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Review article

## **Meta-analysis of Psychosocial Interventions on Survival Time in Patients with Cancer**

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## ABSTRACT

**Objective:** This study was to evaluate the effects of psychosocial interventions on survival in adult patients with cancer. **Method:** MEDLINE via PubMed, Cochrane Library CENTRAL, CINAHL, and Korean electronic databases (September 2014) were searched. Methodological quality was assessed using Cochrane's Risk of Bias for randomized studies. The RevMan 5.3 program of the Cochrane library was used for data analysis. **Results:** Fifteen randomized controlled trials met the inclusion criteria, with a total of 2940 participants. Overall, psychosocial interventions was not associated with better survival ( $HR= 0.83$ , 95%  $CI$  [0.68, 1.10],  $p=.06$ ,  $I^2=64\%$ ). In subgroup analysis, based on six trials with 1448 subjects, psychoeducational interventions for cancer patients with non-metastatic at intervention implementation resulted in a 41% reduction in the risk of dying of cancer ( $HR= 0.59$ , 95%  $CI$  [0.49, 0.71],  $p<.001$ ,  $I^2=0\%$ ). For psychoeducational intervention, significant survival benefit were found when health staff delivered the intervention and at a follow-up time of more than 10-years. **Conclusions:** Use of psychoeducational interventions for cancer patients

at early stage appeared to have beneficial effects on survival, preferably for delivering of health staff. However, conduct of further psychosocial studies with adequate power will lead to better understanding of the effects of treatments on survival outcome.

*Key words:* neoplasm, survival, intervention studies, meta-analysis

### Introduction

Possible association between psychosocial factors and biological outcomes has been questioned. Factors such as stressful life events, attitudes, coping style, social support, psychological distress and emotional repression have been investigated as possible contributors to the disease process (Edelman, Lemon, Bell, & Kidman, 1999). Among those, helplessness/hopelessness, depression and emotional repression were shown to have a greater link to the progression of cancer (Smedslund & Ringda, 2004). There is now considerable evidence that stress-related psychosocial factors activate the neuroendocrine stress response and alter immune and inflammatory pathways important in the development, progression, and control of cancer (Antoni, 2006; Black, 2002; Irwin & Miller, 2007; Lutgendorf et al, 2008). Based on findings from a meta- analysis, it was suggested that stress-related psychosocial factors are associated with higher cancer incidence in initially healthy people and poorer survival in people with cancer (Chida, Hamer, Wardle, & Steptoe, 2008).

Considering psychological factors as modifiable elements, there is a question with regard to whether psychosocial interventions have an effect on cancer outcomes. Psychosocial interventions such as social support might reduce distress, improve health behaviors and facilitate compliance with cancer treatment through education, stress management and coping skill training (Andersen et al, 2008). In addition, supportive social relationship might buffer

the effects of cancer-related stress on immunity and thereby facilitate the recovery of immune mechanisms and may be important for cancer resistance (Spigel, Stroud, & Fyfe, 1998).

The question of whether psychological intervention can influence the disease process in cancer patients is an important issue within the field of psycho-oncology research (Edelman et al, 1999). While there is evidence indicating that psychosocial interventions improve coping, reduce psychological distress (Andrykowski & Manne, 2006; Faller, Schuler, Richard, Heckl, Weis, & Kuffner, 2013; Manne & Andrykowski, 2006; Meyer & Mark, 1995; Oh & Lee, 2013; Osborn, Demoncada, & Feuerstein, 2006; Sheard & Maguire, 1999) reduce pain (Sheinfeld Gorin et al, 2012), and increase wellbeing of cancer patients (Faller et al, 2013; Oh & Lee, 2013; Osborn et al, 2006; Newell, Sanson-Fisher, & Savolainen, 2002; Sheinfeld Gorin et al, 2012), its effectiveness in prolonging survival when added to a standard regimen remains controversial. While two previous meta-analyses (Chow, Tsao, & Harth, 2004; Smedslund & Ringdal, 2004) addressed these issues separately in 2004 and yielded no overall treatment effects with eight RCT trials, a recent meta-analysis with 15 RCTs concluded that psychosocial interventions does prolong survival at least for some cancer patients in the first 2 years after intervention (Xia, Tong, Feng, Chai, Cheng, & Wang, 2014). Across these meta-analyses, the results should be interpreted with caution. There are some limitations in each. Results of two meta-analyses published in 2004 showed moderate to high statistical heterogeneity ( $I^2=54.0\sim74.9$ ) between study estimates. Heterogeneity among studies must be considered more carefully prior to synthesizing findings (Coyne, Stefanek, & Palmer, 2007). Meta-analysis applies well only if the heterogeneity is less than 50% (Higgins & Green, 2011). Even though there were nine studies which followed up more than seven years, a recent meta-analysis (Xia et al, 2014) have reported the relative risks which only indicates time period of 1,2,4 and 6 years of intervention. One pitfall in therapeutic trials is picking a

point in time to express the relative risk ratio of an event. This can be misleading as it could be used to select the point in time at which there was greatest separation between the treatment and the comparator arms (Duerden, 2009). Relative risk ratio is usually calculated at the end of the study, is quoted as having occurred over the average or median duration of the trial, and the point at which the trial ends or is halted should be pre-specified. Thus, using survival data and hazard ratios goes some way to preventing this type of selectivity (Higgins, & Green, 2011). In addition, a previous study (Xia et al, 2014) reported that some relative risk ratios were estimated from published survival curves in studies included in their meta-analysis. This suggests that the relative risk ratio was not based on raw numbers of survival rates and may not be accurate. Thus, hazard ratios are commonly used when presenting results in clinical trials involving survival data.

Thus, there are challenges in evaluation of studies in this area. It remains unclear both whether psychosocial interventions are effective on survival and whether long-term efficiencies of different psychosocial interventions are sustained. In an effort to gain a better understanding of the effectiveness of these interventions and to update findings with studies with a more extended follow-up, we conducted a meta-analysis of all randomized trials of psychosocial interventions and subsequently used hazard ratios to present the results. Meta-analysis is a recognized method for synthesizing the results of controlled trials in order to estimate the strength of evidence for intervention efficacy (Sheinfeld Gorin et al, 2012). Reasons for the heterogeneity of previous studies may stem from the intervention and clinical characteristics. A recent meta-analysis conducted on psychosocial interventions on wellbeing of cancer patients suggested that intervention type (relaxation training), duration of intervention (longer interventions), and distress level were moderators of intervention efficacy (Faller et al, 2013). In addition, one meta-analysis on wellbeing of breast cancer

patients suggests that intervention characteristics (type, practitioner, format, timing of intervention) and clinical characteristics (cancer type, cancer stage) were potential moderators of intervention efficacy (Zimmermann, Heinrichs, & Baucom, 2007). Thus, we examined the intervention and clinical characteristics that may explain the heterogeneity of the treatment effect by performing a subgroup analysis. This study evaluated research studies published between 1966 and 2014 in which survival time was measured as an outcome in adult patients with cancer.

## Methods

This meta-analysis is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (Liberati et al, 2009). This review was approved by the Institutional Review Board at Sahmyook University (SYUIRB2013-029).

### Eligibility criteria

Eligibility criteria are detailed in accordance with the PICOS (Participant, Intervention, Control, Outcome, Study design) framework:

*Participants.* Participants were adults ages 18 or older diagnosed at any time with cancer of any type, tumor stage, and treatment mode.

*Interventions.* Psychosocial interventions were defined as non-pharmacologic interventions that use one or a combination of psychological techniques such as education, coping skills training, psychotherapy, and relaxation, provided by professional therapists in a direct, face-to-face interpersonal process to relieve emotional distress and enhance health-related quality of life in cancer patients (Hodges et al, 2011). Interventions were excluded if psychosocial interventions were used along with pharmacologic interventions.

*Controls.* Studies using either no psychosocial treatment or sham intervention as controls were considered.

*Outcome.* The primary outcome was survival time. Survival time was considered death from initial diagnosis.

*Studies.* Only randomized controlled trials (RCTs) were considered for inclusion.

Studies without hazard ratio or sufficient data ( $\beta$  and SE) enabling calculation of effect size were excluded.

## Information sources

We performed electronic searches through EMBASE, MEDLINE, Cochrane Library CENTRAL, CINAHL, and several Korean databases (KMBASE, KOREAMED, RISS, KISS, and NANET). In addition, we conducted a search of the Google Scholar database, a manual review of reference lists of identified studies and review papers extracted from the database searches. The main search strategy combined terms indicating psychosocial intervention, presence of cancer, and study design (see Appendix 1-3 for full list). Searches were limited to articles in Korean or English, and any article published from the earliest publication date within each database to September 2014 was considered. We attempted to acquire missing information. One case was an old study, and we were not able to contact the authors.

## Study selection

All studies identified through electronic searches were downloaded to Refworks, a reference management database, and duplicates were removed. Study selection was performed on two levels: studies were primarily screened using titles and abstracts, and, if necessary, studies were then screened using the full text. Two authors independently screened each study through defined inclusion criteria.

Studies were included if they: a) include adult participants ( $\geq 18$ ) diagnosed with cancer, b) measure psychosocial interventions, c) measure survival time, d) are randomized control trials (RCTs), and e) include sufficient data to calculate survival hazard ratios (*HR*) between



the treatment and control group.

## **Data extraction:**

We extracted the following information for each study based on a predesigned coding manual form: a) authors and years of publication, b) country, and study design, c) number and characteristics of participants (mean age, cancer stage, and cancer sites), d) intervention details (type, format of delivery, profession of therapist, duration), e) condition of control and follow-up time. Pilot testing was performed on five studies before data extraction by two independent reviewers. The lowest agreement on a variable was on the type of intervention (Cohen's kappa coefficient=.79). Disagreements were resolved by discussion. For types of intervention, supportive expressive psychotherapy was defined as building relationships, expressing emotions, overcoming fear of death and dying, prioritizing, strengthening coping skills, enhancing communication skills, and building supportive relationship with family (Spiegel & Classen, 2000; Spiegel et al, 2007). Cognitive behavioral therapy has focused on reducing emotional distress, thought monitoring, cognitive restructuring, utilization of active coping strategies and relaxation techniques (Choi et al, 2012; Edelman et al, 1999). Psycho-educational intervention was defined as multimethod comprehensive interventions covering health education, coping skills training, stress management and psychological support (Fawzy & Fawzy, 1994).

## **Risk of bias assessment**

Two authors independently reviewed each study for methodological qualities. Pilot test was performed on 4 studies before two authors independently assessed study quality. Disagreements were resolved during meetings between the authors. Proportion of interrater agreement for study quality was 0.86.

Identified RCT studies were assessed for the five sources of bias: selection, performance,

attrition, detection, and reporting bias. The seven-item scale of RoB (Risk of Bias), developed by the Cochrane Bias Method Group, was used to evaluate the studies. In other bias, use of an intervention manual and monitoring of the intervention procedure were considered essential for the risk of bias assessment in psychological intervention studies (Ranchor, Fleer, Sanderman, Van der Ploeg, Coyne, & Schroevers, 2012). Results are described in the 'Risk of Bias' tables (Appendix 4).

## Summary measures

For studies with data of sufficient quality and similar in intervention and outcome measures, we combined data in a meta-analysis to provide a pooled effect estimate. Our main analysis was on the effect of psychosocial interventions and survival time of cancer patients. We compared the survival times between the intervention and control groups using the log hazard ratio (*lnHR*). The reported *lnHR* and its standard error were used for studies that reported them, while we calculated *lnHR* and its standard error for studies that did not. In cases where these parameters were not reported, we had to estimate them from other reported study.

As we compared the effects of a wide range of interventions on a wide range of cancers, we used random effect models, which takes the variance from differences among studies and subjects within studies into account (Smedslund & Ringdal, 2004). All data were entered into RevMan 5.3 (<http://tech.cochrane.org/revman/download>), where standardized error (*SE*) and 95% confidence intervals (*CI*) were calculated and pooled. Each effect size was weighed by its inverse variance weight in calculating mean effect sizes. Inverse variance approach gives more weight to studies with larger sample sizes and minimizes the imprecision (uncertainty) of the pooled effect estimate (Higgins & Green, 2011). Heterogeneity was assessed using the

$I^2$  statistics, which measure the extent of inconsistency among results and is interpreted approximately as the proportion of total variation across studies attributable to heterogeneity and not to chance.  $I^2 = 25\%$  was considered low, 50% moderate, and 75% high (Higgins & Green, 2011). If  $I^2$  was more than 50%, we performed subgroup analysis according to prespecified variables, including clinical characteristics (cancer sites, cancer stage) and intervention characteristics (type, format, provider, follow-up time). We also used a test of significance based on the  $Q$  statistic to identify heterogeneity in effect sizes. The size of the  $Q$  provides information about the probability of the results if all the effect sizes were sampled from the same population. A low  $P$  value provides evidence of heterogeneity of intervention effects (Higgins & Green, 2011).

For assessing for degree of publication bias, we used the two following method: funnel plot and trim and fill. The funnel plot graphs the effect size of each study according to its respective  $SE$ . In the absence of bias the plot should approximately resemble a symmetrical (inverted) funnel. We assumed publication bias to exist if there were no small studies without statistically significant effects (Higgins & Green, 2011). A test of statistical significance for funnel plot asymmetry was performed using Egger's linear regression asymmetry test (Egger, Smith, Schneider, & Minder, 1997). Trim and fill method assess the symmetry of the funnel plot under the assumption that when publication bias exists, a disproportionate number of studies will fall to the bottom right of the plot. The basis of this method is to remove the smaller studies causing funnel plot asymmetry, then use the trimmed funnel plot to estimate the true center of the funnel, finally, replace the omitted studies and their missing counterparts around the center for filling (Higgins & Green, 2011). If the trim and fill method results are comparably similar to the original and re-calculated HR, the results of a meta-analysis are considered to be unbiased and robust (Duval & Tweedie, 2000). A two-tailed  $P$

value of less than .05 was considered significant.

Potential publication bias was estimated using Rosenthal's "fail-safe N," which indicates the number of unpublished studies having zero or nonsignificant results, which would be required to reduce the mean ES to a specific level. If the level of fail-safe N exceeds 5K+10, the effect size can be considered to be robust (Rosenthal, 1979).

## Results

### Study selection

A total of 6977 studies were retrieved through databases and from other references. After eliminating the duplicates, 4030 publications were identified for screening. From the screening of titles and abstracts we identified 69 potentially relevant studies. Full text was retrieved for 69 studies. On review of these studies, 56 studies failed to meet inclusion criteria for the following reasons: 47 studies had irrelevant outcomes (i.e., immune, fatigue, pain, QOL), three studies were descriptive, two were non cancer studies, two studies reported earlier results (i.e., shorter follow-up) on the same sample, one study did not provide sufficient data for computation of HR, and one was a duplicate study. Two studies were identified through a hand search of reference lists. A total of 15 English studies were included in the current meta-analysis (Fig 1).

### Overall description of the studies

The key characteristics of the studies are shown in Table 1. The studies were conducted in five countries and six studies (40%) were conducted in the U.S. Cancer types were breast cancer (k=8), gastrointestinal cancer (k=2), melanoma (k=2), and mixed cancer (k=3). Six studies examined cancer patients with metastases (Cunningham, Edmonds, Jenkins, Pollack, Lockwood, & Warr, 1998; Edelman et al, 1999, Goodwin et al, 2001; Kissane et al, 2007; Spiegel, Bloom, Kraemer, & Gottheil, 1989; Spiegel et al, 2007). Four trials included patients

with cancer in various stages (Choi et al, 2012; Ilnyckyj, Farber, Cheang, & Weinerman, 1994; Kuchler, Bestmann, Rappat, Henne-Bruns, & Wood-Dauphinee, 2007; Ross et al, 2009). The remaining five trials had stage I -III (Andersen et al, 2008; Boesen et al, 2007; Fawzy, Canada, & Fawzy, 2003; Kissane et al, 2004; McCorkle et al, 2000). The mean age of study participants was 52.6 years. The sample size across the 15 included studies varied between 66 and 303, with a total of 2940 participants. The following time points of intervention were reported as follows: a) 1-3year (two studies), b) 4-6 year (six studies), c) 7-9 year (three studies), d) 10-12 year (five studies), and e) 13-15 year (one study). Note that two studies (Fawzy et al, 1993; Kuchler et al, 1999) are included in the follow-up time analysis because they report survival time at different time points on the same sample. The interventions were diverse with elements of supportive-expressive group (k=5), cognitive behavioral (k=3), psychoeducational (k=6), and CBT plus supportive-expressive therapy (k=1). Group approach was the most frequently used treatment format (73.3%), while 26.6% of studies used an individual approach. Most interventions were provided in a general hospital and a general medicine outpatient clinic. In two studies, the intervention was provided in a patient's home. Across six trials, the most common discipline for providing psychosocial interventions was multi-disciplinary teams including a psychologist, nurse, social worker, and psychiatrist. Interventions were delivered by psychologists in three studies and nurses or doctors were the interventionists in five studies. One study was delivered by a social worker. Among 15 studies, the duration of intervention ranged from four weeks to more than one year, and intervention dose varied from 9 hours to 90 hours. Thirteen studies (86.6%) provided an intervention manual. All studies included one control group. Usual care control groups were most common (73.4%); however, in four studies (16.6%), an additional intervention such as relaxation class was included.

### **Quality of studies**

A summary of methodological quality in included studies is shown in Appendix 4. Of the 15 RCT studies, 10 studies (66.6%) reported adequate details on randomization sequence, and seven studies (46.6%) reported on allocation concealment. One study was reported to have a severe selection bias, by poor survival in the control group (2.8% survival at 5 years) compared with national data (32% survival at 5 years) (Spiegel et al, 1989). For practical reasons, neither providers of the intervention nor participants were blinded to group allocation in these psychosocial intervention studies, all studies were rated as low risk. In terms of blinding outcome assessor, four studies (26.6%) reported on blinding of outcome assessment. Survival analysis in 14 studies (93.3%) included all randomly assigned participants on an intention to treat basis. One study was not conducted by ITT analysis (Fawzy et al, 2003), thus, we rated it as high risk. It was clear that the studies' pre specified expected outcome of interest was reported. As a result, they were all judged to be at low risk of reporting bias. In other bias, use of an intervention manual and monitoring of the intervention procedure were considered essential for the risk of bias assessment in psychological intervention studies (Ranchor et al, 2012). Thirteen studies (86.6%) provided an intervention manual and evaluated the intervention procedure. Therefore, we judged that as low risk.

### **Studies not included in the final analysis**

The search resulted in nineteen papers. Four studies were considered inappropriate for inclusion in our analysis. Two studies (Fawzy et al, 2003; Kuchler et al, 2007) reported earlier results (i.e., shorter follow-up) on the same sample (Fawzy et al, 1993; Kuchler et al, 1999). Thus, we selected the late publications. The third study did not report the necessary data for computing an HR (Linn, Linn, & Harris, 1982). Since this is an old study, we did not

try to contact the authors. One study was considered a same research (Andersen et al, 2010).

### Effects of psychosocial interventions on survival

Fig 2 shows results of a combined analysis across 15 studies (2940 subjects) that measured survival. Results of the analysis showed the effect sizes (*HR*) with 5% confidence and a non-significant psychosocial intervention effect. Medium statistical heterogeneity was observed between study estimates ( $\chi^2=38.45$ ,  $df=14$ ,  $p<.001$ ,  $I^2 = 64\%$ ) and a random-effects model was used. The overall *HR* for death was 0.83 (95% *CI* [0.68, 1.01],  $p=.06$ ). In examination of publication bias, review of the funnel plot of effect sizes by SEs showed an even distribution of outcome. In addition, a test of statistical significance for funnel plot asymmetry was performed by using Egger's linear regression asymmetry test and **it supported an even distribution ( $p=.411$ )**. Trim and fill analysis imputed two studies and the re-calculated *HR* shows the level of the original *HR* ( $HR=0.87$ ,  $p=.20$ ) (Fig 2).

### Subgroup analysis

#### Effects according to clinical characteristics

Cancer stage is an important predictor of the prognosis of cancer (Edelman et al, 1999). In the present study, reporting of mixed stage (stage I -IV) forced us to divide studies into those with more or less than 50% of cases having metastasis at the time of entry into the study. Thus, effects are described according to metastasis (100% of cases having metastasis) vs non-metastatic (early and mixed stage-less than 50% of cases having metastasis). Nine studies involving an early and mixed stage showed a significant effect on survival ( $HR= 0.73$ , 95% *CI* [0.56, 0.95],  $p=.02$ ). There was some heterogeneity ( $\chi^2=19.46$ ,  $df=8$ ,  $p=.01$ ,  $I^2=59\%$ ). There were no significant effects in the subgroups of metastasis cancer patients ( $HR=0.95$ , 95% *CI* [0.73, 1.24],  $p=0.72$ ,  $I^2 = 56\%$ ).

In subgroup analyses according to cancer sites, two studies that included 520

gastrointestinal cancer patients showed significant effects on survival ( $HR= 0.66$ , 95%  $CI$  [0.52, 0.84],  $p<.001$ ,  $I^2 = 0\%$ ). There were no significant effects in the subgroups of breast cancer patients involving eight trials ( $HR= 0.90$ , 95%  $CI$  [0.69, 1.18],  $p=0.45$ ,  $I^2 = 59\%$ ), melanoma cancer patients ( $HR= 0.53$ , 95%  $CI$  [0.25, 1.12],  $p=0.10$ ,  $I^2 = 12\%$ ), and mixed cancer patients ( $HR= 0.85$ , 95%  $CI$  [0.50, 1.45],  $p=.56$ ,  $I^2 = 81\%$ ).

### Effects according to intervention characteristics

In subgroup analyses by intervention types, six studies examined psychoeducational therapy involving 1448 patients showed significant effects on survival ( $HR= 0.59$ , 95%  $CI$  [0.49, 0.71],  $p<.001$ ) and statistical homogeneity was observed between study estimates ( $I^2 =0$ ) (Fig 3). The fail-safe N was 11.7. There were no significant effects in the subgroups of supportive-expressive group therapy studies ( $HR=0.97$ , 95%  $CI$  [0.73, 1.27],  $p=.80$ ,  $I^2 = 59\%$ ) and cognitive behavioral therapy studies ( $HR= 1.18$ , 95%  $CI$  [0.90, 1.53],  $p=.23$ ,  $I^2 = 0\%$ ).

According to intervention format (group approach vs individual approach) analysis, four studies using individual therapy involving 1132 patients found a significant effect on survival ( $HR= 0.70$ , 95%  $CI$  [0.51, 0.96],  $p=.03$ ) and moderate homogeneity was observed between study estimates ( $I^2 =65\%$ ). Group therapy was evaluated in 11 trials involving 1808 participants and showed no significant differences in survival ( $HR= 0.89$ , 95%  $CI$  [0.70, 1.13],  $p=.33$ ,  $I^2 =55\%$ ).

In subgroup analyses performed by intervention providers, five studies conducted by health personnel (nurse or doctor) showed a tendency indicating that intervention might have been successful ( $HR= 0.67$ , 95%  $CI$  [0.45, 0.99],  $p=.05$ ,  $I^2 =60\%$ ). However, six studies conducted by multi-disciplinary teams ( $HR= 0.92$ , 95%  $CI$  [0.70, 1.21],  $p=.56$ ,  $I^2 =51\%$ ) and three studies conducted by clinical psychologists ( $HR= 0.74$ , 95%  $CI$  [0.42, 1.31],  $p=.31$ ,  $I^2 =79\%$ ) showed no significant differences in survival.



In subgroup analyses according to follow-up time, the 1-3 year, 4-6 year, 7-9 year, 10-12 year and 13-15 year survival were available in 2, 6, 3, 5, and 1 trial, respectively. The HR ranged from 0.63 to 1.08 and heterogeneity was 52% to 87%; 10 year to 12 year HR of these 5 HRs showed significant effects on survival ( $HR= 0.63$ , 95%  $CI$  [0.43, 0.91],  $p=.02$ ,  $I^2 = 64\%$ ).

In subgroup analyses according to the length of intervention (dose), out of 15 studies, 8 studies were put in less than 30 hours of intervention ( $HR= 0.82$ , 95%  $CI$  [0.61, 1.10],  $p=.18$ ,  $I^2 = 68\%$ ) and 7 studies were put in more than 30 hours ( $HR= 0.87$ , 95%  $CI$  [0.65, 1.16],  $p=.33$ ,  $I^2 = 62\%$ ). Both of the doses showed no significant differences in survival.

#### **Effects according to clinical and intervention characteristics**

As shown in Fig 4, based on six trials with 1448 subjects, psychoeducational intervention for cancer patients with nonmetastasis at intervention implementation resulted in a 41% reduction in the risk of dying of cancer ( $HR= 0.59$ , 95%  $CI$  [0.49, 0.71],  $p<.001$ ,  $I^2 = 0\%$ ). For psychoeducational intervention, significant survival benefit were found when health staff delivered the intervention ( $HR= 0.56$ , 95%  $CI$  [0.42, 0.74],  $p<.001$ ), indicating homogeneity between studies ( $I^2 = 0\%$ ). Three trials among those six studies imparted a statistically significant survival benefit at a follow-up time of more than 10-years ( $HR= 0.58$ , 95%  $CI$  [0.43, 0.78],  $p<.001$ ), indicating homogeneity between studies ( $I^2 = 11\%$ ).

## Discussion

Although there is growing evidence indicating that psychosocial intervention improves the wellbeing of cancer patients, the question of whether or not psychosocial interventions with routine medical treatments can result in prolonged survival has been under debate (Chow et al, 2004). In response to this need, we conducted a meta-analysis of the effects of psychosocial intervention on survival in patients with cancer. A comprehensive literature search found only 15 RCT studies (covering 2940 patients). Although we retrieved studies from the Korean DB, none of the studies met the inclusion criteria.

According to results of our meta-analyses, psychosocial interventions, including supportive expressive group psychotherapy, cognitive behavioral therapy, and psycho-educational therapy had a non-significant effect on survival. Prior to making a conclusion regarding the findings, more careful consideration of heterogeneity ( $I^2 = 64\%$ ) among studies was needed. We assumed that heterogeneity was due to systematic differences among the studies. The studies in a meta-analysis used different types of interventions with different types of cancer, which could affect the direction and magnitude of effects. In our subgroup analyses according to clinical characteristics (stage and cancer sites), based on nine trials with 1831 subjects, psychosocial interventions for cancer patients with early and late-stage disease mixed imparted a statistically significant survival benefit ( $HR = 0.73$ ,  $p = .02$ ), which means intervention implementation resulted in a 27% reduction in the risk of dying of cancer. The current results suggest that psychosocial intervention might work better in the early stages of cancer diagnosis and are in accordance with those of meta-analysis on wellbeing of cancer patients (Zimmermann et al, 2007). Although the previous study suggests that patients with metastatic disease could be more distressed than patients with early stage and therefore could benefit more from interventions (Zimmermann et al, 2007), our study results suggest that

cancer stage is a more potential moderator than psychological distress on survival. Perhaps expecting positive effects from psychotherapeutic treatment in patients with metastatic disease is often too late in the course of the disease to have an impact. Stress reduction, if that is the causal mechanism, may have to occur earlier to achieve positive results (Kuchler et al, 2007).

In subgroup analyses by cancer sites, a higher survival rate was observed for the gastrointestinal cancer group ( $I^2 = 0\%$ ) than for other cancers. This effect was not found for the eight controlled trials with breast cancer patients, two trials with malignant melanoma and the two remaining trials of different tumor sites. The result is in accordance with that of previous meta-analysis studies in this field (Chow et al, 2004). Because only two trials reported on the survival of patients with gastrointestinal cancer, conduct of more RCT studies on various cancer types will be needed before we can draw a more accurate conclusion.

In subgroup analyses according to intervention type, psychoeducational intervention, based on six trials, imparted a statistically significant survival benefit ( $HR = 0.59, p < .001$ ). The effect size cannot be considered to be robust. Our fail-safe N was 11.7 which did not exceed  $5K + 10$ . That is, 11.7 trials with no significant results required to bring the mean effect to no significance. The current results are in accordance with those of a previous meta-analysis study, which reported that psychoeducational therapy yielded the strongest effect size among CBT, supportive expressive group psychotherapy, relaxation and mindful based therapy for breast cancer patients (Zimmermann et al, 2007). Psychoeducational interventions were defined as multimethod comprehensive interventions covering health education, coping skills training, stress management and psychological support (Fawzy & Fawzy, 1994). In this study, in particular, psychoeducational interventions worked better when offered by health staff (nurse or doctor). **Although there were heterogeneity by the five studies conducted**

by health personnel ( $I^2=60\%$ ), we can speculate that health staffs such as doctors or nurses seem to be the best choice for psychoeducational interventions involving cancer education. This result supports that of a meta-analysis study suggesting that psychoeducation intervention is a treatment of choice for cancer patients, preferably led by individuals with a medical expertise and other psychosocial interventions such as CBT appear most effective when administered led by a psychologist (Zimmermann et al, 2007).

The main finding according to subgroup analyses is that psychoeducational intervention for cancer patients with less than 50% metastasis resulted in a 41% reduction in the risk of dying of cancer. This finding seems to be noteworthy. Based on six trials with 1448 subjects, no statistical heterogeneity was observed between study estimates ( $I^2=0\%$ ). As psychoeducational intervention is considered most beneficial for newly diagnosed or early stage cancer patients (Fawzy, Fawzy, & Canada, 2000), in this study, psychoeducational intervention worked better on cancer patients with less than 50% metastasis. This result remained unchanged after excluding one study of low quality (Fawzy et al, 2003). Our six psychoeducational interventions seemed to have some factors in common: a) homogeneous groups to cancer stage (early and mixed); b) an educational component; and c) stress management and coping skill training. The current results may stem from reducing distress, improving health behaviors (Oh & Lee, 2013) and facilitating cancer treatment compliance and medical follow-up through psychoeducation intervention (Andersen et al, 2008). In addition, supportive social relationship might buffer the effects of cancer-related stress on immunity and thereby facilitate the recovery of immune mechanisms (McGregor et al., 2004; Oh & Jang, 2014) and may be important for cancer resistance (Spigel et al, 1998). However, we need to consider whether other adjuvant treatment compliance has a major impact on long-term outcome. In a previous systematic study review (Mustafa, Carson-Stevens,

Gillespie, & Edwards, 2013), psychological intervention using supportive expressive therapy for women with metastatic breast cancer showed an association with a survival benefit at one year, however, the OR (odd ratio) for cognitive behavioral therapies was not statistically significant.

In subgroup analyses according to intervention format, our results suggest that cancer patients benefit more than from an individual approach. Even though group approach interventions were somewhat effective in decreasing the psychological distress in primary studies, the current results are in agreement with those of previous meta-analyses in concluding that psychosocial interventions using individual treatments (k=3) were more effective in increasing survival time than group intervention (k=9) (Smedslund, & Ringdal, 2004). However, since only three individual studies out of four were based on psychoeducational intervention, further research will be necessary for the intervention format.

In the 1-3 year, 4-6 year, 7-9 year, 10-12 year and 13-15 year follow-up, five trials with 10 to 12 year follow-up showed significant effects on survival. Previous meta-analysis reported a “tapering off” trend in the effects of psychosocial intervention year after year (Xia et al, 2014). However, our results suggest that psychosocial intervention benefit was maintained for some cancer patients in the late years after intervention. Three studies of five trials with 10 to 12 year follow-up used psychoeducational therapy in cancer patients with early and mixed stage disease. These suggest that significant late effects on survival may stem from early stage cancer patients. When we excluded the two trials of low quality [36,43], there were no significant late effects on survival. Thus, further trials are needed to determine longer term effects of psychosocial interventions.

In subgroup analyses according to the length of intervention (dose), our results have shown that both of the doses (less than 30 hours, more than 30 hours) had no significant

differences in survival. However, when the previous study (Xia et al, 2014) excluded the RCTs with less than 30 hours of psychosocial intervention, it had slightly decreased the RR of death and **it suggested that the efficiency of the psychosocial intervention may be increased when doses are greater than 30 hours**. Also, a recent meta-analysis conducted on psychosocial interventions on wellbeing of cancer patients suggested that the duration of intervention (longer interventions) was one of the moderators of intervention efficacy (Faller et al, 2013). Therefore, further study is seemingly necessary in the future.

Based on the findings presented here, health staff appears to be suited for delivery of psychoeducational programs, in individual format, preferably for early stage disease (Zimmermann et al, 2007).

## Limitation

This review has several limitations. First, domestic searches retrieved several gray literature reports (i.e., dissertations), while international searches did not retrieve unpublished researches and non-English studies (e.g., German and Spanish); therefore, some studies might have been missed, resulting in a small number of RCT studies. Second, not all studies measured survival as the primary outcome and secondary analysis was performed (Choi et al, 2012; Fawzy et al, 2003; Ilnyckyj et al, 1994). Thus, use of post hoc subgroup analyses resulted in further reduction in sample size resulting in inadequate power. As such, conduct of further studies with sufficient power will promote better understanding of the survival effects. Third, even though subgroup analysis according to intervention characteristics was performed, there was still medium statistical heterogeneity between study estimates ( $I^2$  range =0% to 79%). There may be questions on whether meta-analysis is a meaningful statistical tool to compare psychological interventions, because the interventions vary greatly with respect to various variables such as intervention strategies used, quality, focus, duration, and dose

(Faller et al, 2013). Because psychological interventions are so diverse, it is important that investigators provide information a) intervention strategies, such as quality, focus, duration, dose and sustainability; b) medical treatments and other interventions used during and after the intervention period; c) compliance with psychosocial interventions and medical treatments (Xia et al, 2014). The final limitation involves the methodological quality of selected studies; a key feature of the RCT methodology design is the aspect of blinding. However, due to the practical nature of psychosocial interventions, its application could have been insufficiently administered.

### **Conclusion**

Previous meta-analysis studies have not agreed on whether or not psychosocial interventions delivered to cancer patients have had any effect on survival. What is new in the current meta-analysis is the quantification of the findings with inclusion of seven recent studies. Despite some limitations in this study, a tentative conclusion can be reached, that psychoeducational interventions offered at early stage may provide enduring late benefits and possibly longer survival. Further studies on survival should focus on identification of the underlying mechanisms that would improve survival outcome.

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## Appendices

### Search strategy

#### Appendix 1. Search strategy - MEDLINE (Pubmed) (September 2014)

#1. (((((((("Social Support"[Mesh])) OR "Behavior Therapy"[Mesh]) OR "Cognitive Therapy"[Mesh]) OR "Relaxation Therapy"[Mesh]) OR "Meditation"[Mesh]) OR "Hypnosis"[Mesh]) OR "Imagery (Psychotherapy)"[Mesh]) OR "Directive Counseling"[Mesh] OR "Psychotherapy"[Mesh:NoExp]) **153531**

#2. ((("Social Support"[tiab] OR "Psychosocial Support"[tiab] OR "Behavior Modification"[tiab] OR "Behavior Modifications"[tiab] OR "Behavior Therapies"[tiab] OR "Hypnoses"[tiab] OR "Psychotherapy"[tiab] OR "supportive expressive"[tiab] OR "Cognitive Therapy"[tiab] OR "group support"[tiab] OR "Counselors"[tiab] OR "Counselor"[tiab] OR "Counseling"[tiab] OR "counsel"[tiab] OR "expressive writing"[tiab] OR "psychotherapeutic"[tiab] OR "psychosocial intervention"[tiab] OR "cognitive behavioral"[tiab] OR "Psycho education"[tiab] OR "Mindfulness based stress reduction"[tiab] OR "cognitive-existential"[tiab] OR "CBT"[tiab] OR "psychological therapy"[tiab] OR "psychosocial support"[tiab] OR "imagery"[tiab] OR "relaxation"[tiab] OR "meditation"[tiab])) **220645**

#3. 1 or 2 **325904**

## META-ANALYSIS OF PSYCHOSOCIAL INTERVENTION ON SURVIVAL

#4. "Neoplasms"[Mesh] /**2633789**

#5. ((“Neoplasms“[tiab] OR “Tumors“[tiab] OR “Tumor“[tiab] OR “Neoplasm“[tiab] OR “Cancer“[tiab] OR “Cancers“[tiab] OR “tumour“[tiab] OR “carcinoma“[tiab] OR “tumours“[tiab])) **2115722**

#6. 4 OR 5 **3131247**

#7. 3 AND 6 **20176**

#8. ("controlled clinical trial"[ptyp]) OR ("randomized controlled trial"[ptyp]) **465412**

#9. #7 AND #8 **1321**

### **Appendix 2.** Search strategy - EMBASE (September 2014)

#1(EMTREE). 'social support'/exp OR 'psychosocial care'/exp OR 'psychotherapy'/de OR 'behavior modification'/exp OR 'behavior therapy'/exp OR 'cognitive behavioral stress management'/exp OR 'cognitive therapy'/exp OR 'group therapy'/exp OR 'guided imagery'/exp OR 'relaxation training'/exp OR 'sociotherapy'/exp OR 'hypnosis'/exp OR 'directive counseling'/exp OR 'patient counseling'/exp OR 'patient guidance'/exp **281,870**

#2 'social support':ab,ti OR 'behavior modification':ab,ti OR 'behavior modifications':ab,ti OR 'behavior therapies':ab,ti OR 'hypnoses':ab,ti OR 'psychotherapy':ab,ti OR 'supportive expressive':ab,ti OR 'cognitive therapy':ab,ti OR 'group support':ab,ti OR 'counselors':ab,ti OR 'counselor':ab,ti OR 'counseling':ab,ti OR 'counsel':ab,ti OR 'expressive writing':ab,ti OR 'psychotherapeutic':ab,ti OR 'psychosocial intervention':ab,ti OR 'cognitive behavioral':ab,ti OR 'psycho education':ab,ti OR 'mindfulness based stress reduction':ab,ti OR 'cognitive-existential':ab,ti OR 'cbt':ab,ti OR 'psychological therapy':ab,ti OR 'psychosocial support':ab,ti OR 'imagery':ab,ti OR 'relaxation':ab,ti OR 'meditation':ab,ti **249,930**

#3. #1 OR #2 **442,679**

#4(EMTREE). 'neoplasm'/exp **3,367,953**



## META-ANALYSIS OF PSYCHOSOCIAL INTERVENTION ON SURVIVAL

#5 'neoplasms':ab,ti OR 'tumors':ab,ti OR 'tumor':ab,ti OR 'neoplasm':ab,ti OR 'cancer':ab,ti OR 'cancers':ab,ti OR 'tumour':ab,ti OR 'carcinoma':ab,ti OR 'tumours':ab,ti **2,470,938**

#6. #4 OR #5 **3,739,777**

#7. #3 AND #6 **31,761**

#8. ('controlled clinical trial'/de OR 'randomized controlled trial'/de) **508,921**

#9. #7 AND #8 **1,933**

### **Appendix 3.** Search strategy –Cochrane Library CENTRAL (September 2014)

#1 MeSH descriptor: [Social Support] explode all trees **2164**

#2 MeSH descriptor: [Imagery (Psychotherapy)] explode all trees **259**

#3 MeSH descriptor: [Psychotherapy] this term only **1878**

#4 MeSH descriptor: [Behavior Therapy] explode all trees **9498**

#5 MeSH descriptor: [Hypnosis] explode all trees **566**

#6 MeSH descriptor: [Directive Counseling] explode all trees **275**

#7 MeSH descriptor: [Cognitive Therapy] explode all trees **4419**

#8 MeSH descriptor: [Relaxation Therapy] explode all trees **1343**

#9 MeSH descriptor: [Meditation] explode all trees **246**

#10 "Social Support" or "Psychosocial Support" or "Behavior Modification" or "Behavior Modifications" or "Behavior Therapies" or "Hypnoses" or "Psychotherapy" or "supportive expressive" or "Cognitive Therapy" or "group support" or "Counselors" or "Counselor" or "Counseling" or "counsel" or "expressive writing" or "psychotherapeutic" or "psychosocial intervention" or "cognitive behavioral" or "Psycho education" or "Mindfulness based stress reduction" or "cognitive-existential" or "CBT" or "psychological therapy" or "psychosocial support" or "imagery" or "relaxation" or "meditation":ti,ab,kw (Word variations have been searched) **30250**

# META-ANALYSIS OF PSYCHOSOCIAL INTERVENTION ON SURVIVAL

#11. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 **33264**

#12. MeSH descriptor: [Neoplasms] explode all trees **49379**

#13. "Neoplasms" or "Tumors" or "Tumor" or "Neoplasm" or "Cancer" or "Cancers" or "tumour" or "carcinoma" or "tumours":ti,ab,kw (Word variations have been searched) **92708**

#14. #12 or #13 **95711**

#15. #11 and #14 **2774**    => **Trials 1854**

## Appendix 4. Risk of bias summary for each included study

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Andersen et al 2008	+	?	+	?	+	+	+
Boesen et al 2007	+	?	+	+	+	+	+
Choi et al 2012	+	?	+	+	+	+	+
Cunningham et al 1998	+	?	+	?	+	+	+
Edelman et al 1999	+	?	+	?	+	+	+
Fawzy et al 2003	+	?	+	?	+	+	+
Goodwin et al 2001	+	+	+	+	+	+	+
Illych et al 1994	+	+	+	?	+	+	+
Kissane et al 2004	+	+	+	+	+	+	+
Kissane et al 2007	+	+	+	?	+	+	+
Kurthier et al 2007	+	?	+	?	+	+	+
McCorkle et al 2000	+	?	+	?	+	+	+
Ross et al 2009	+	+	+	?	+	+	+
Spielgel et al 1989	+	+	+	?	+	+	+
Spielgel et al 2007	+	?	+	?	+	+	+

**Table 1.** Descriptive Summary of Included Studies

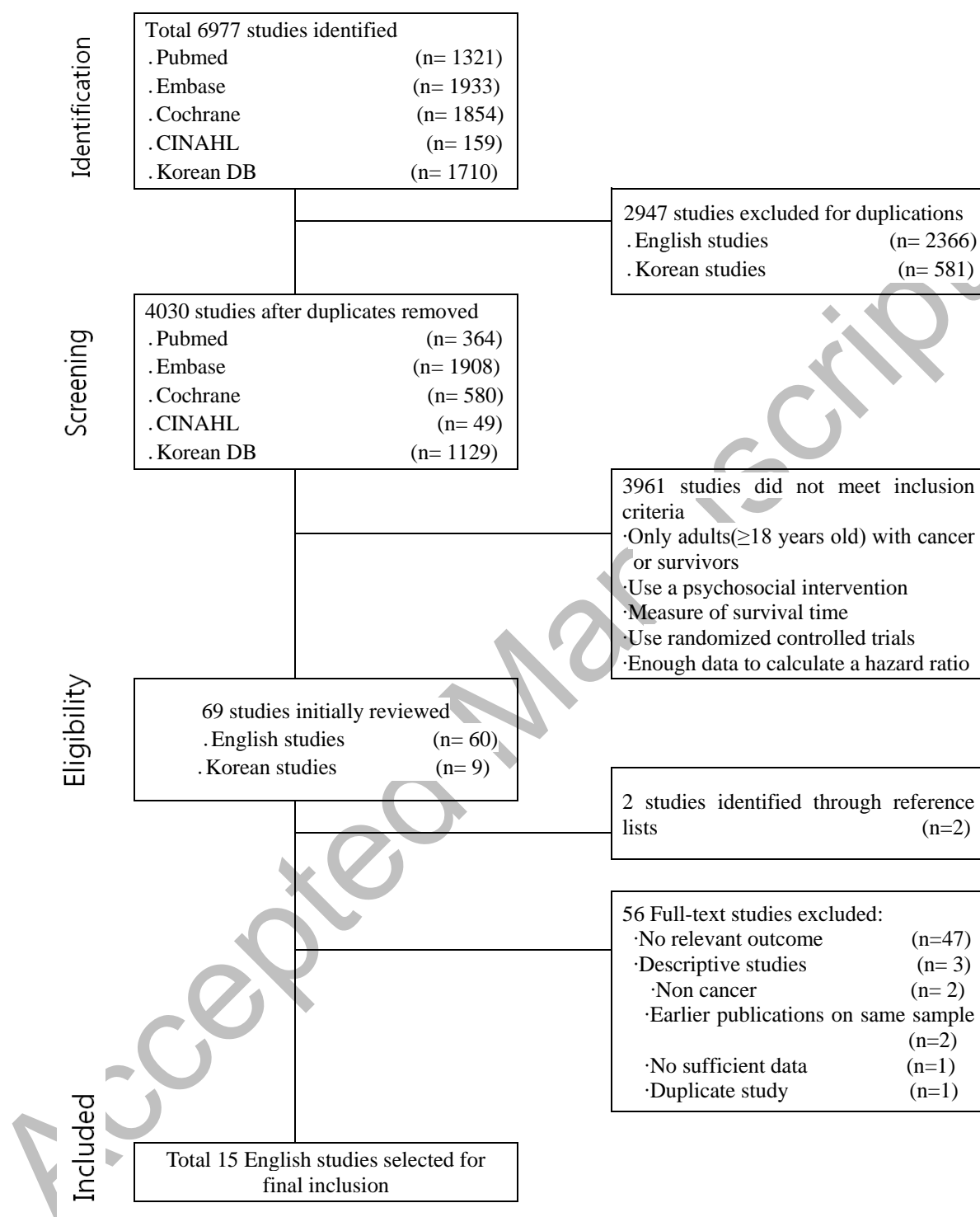
(N=15)

Study	Country	Cancer site (stage)	Mean age (year)	Sample size	Interventions					Control group	Follow-up time (Result)
					Name	Format	Providers	Duration	Dose		
Spiegel et al 1989 [36]	United States	Breast cancer (metastasis)	Exp (54.7) Con (54.6)	Exp (n = 50) Con (n = 36)	Psychosocial treatment(Supportive group therapy)	Group	Psychiatrist or social worker	1years	78hours (1.5h/wk)	Usual care	10years (p<.001)
Illycky et al 1994 [39]	Canada	Various Cancer( I -IV)	Unclear	Exp (n = 61) Con (n = 31)	Supportive group therapy	Group	Social worker	6months	26hours (1h/wk)	Usual care	11years (NS)
Cunningham et al 1998 [35]	Canada	Breast cancer patients (metastasis)	Exp (49.5) Con (51.5)	Exp (n = 30) Con (n = 36)	Supportive plus cognitive behavioral therapy	Group	Psychologist and social worker	35wks	70hours (2h/wk)	Home study cognitive behavioral package	5years (NS)
Edelman et al 1999 [1]	Australia	Breast cancer (metastasis)	Exp (49.3) Con (50.4)	Exp (n = 60) Con (n = 61)	Cognitive Behavior Therapy (CBT) intervention	Group	Psychologists	8wks plus 3months	17hours (1.6h/wk)	Usual care	5years (NS)
McCorkle et al 2000 [42]	United States	Solid Tumors ( I -IV)	60 or older	Exp (n = 190) Con (n = 185)	Home care intervention	Individual	Advanced practice nurses	4wks	12hours	Usual care	4years (p=.002)
Goodwin et al 2001 [37]	Canada	Breast cancer (recurrent or metastasis)	Exp (49) Con (51.5)	Exp (n = 158) Con (n = 77)	Supportive- expressive group therapy	Group	Psychiatrists, psychologists, social workers, nurse, clinicians	>1 year	78hrs (1.5h/wk)	Usual care	7years (NS)
Fawzy et al 2003 [43]	United States	Malignant Melanoma ( I )	Exp (45.7) Con (39.3)	Exp (n = 34) Con (n = 34)	Psychiatric group intervention	Group	Doctor, nurse	6wks	9hours	Usual care	10years (NS)
Kissane et al 2004 [44]	Australia	Breast cancer ( I , II )	Exp (45.4) Con (47.3)	Exp (n = 154) Con (n = 149)	Cognitive-Existential group therapy + 3 Relaxation classes	Group	Psychiatry, psychology, social work and nurse	20wks	30hours (1.5hr/wk)	3 Relaxation classes	5years (NS)
Boesen et al 2007 [45]	Denmark	Malignant Melanoma (T1-4,N1a-2a)	Exp (45.9) Con (45.8)	Exp (n = 128) Con (n = 130)	Psycho educational Intervention	Group	Health staff and group leader	6wks	12hours (2h/wk)	Usual care	6years (NS)
Kissane et al 2007 [38]	Australia	Breast cancer (metastasis)	Exp (51.9) Con (51.3)	Exp (n = 147) Con (n = 80)	Supportive-expressive group therapy + 3 Relaxation classes	Group	Psychiatry, psychology or social worker	≥ 1year plus weekly relaxation:3	90hours (1.5hr/wk)	3 Relaxation classes	2years (NS)
"Ku"chler et al 2007 [40]	Germany	Gastrointestinal cancer (mixed)	Exp (56.9) Con (56.7)	Exp (n = 136) Con (n = 135)	Psychotherapeutic support	Individual	Psychotherapist	Median 22days	22hours	Usual care	10years (p=.0006)
Spiegel et al 2007 [26]	United States	Breast cancer (recurrent or metastasis)	Exp (53.1) Con (53.3)	Exp (n = 64) Con (n = 61)	Supportive-expressive group therapy	Group	Psychiatrist, psychologist, social worker	1years	78hours (1.5h/wk)	Educational materials(1year membership )	14years (NS)
Andersen et al 2008 [8]	United States	Breast cancer (IIA~IIIB)	Exp (50.8) Con (50.8)	Exp (n = 114) Con (n = 113)	Psychological intervention	Group	Clinical psychologist	≥ 1year (26sessions )	39hours	Usual care	11 years (p=.016)

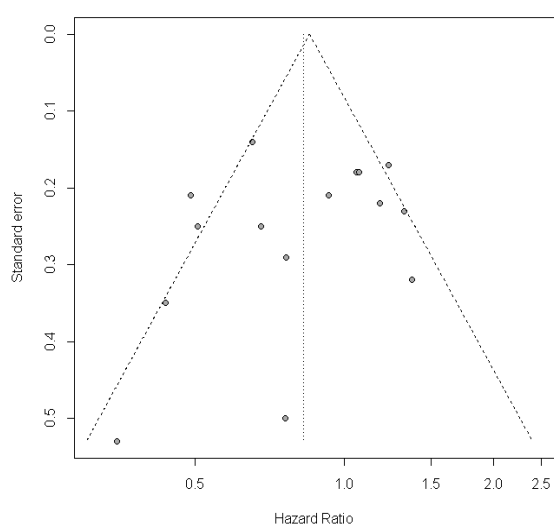
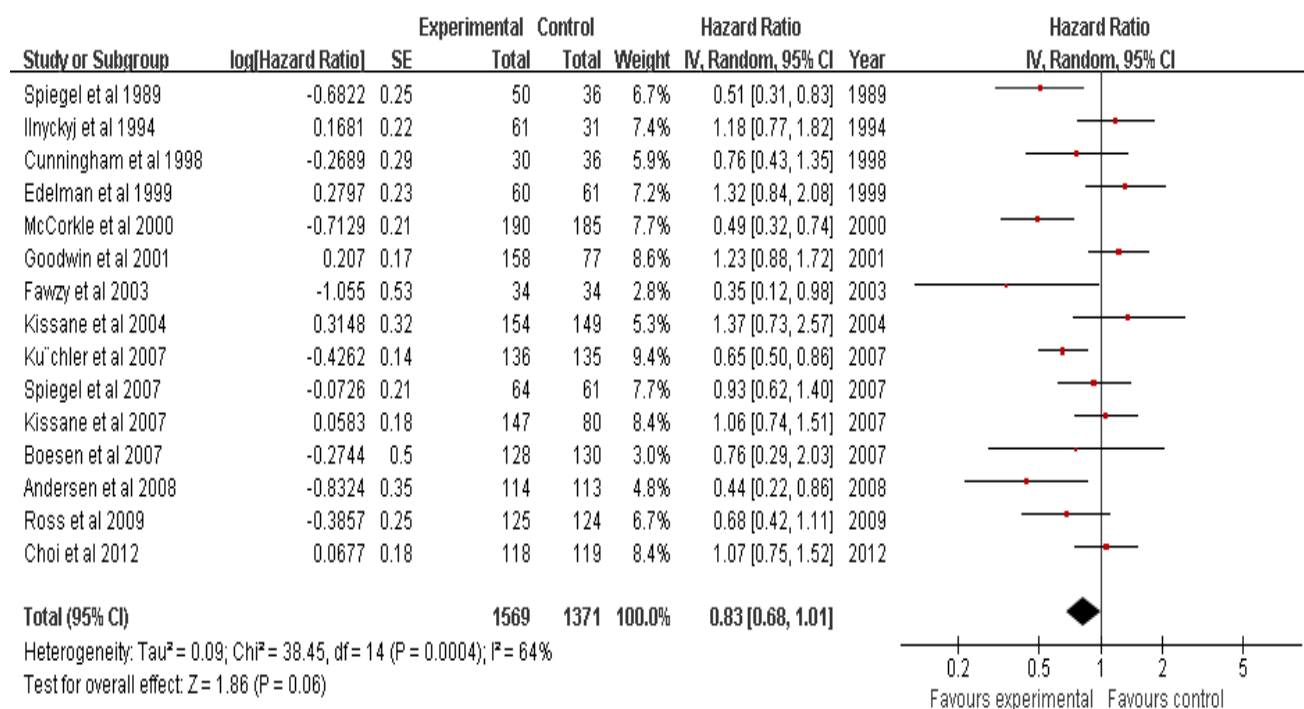
**Table 1.** Descriptive Summary of Included Studies (continued)

Study	Country	Cancer site (stage)	Mean age (year)	Sample size	Interventions					Control group	Follow-up time (Result)
					Name	Format	Providers	Duration	Dose		
Ross et al 2009 [41]	Denmark	Colorectal cancer (Duke's stage(A, B, C, D))	Exp (68.8) Con (68.1)	Exp (n = 125) Con (n = 124)	Home psychosocial intervention	Individual	Nurse or doctor	10 visits	15hours (1.5hr/visit)	Usual care	6.5-9.5years (NS)
Choi et al 2012 [28]	United States	Solid tumors ( I -IV)	Exp (60.4) Con (58.7)	Exp (n = 118) Con (n = 119)	Cognitive behavioral symptom management intervention	Individual	Nurses	20wks	10contacts	Usual care	7.5years (NS)

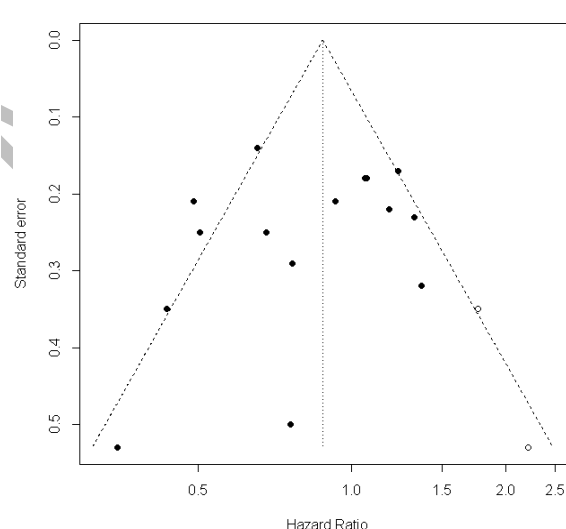
Exp.= Experimental group; Con.= Control group; NS=Not significant



**Fig 1.** Selection of included studies.

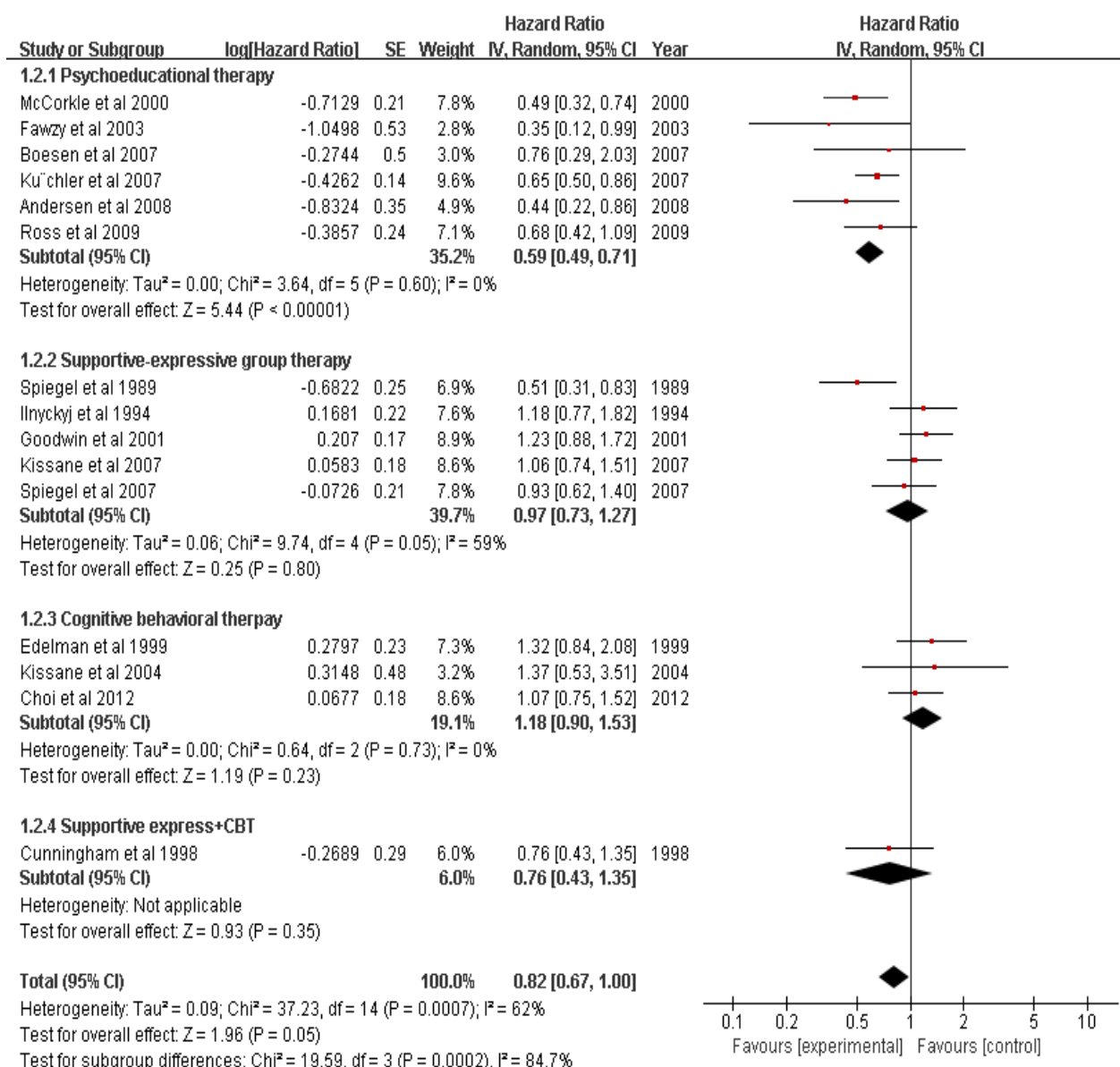


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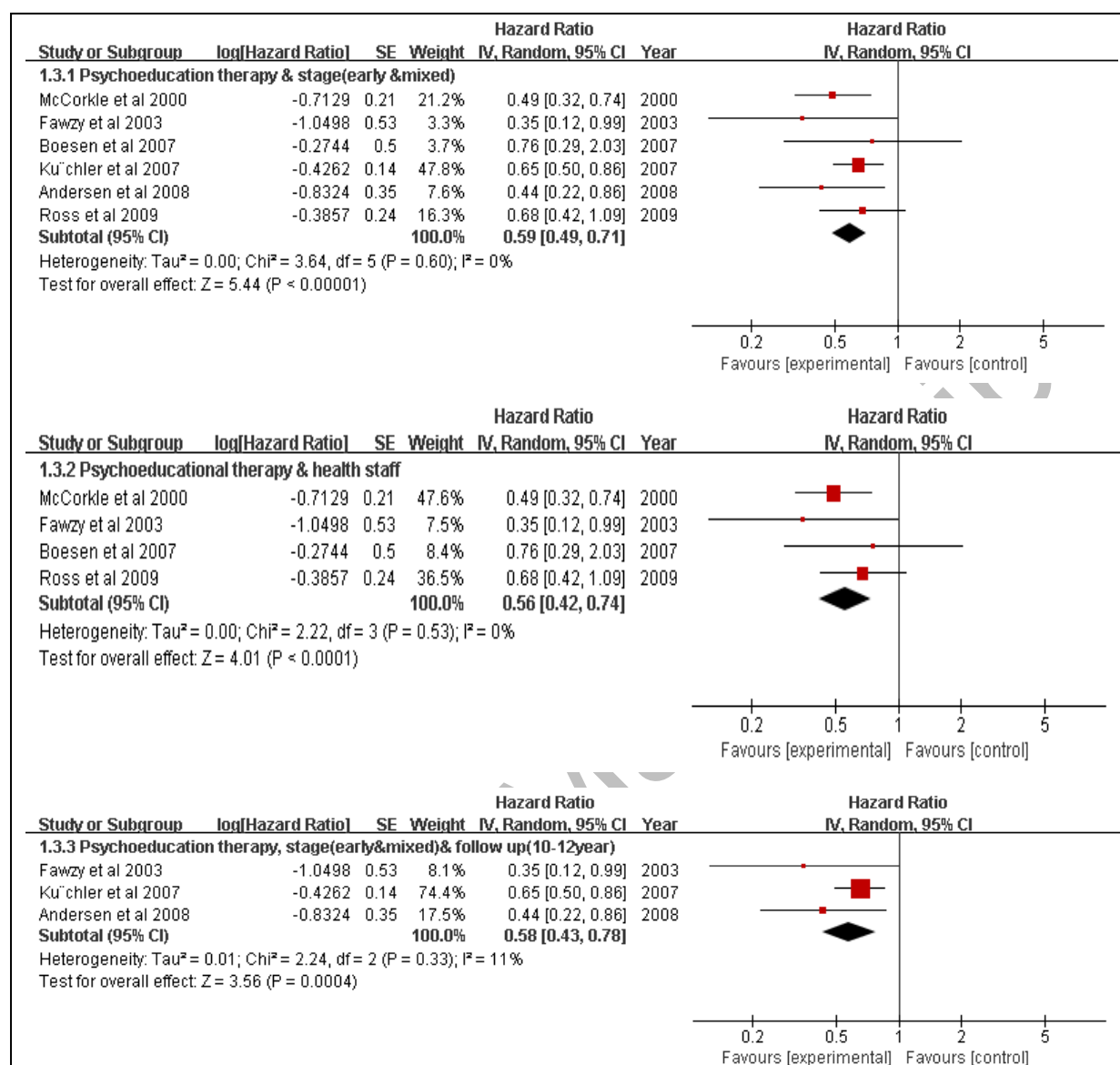


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**Fig 2.** Forest plot of effect size by psychosocial interventions on survival and funnel plot of effective sizes by standard error for survival.



**Fig 3.** Forest plot of effect size by intervention type: Psychosocial intervention studies on survival.



**Fig 4.** Forest plot of effect size by intervention type, provider, follow-up time and stage:  
 Psychosocial intervention studies on survival



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