehavioral outcomes.

With focus shifted to moderate- and high-distress individuals, there will likely be a higher prevalence of adjustment disorders with depressed and/or anxious symptoms and premorbid major depression and anxiety disorders (Roth & Massie, 2001). Investigators who selectively accrue these individuals, with or without prior psychiatric histories, might consider pharmacologic therapy in combination with psychological–behavioral components, as is common in contemporary treatment-outcome research for depressive and anxiety disorders (e.g., Heimburg et al., 1998).

Interventions for compliance and health behaviors have included strong educational components and behavioral strategies for change and maintenance. For health behavior interventions, the cancer dietary, exercise, and smoking cessation interventions can benefit from the basic research and intervention developments within these respective content areas (see Wadden, Brownell, & Foster, 2002; Dubbert, 2002; Niaura & Abrams, 2002, respectively, in this issue). It would seem important to incorporate these advances (e.g., use of nicotine replacement), as the early intervention efforts are encouraging, particularly for diet and exercise.

Finally, of the outcomes examined, interventions for compliance have been largely ignored. Descriptive studies with large samples of common drug regimens, chemoradiation regimens with high

toxicity, as well as the newer, promising therapies (e.g., Herceptin, Taxotere), are needed. Moreover, individuals at highest risk for compliance problems (e.g., those with complex and/or high toxicity regimens, those with limited economic resources) need special attention, as was illustrated by Richardson (J. L. Richardson et al., 1987).

Assessment Strategies and Outcomes

Significant progress has been made in the domain of assessment. Reliable and valid strategies have emerged for assessing self reports of mood (e.g., POMS), depressive symptoms (e.g., CES–D), quality of life (e.g., SF-36, FACT scales), stress (e.g., Impact of Event Scale, Perceived Stress Scale; Cohen, Kamarck, & Mermelstein, 1983), and related concepts. These measures can be sensitive to differences between groups and change across time. However, if patients with premorbid difficulties, higher distress, or both are included and/or oversampled, formal assessments of psychopathology (e.g., diagnostic interviews) will likely be necessary to document past and current psychopathology.

Beyond stress and quality-of-life outcomes, assessment of behavioral and biologic outcomes for the compliance and health behavior areas is needed. Notably, some investigators have accomplished this. For example, J. L. Richardson et al. (1987) took blood samples for drug metabolite studies, Dimeo et al. (1997) assessed cardiac indices and functional status, Pierce et al. (1997) assessed biomarkers, and Wewers and colleagues (e.g., Stanislaw & Wewers, 1994) used saliva cotinine samples for nicotine intake. Despite the logistic difficulties and costs of these efforts, only measures of this sort can validate self report data and confirm that interventions have the predicted health effects.

A Final Comment

Intervention studies with cancer patients are being conducted around the globe. More rapidly than ever, findings are disseminated and replications and extensions are underway. This is heartening, as the need for progress in addressing the behavioral issues of cancer is great. Yet, accrual bases need to be widened so that study participants represent the diversity of cancer, as the disease spares no gender, age, ethnic or economic group, or nationality. This is also true when considering issues of cancer survivorship. In the United States, for example, 25% of all survivors have been treated for breast cancer, 15% for colorectal, and 12% for prostate, but the rest (48%) are survivors of other disease sites (Stat bite, 1998). With the database of the past 3 decades on psychological and behavioral outcomes, there is no justification for continuation of the narrowed focus that has evolved. In contrast, the database on biologic and or disease outcomes following psychological interventions is sparse, and homogeneous study samples may be needed as effect sizes are likely small. As the financial investment for the latter studies is substantial, strategies for accrual and retention of study participants must be piloted so that samples are not biased and studies are efficient, cost-effective, and maximally informative.

The prior review concluded that progress in the area would be limited without advocacy and changes in funding patterns. Indeed, progress has been made. In the United States, for example, presidents of the American Psychological Association have raised the banner for cancer patients (Rozendy, Johnson, Goodheart, & Hammond, in press; Suinn & VandenBos, 1999), and behavioral scientists currently have a significant presence in cancer prevention and control at the National Cancer Institute. For scientists in the area, this turnaround has been no less than remarkable. It is hoped that these changes are stable and can grow. One area for continued vigilance is training. That is, increasing the numbers of new behavioral scientists entering the area and training with interdisciplinary mentors with a biobehavioral perspective on the cancer problem is important. These are the issues of a maturing discipline, and it is exciting that psychological research in cancer has reached this milestone.

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