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Meta-analysis of the effects of psychosocial interventions on survival time in cancer patients

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Abstract

Objective: To provide a quantitative summary of effects of psychosocial interventions on cancer survival, and to present an overview of methodological and reporting aspects of the studies. **Method:** Electronic searches and manual searches of reference lists from review articles and retrieved papers. Two coders independently coded study, participant, treatment, and outcome characteristics of the studies meeting selection criteria. **Results:** Thirteen journal articles published between 1989 and 2003 reporting results from 14 controlled intervention studies were included. Results are based on data obtained from 2626 subjects. Effect sizes [hazard ratios (HR)] were heterogeneous and random effects models were used in the analyses. The total mean inverse-variance-weighted HR was 0.85 (95% CI: 0.65–1.11). Randomized studies ($n = 8$) showed no overall treatment effect (HR: 0.77, 95% CI: 0.56–1.06), neither did the nonrandomized studies (HR: 1.00, 95% CI: 0.61–1.62). Interventions using individual treatment ($n = 3$) were, however, found to be effective (HR: 0.55, 95% CI: 0.43–0.70) but interventions using group treatment ($n = 9$) were ineffective (HR: 0.97, 95% CI: 0.73–1.27). Group treatments of breast cancer ($n = 6$) were ineffective (HR: 0.95, 95% CI: 0.69–1.31). **Conclusion:** A definite conclusion about whether psychosocial interventions prolong cancer survival seems premature. Future studies should use randomization to avoid self-selection of patients with poor prognosis. Interventions should focus on a single diagnosis, take into account known risk factors, and describe their interventions thoroughly.

Keywords: Cancer; Meta-analysis; Psychosocial; Psychotherapy; Survival

Introduction

Cancer is currently the second leading cause of death in the developed countries, only exceeded by cardiovascular diseases, and one out of four deaths is from cancer [1,2]. In the year 2000, 5.3 million men and 4.7 million women worldwide developed cancer and altogether 6.2 million died from the disease. Approximately 22 million people are living with cancer worldwide, and in the next 20 years the number of cancer patients is expected to double [2].

There are more than 110 different types of human cancer [3]. Different cancer types vary according to whether they are influenced by immune parameters, viruses, hormones, or faulty DNA repair [4]. The knowledge of the causes of cancer varies by type. In the case of female breast cancer, only about 41% of cases can, for example, be explained by the currently recognized risk factors [5]. The most important ones include age, mutation of the genes BRCA1, BRCA2, and p53, having first-degree relatives with breast cancer diagnosed under the age of 50, first menstruation before age 12, menopause after age 50, having no children or first child after age 30, and overweight after menopause.

Some of the unexplained causality may be attributed to psychosocial factors. There is a large literature on the subject of psychosocial factors and cancer. Research on the relations among personality, coping, stress, and cancer has produced highly conflicting results [4,6–11]. Eysenck [12] suggested that this might be because few studies have tested specific theories using adequate methodology. Pioneers in the field [13–15] studied each patient carefully while being largely ignorant about methodological aspects like randomization, control groups, and masking (blinding). On the other hand, according to Eysenck [12], there are studies conducted by epidemiologists with little psychological insight. They have

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employed modern methodology, but they have not really tested the theories put forth in the field.

Most studies on psychological aspects of cancer have used case control [16–19] or prospective [20–25] designs. Unfortunately, these types of designs cannot tell us much about the causality involved. The three psychological factors that have been more prominent in cases compared to controls are hopelessness, depression, and suppression of emotion. But these are only a few. Fox [26] has provided a list of 59 psychosocial variables that have been associated with the presence of cancer or its prognosis. It seems highly probable that persons develop feelings of depression and hopelessness because they have cancer. It is equally probable that they react by denying or suppressing these painful emotions. In order to avoid this bias, some researchers have used something called ''limited prospective designs.'' Here, patients referred to a hospital are interviewed before they receive a final diagnosis. Some will later turn out to have cancer and others will have benign conditions. But this design is not much better than the original case control design. One study found that most patients (74%) were aware of their disease status prior to the biopsy [27]. The referring physicians will also in most cases have a good idea of what the diagnosis eventually will be and he or she will tend to communicate this nonverbally.

The best method of studying associations between psychosocial factors and cancer is the controlled intervention study. With proper randomization, one is assured that any difference between the groups at the start of the study is due to chance. And one can be reasonably confident that the aggregated poststudy differences are due to the intervention. Most published studies have looked at psychological outcome variables, and there is a need for more studies that have survival time and mortality as the outcome variables [28].

Possible reasons why psychological interventions might be expected to have an impact upon survival (biological endpoints)

Psychosocial factors have been linked to the development and progression of cancer and shown to be relevant in cancer care. However, the evidence that psychosocial interventions affect cancer survival is less conclusive [29]. Some studies have reported that psychosocial interventions that encourage the expression of emotions, provide social support, and teach coping skills can prolong survival in patients with cancer [30–34] while others have not found any significant survival benefit from various forms of psychotherapy [35–37].

The importance of social support for patients' adaptation to the illness has been underscored in large community cohort studies. Population-based studies of adults with cancer indicate that unmarried patients and patients lacking social support have a decreased overall survival and poorer treatment response than married people [38]. One psychological factor shown to have a significant detrimental effect on both quality of life and survival of cancer patients is the coping response of helplessness/hopelessness, a response that can be altered by psychotherapy [6,39]. Although more research is clearly needed in this area, initial studies of the effects of psychosocial intervention with cancer suggest that psychosocial factors have potentially powerful modulating effects on the course of disease. In a review of the possible mechanisms whereby psychosocial factors may influence disease-resistance capabilities, Spiegel et al. [40] reported that suppressive effects of stress on immune function have been shown to be modulated by social support. Thus, they found it reasonable to hypothesize that supportive social relationships might buffer the effects of cancer-related stress on immunity and thereby facilitate the recovery of immune mechanisms that may be important for cancer resistance.

Previous reviews

To our knowledge, there are no published meta-analyses on psychosocial intervention studies looking at survival from cancer as the outcome variable. But there are some narrative reviews on the subject (e.g., Refs. [7,11,26,28,41,42]). Fox [26] wrote, ''It is clear that the issue of extension of life among cancer patients by psychotherapeutic intervention is quite unsettled. Too many differences exist in procedures, samples, disease types, stages, experimental designs, approaches to therapy, durations of treatment, etc. to allow a clear conclusion'' (p. 121). Classen et al. [7] discussed six controlled trials of which three had found life extending effects of psychosocial interventions and three had not. The three effective interventions [30,32,61] seemed to have some factors in common that were lacking in the ineffective ones [35,43,44]: (1) a supportive, stable, and consistent environment; (2) homogeneous groups to cancer type and stage; (3) an educational component; and (4) stress management and coping skills training.

Aims

The present paper describes an effort to synthesize the current evidence for an effect of psychosocial interventions on cancer survival. Because of the methodological shortcomings of case control and prospective cohort studies, we limited the analysis to controlled intervention studies. By including both randomized and nonrandomized studies, it was possible to compare how the two designs influence effect sizes. We also wanted to compare the different studies on the reporting of study information in order to point out gaps in the literature and ideas for future studies.

Methods

Search strategy

We performed electronic searches in Psychinfo (1887–2003, Week 25), Pubmed (1960–2003, Week 25), Embase

(1980–2003, Week 25), Allied and Complementary Medicine (AMED; 1985–June 2003), and Google. The main search strategy was (''neoplasm'' OR ''cancer'') AND (''psych?'' OR ''intervention'' OR ''treatment'') AND (''survival'' OR ''mortality''). In addition, we manually searched the reference lists of retrieved publications and reviews. Supplementary information was sometimes obtained directly from the authors or from another published report.

Inclusion criteria

1. Participants must have a cancer diagnosis.
2. Intervention variables must involve some kind of or combination of education, social support, psychotherapy, skills training, relaxation, etc.
3. Studies must be controlled interventions.
4. Outcome variable must be survival time.
5. It must be possible to calculate a hazard ratio (HR) between the treatment and control group for survival with an associated variance. If this is not directly reported in the primary report, it must be possible to obtain it by other means. This can, for example, be from personal communication with the authors or from indirect calculation.

Exclusion criteria

1. Cancer incidence as outcome.
2. Another publication reported earlier results (i.e., shorter follow-up) on the same sample.

Coding variables

A coding manual was prepared before coding the studies. The manual was revised during the coding to incorporate important aspects of the located studies. The final list of variables included the following: publication year, number of subjects in the control and intervention groups, mean age, percentage of males, type of cancer, terminal/nonterminal cancer, metastatic/non-metastatic cancer, random/nonrandom allocation, type of control group, preintervention check of equality of groups, differences found/not found preintervention, group/individual intervention, chemotherapy, radiotherapy, surgery, page number where the effect size data were found, and which group was the most successful.

Table 1
Overview of the studies

Study ID	Publication year	Country	Intervention	Control group, *n*	Treatment group, *n*	Cancer type	Random treatment	Group intervention	Follow-up time
Bagenal et al. [53]	1990	United Kingdom	Counseling, healing, positive attitude	461	334	Breast	No	Not reported	9 months–2 years
Cunningham et al. [36]	1998	Canada	Supportive+cognitive–behavioral therapy	36	30	Breast	Yes	Yes	5 years
Edelman et al. [54]	1999	Australia	Cognitive–behavioral therapy	61	60	Breast	Yes	Yes	5 years
Fawzy et al. [33]	2003	United States	Education, stress management, coping skills, support	34	34	Melanoma	Yes	Yes	10 years
Gellert et al. [44]	1993	United States	Counseling, peer support, positive mental imagery	102	34	Breast	No	Yes	20 years
Goodwin et al. [37]	2001	Canada	Supportive, expressive	77	158	Breast	Yes	Yes	7 years
Ilnyckyj et al. [35]	1994	Canada	Weekly supportive group therapy	31	96	Several	Yes	Yes	11 years
Kuchler et al. [34]	1999	Germany	Psychotherapy	135	136	Several	Yes	No	2 years
McCorkle et al. [57]	2000	United States	Psychosocial and physical postsurgical home care by advanced practice nurses	185	190	Several	Yes	No	3 years and 8 months
Ratcliffe et al. [58]	1995	United Kingdom	Hypnotherapy	27	36	Hodgkin's disease and non-Hodgkin's lymphoma	Unclear	Unclear	5 years
Richardson et al. [32]	1990	United States	Intervention to improve compliance	25	69	Hematologic	No	No	5 years
Shrock et al. [29]	1999	United States	Health psychology classes	74	21	Breast	No	Yes	6 years
Shrock et al. [29]	1999	United States	Health psychology classes	65	29	Prostate	No	Yes	6 years
Spiegel et al. [30]	1989	United States	Supportive, expressive	36	50	Breast	Yes	Yes	10 years

A copy of the coding manual is available by contacting the first author.

Interrater reliability

The two authors independently coded the studies according to the coding scheme. Disagreements were resolved during meetings between the two authors.

Statistical analysis

Type of effect size

When the outcome involves the comparison of two survival curves, the correct statistic to use is the log hazard ratio (lnHR). It is the only measure that takes into account all the information in the curves and the censored cases. For each study, an lnHR with its standard error was calculated. In some of the primary reports, these parameters were reported directly. In other studies, we had to estimate them from other reported data using the methods provided in Ref. [45]. In still other studies, we contacted the authors in order to obtain the data.

Type of statistical model

Because we compared the effect of a wide range of interventions on a wide range of different cancers, we decided to use random effects modeling overall. Random effects models take into account the amount of variance caused by differences between studies as well as differences among subjects within studies. The analyses were done using Review Manager 4.2 and RevMan Analyses software [46].

Statistical heterogeneity

For each subgroup, a homogeneity test [47] was calculated. This test produces a statistic called Q, with a chi-square distribution. The size of the Q provides information about the probability of the results if all the effect sizes were sampled from the same population. We also calculated a statistic called I^2 [48]. This measures the extent of inconsistency among results and is interpreted as approximately the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error.

Publication bias

A funnel plot was produced to get a graphical impression of the relation between the effect size and the precision of each study. Publication bias can be detected as a lack of small (imprecise estimates) studies with effect sizes favoring the control group. Funnel plots are not very useful with a small number of studies though. Specifically, publication bias would be seen in Fig. 3 as a relative lack of studies in the lower right portion.

Planned comparisons

We analyzed randomized and nonrandomized studies separately. In addition, we separately analyzed group interventions and individual interventions. Finally, the subgroup of studies treating breast cancer was analyzed.

Results

The search resulted in 13 papers published between 1989 and 2003 [29,30,32–37,44,53,54,57,58]. Because one paper [29] reported results from two interventions, the total number of interventions was 14. This resulted in a total of 14 effect sizes based on data obtained from 2626 subjects. Table 1 gives an overview of the designs and settings of the included studies.

The studies are conducted in only five countries, and half of the studies are U.S. studies. The interventions are diverse with elements of education, support, and skills training.

Studies that were not included

In order to make our decisions regarding inclusion and exclusion of studies transparent, we considered it informative to briefly describe the excluded studies that came closest to inclusion.

Eysenck and Grossarth-Maticek [49,50] have reported a study that found a synergistic effect of combining chemotherapy with psychotherapy, but the reported data were not sufficient to compute an effect size.

Grossarth-Maticek [55] reported results from a study that fulfilled all the inclusion criteria for this review. However, the credibility of these results has been seriously questioned [56].

Table 2
Reporting of key variables

Variable	Mean/frequencies	Proportion reported
Mean age	52.6 (6.4)	9/14
Type(s) of cancer	3 several types	14/14
Stage of cancer	7 with more than 50% metastases, 7 with less than 50% metastases	13/14
Randomization	8 randomized, 5 nonrandomized	13/14
Preequivalence of groups tested	13 tested	13/14
Predifferences found	1 not found, 12 incorporated into analysis	13/14
Group or individual intervention	4 individual, 8 group, 1 both	13/14
Percentage of patients receiving chemotherapy	Range: 1–100%	7/14
Percentage of patients receiving radiotherapy	Range: 3–88%	6/14
Percentage of patients receiving surgery	Range: 0–100%	7/14

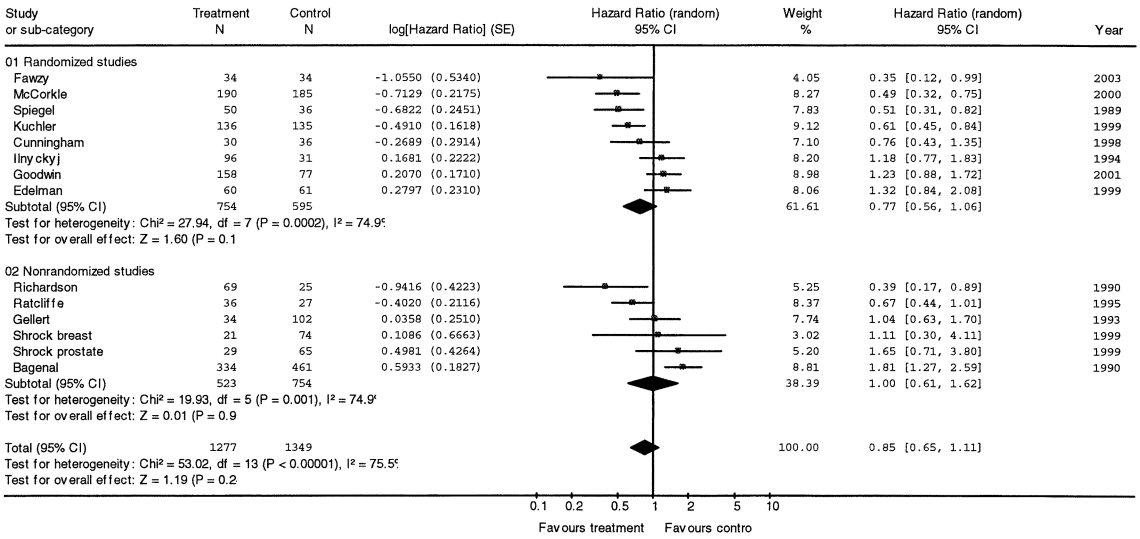

Fig. 1. Meta-analysis of the subgroups of randomised and nonrandomised studies.

Newton [51] studied the effect of hypnosis on survival in cancer patients. In this nonrandomized study, ''adequate treatment'' was defined as a minimum of ten 1-h sessions over a 3-month period, and ''inadequate treatment'' was defined as having been treated more than three times but less than ten. We did not judge these groups to qualify as proper treatment and control groups.

Linn et al. [43] did not report the necessary data for computing an HR. Since this is an old study, we did not try to contact the authors.

The reports of two studies by Walker et al. [59,60] were only abstracts that did not report sufficient data, and a request to the authors did not help.

Morgenstern et al. [52] reported preliminary follow-up data, but Gellert et al. [44] reported survival data on the same sample with longer follow-up times, and the last mentioned report was therefore chosen.

Finally, Fawzy et al. [61] reported 6-year follow-up on a sample, but they recently reported a 10-year follow up on the same sample [33].

Interrater reliability

A total of 660 ratings were made. We agreed on 583 ratings (88.3%). We attained perfect agreement on publication year, type of control group, and testing of prestudy differences. The lowest agreement on a variable was on the percentage of patients having received chemotherapy (68.8%), but this variable was not very helpful anyway because only eight studies reported data on this.

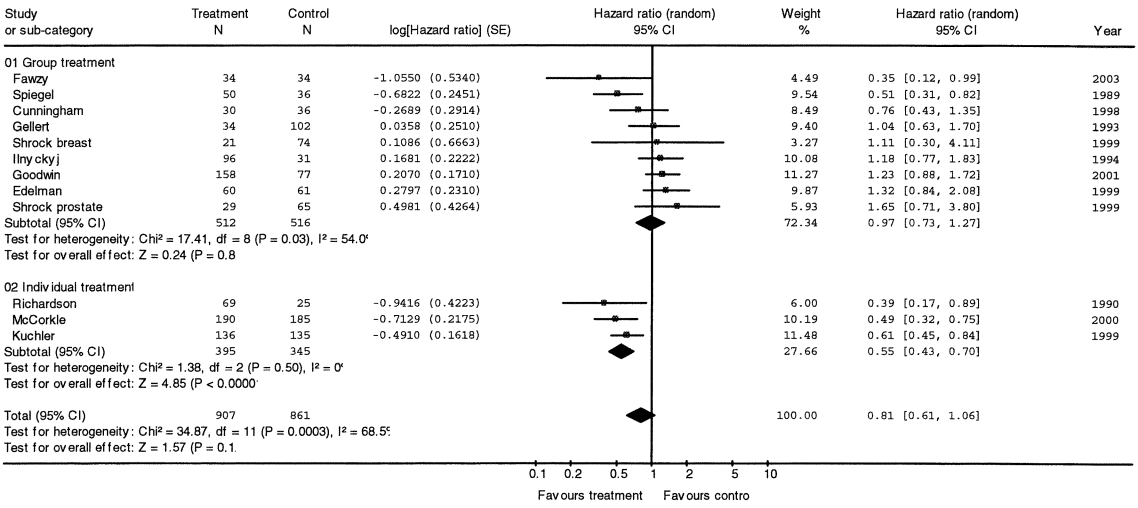

Fig. 2. Meta-analysis of the subgroups of studies using individual or group interventions.

Reporting of information

Table 2 provides an overview of the reporting of some key variables.

Age is an important predictor of the prognosis of most diseases, but we were only able to find data on this variable in 9 of the 14 studies. Most cancer types, except for leukemias, can be stage classified. There are two general stage classification systems; the overall stage groupings (I–IV) and the TNM staging. In the present study, insufficient reporting of stage forced us to divide studies into those with more or less than 50% of cases having metastases. The treatment history is important for prognosis and should be reported. Only about half of the studies did this. The following time points in cancer are important: time of first diagnosis, time of treatment (surgery, radiotherapy, and chemotherapy), time of entry into the study, time of disease recurrence, and time of death. Unfortunately, information about these time points was so scarce that we could not use it.

Effect Sizes

A total of 13 papers fulfilling the inclusion criteria were found. One paper reported results from two independent groups with different types of cancer [29]. This resulted in a total of 14 comparisons. Fig. 1 shows the effect sizes (HR) with 95% confidence intervals for the 14 treatment studies categorized into randomized and nonrandomized studies.

The meta-analysis for the total sample of studies shows a nonsignificant treatment effect. The overall HR is 0.85 (95% CI: 0.65–1.11, $Z = 1.19$, $P = .2$). There is a large amount of heterogeneity ($\chi^2 = 53.02$, $df = 13$, $P < .00001$, $I^2 = 75.5\%$). There were also nonsignificant treatment effects in the subgroups of randomized studies (HR = 0.77, 95% CI: 0.56–1.06) and nonrandomized studies (HR = 1.00, 95% CI: 0.61–1.62). No randomized and only one nonrandomized study have found a significant better survival in the control group [53].

Fig. 2 shows the results broken down into studies using individual treatments and studies using group treatment.

Note that two studies [53,58] are missing from the analysis in Fig. 2 because we could not determine whether they used group or individual therapy. According to this analysis, the studies using group treatment have not found an overall effect on survival (HR = 0.97, 95% CI: 0.73–1.27). There is some heterogeneity but much less so compared to the whole sample of primary studies ($\chi^2 = 17.41$, $df = 8$, $P = .03$, $I^2 = 54\%$). But the three individual treatment studies show a large treatment effect (HR = 0.55, 95% CI: 0.43–0.70) and this subgroup is homogeneous ($\chi^2 = 1.38$, $df = 2$, $P = .50$, $I^2 = 0\%$). In fact, all the individual studies show a significant treatment effect.

The separate analysis involving group interventions for women with breast cancer ($n = 6$) did not show any treatment effect (HR = 0.95, 95% CI: 0.69–1.31). The sample was marginally heterogeneous ($\chi^2 = 11.56$, $df = 5$, $P = .04$, $I^2 = 56.7\%$).

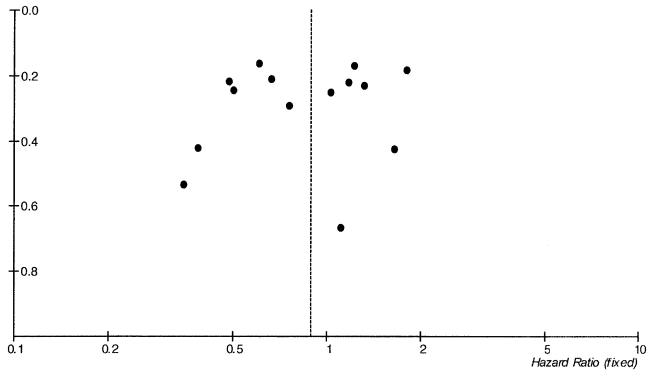

Fig. 3. Funnel plot of the effective sizes against the inverse variance weights of the individual studies.

A funnel plot was produced to detect the presence of publication bias (Fig. 3). Because of the low number of studies, this is not very informative but it is regarded as good practice to routinely publish such plots in meta-analyses.

Discussion

To our best knowledge, this is the first attempt at quantifying the effects of psychosocial interventions on cancer survival. A comprehensive literature search resulted in only 13 published papers reporting effects of psychosocial interventions on cancer survival time, and the median publication year was 1999. This meta-analysis suffers from the so-called ''apples and oranges'' problem. We assume that the large variation in effect sizes (heterogeneity) is due not only to sampling error, but also to systematic differences among the studies. The studies used different types of interventions with different types of subjects in different settings. On the other hand, there may be unspecific therapeutic factors operating, which are common to all interventions. This may for example be receiving attention and information, having the opportunity to share thoughts and feelings, and belief in the efficacy of the interventions. In addition, having a diverse set of studies heightens the external validity of the meta-analysis.

Both the results from the randomized and the nonrandomized studies agree that there is no evidence of effect. But we have more faith in the estimate from the randomized studies because they avoid self-selection bias. It may be that the patients that agree to receive psychosocial interventions are the ones that initially have the worst prognosis because everything else has failed. This could explain why the control subjects in the nonrandomized Bagenal et al. [53] study outlived the intervention subjects.

Another main finding from the present analysis is that individual treatments have worked but group treatments

have not. Only one primary study of group therapy for breast cancer found a significant effect [30]. In this study, the intervention group did no better than what was common among patients in the particular geographical area where the study was conducted [62].

While doing the literature search, we came across a set of somewhat different studies. Instead of treating cancer patients, these four randomized controlled intervention studies [63–65] delivered cognitive behavior therapy to healthy subjects in order to try and prevent cancer in the future. The idea of using psychotherapy in healthy individuals to prevent cancer is interesting, but independent replications are necessary in order to make strong causal claims for effects. Indeed, there is a special need for replication of these particular studies because of the aforementioned critique of the credibility of the data [56]. But if this really works, it suggests that psychotherapists around the world are doing cancer prevention as well as helping their clients with mental problems.

Conclusion

Previous narrative reviewers [7,8,11,26] have not agreed on whether psychosocial interventions delivered to cancer patients have had any effect on survival whatsoever. The present meta-analysis is in accordance with the narrative reviews in concluding that the matter is not resolved. What is new is the quantification of the findings and the inclusion of some recent studies.

Because psychooncology is extremely complicated, studies should, accordingly, be methodologically highly sophisticated. Because different cancers have different causes, only one type of cancer should be studied at a time. And it is important to measure and report risk factors. Because psychosocial interventions are so diverse, it is important that authors describe their interventions in sufficient detail, including any deviation from what was planned [41]. Papers should also routinely give information on whether survival time was from first diagnosis to death, from surgery to death, from inclusion in the study to death, etc. Only with high-quality studies can we hope that future meta-analyses will find effect sizes converging on specific effect magnitudes. Looking back, the quality of studies has improved greatly over the years, and this will certainly continue. We are aware of an ongoing study [66] that meets the inclusion criteria for this meta-analysis, but the results have not yet been analyzed awaiting a predetermined 90% mortality rate.

A meta-analysis is only as good as its available data. The small number of diverse studies and the lack of complete data on variables such as cancer treatment may lead one to conclude that this meta-analysis is premature. On the other hand, this should only be regarded as a starting point for future updates. Our aim was not to speculate about what works in general but to provide a quantitative summary of what has worked in the existing studies. However, effects may change over time. When this kind of therapy was first started in the late 1970s [67], the main problem was convincing patients who were randomly assigned to group therapy to attend the sessions, while in the 1990s patients were disappointed about being assigned to the control group.

Acknowledgments

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