The impact of psychosocial intervention on survival in cancer: a meta-analysis

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Background: The impact of psychosocial interventions on survival remains controversial in patients with cancer. A meta-analysis of the recent literature was conducted to evaluate the potential survival benefit associated with psychosocial interventions for cancer patients.

Methods: MEDLINE, EMBASE, and Cochrane Central were searched from January 2004 to May 2015 for all randomized controlled trials (RCTs) that compared survival outcomes between cancer patients receiving a psychosocial intervention and those receiving other, or no interventions. Endpoints included one-, two-, and four-year overall survival. Subgroup analyses were performed to compare group-versus individually-delivered interventions, and to assess breast cancer-only trials.

Results: Of 5,080 identified articles, thirteen trials were included for analysis. There was a significant survival benefit for the intervention group at one year [risk ratio (RR) =0.82; 95% confidence interval (CI), 0.67–1.00; P=0.04] and two years (RR =0.86; 95% CI, 0.78–0.95; P=0.003). However, no significant difference was detected at four years (RR =0.94; 95% CI, 0.85–1.04; P=0.24). Among patients with breast cancer, there was a significant survival benefit of psychosocial interventions at one year (RR =0.59; 95% CI, 0.42–0.82; P=0.002), but no difference at two years (RR =0.82; 95% CI, 0.67–1.02; P=0.07) or four years (RR =0.95; 95% CI, 0.73–1.23; P=0.68). Group-delivered interventions had a significant survival benefit favouring the intervention group at one year (RR =0.57; 95% CI, 0.41–0.79; P=0.0008), but no difference at two years (RR =0.57; 95% CI, 0.41–0.79; P=0.0008), but no difference at two years (RR =0.57; 95% CI, 0.41–0.79; P=0.0008), but no difference at two years (RR =0.57; 95% CI, 0.41–0.79; P=0.0008), but no difference at two years (RR =0.84; 95% CI, 0.68–1.02; P=0.08) or four years (RR =0.94; 95% CI, 0.75–1.20; P=0.64). Individually-delivered interventions had no significant survival benefit at one year (RR =0.92; 95% CI, 0.79–1.08; P=0.32), two years (RR =0.87; 95% CI, 0.75–1.00; P=0.05), or four years (RR =0.93; 95% CI, 0.84–1.04; P=0.21).

Conclusions: For the main analysis and group-delivered treatments, psychosocial interventions demonstrated only short-term improvements in survival. Individually-delivered interventions failed to show any survival benefit. Future studies with longer follow-up are warranted to investigate long-term survival outcomes.

Keywords: Psychosocial; intervention; cancer; survival; meta-analysis

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Introduction

Cancer is a leading global cause of death and represents an important public health problem. In 2012, there were an estimated 14.1 million new cancer cases and 8.2 million deaths due to cancer worldwide (1). In addition to a variety of physical symptoms, cancer and its treatments are often associated with significant psychosocial effects, including disruption to social, physical, and cognitive functioning (2-5). Studies show that about one-third of cancer patients are affected by long-term clinical anxiety and depression compared to only about one-fifth of the general population (6-8). To make matters worse, about 40% of young adult cancer patients are unsatisfied with their counseling and psychosocial support (9).

Since the 1980s, a wide variety of psychosocial interventions have been used to treat pain and mood symptoms in cancer patients (10-13). These interventions typically include one or a combination of the following: (I) cognitive-existential group therapy (CEGT); (II) cognitive-behavioral therapy (CBT); (III) supportive-expressive group therapy; and (IV) psychoeducational therapy. Initial studies demonstrated that psychosocial interventions can prolong survival (14,15); however, later studies reported conflicting results regarding the survival benefit of these interventions (16-19). Two independent meta-analyses in 2004 by Chow et al. (20) and Smedslund and Ringdal (21) were conducted to determine the pooled treatment effects of psychosocial interventions on overall survival. Both studies failed to detect a survival difference between intervention and control groups. More recently, a meta-analysis by Xia et al. (22) studied fifteen randomized controlled trials (RCTs) published between 1989 and 2009 and compared survival outcomes at one, two, four, and six years following psychosocial interventions. In contrast to previous analyses, Xia et al. found a significant survival difference at two years of follow-up (RR =0.85; 95%) CI, 0.75–0.96; P=0.01). Furthermore, subgroup analysis of seven RCTs exceeding 30 hours in psychosocial treatment revealed a decrease in all RRs and yielded a significant survival benefit in the first two years following intervention.

While the mechanism behind the effect of psychosocial interventions remains unclear, several theories have been proposed. The primary rationale behind CEGT, CBT, and supportive-expressive therapy is to reduce the anxiety and depression associated with cancer treatments; these negative emotional states are believed to impact survival by suppressing immune and neuroendocrine systems (23,24). Patients are also taught problem-solving skills, cognitive

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flexibility, and relaxation techniques to better cope with stressful situations. Furthermore, psychoeducational therapies have been used to improve patient engagement and compliance in the course of their treatment (25,26).

The management and prognosis of cancer has changed radically over the past few decades and additional RCTs have been published recently (27-31). To our knowledge, there are no reviews that specifically examine recently published RCTs to determine the impact of psychosocial interventions on survival outcomes in cancer patients. The purpose of this meta-analysis is to synthesize evidence from the most recent literature on the survival benefit associated with psychosocial interventions among cancer patients.

Methods

Search strategy

Eligible studies were identified by searching Ovid MEDLINE (2004–May week 3 2015), EMBASE Classic and EMBASE (2004–2015 week 21), and Cochrane Central Register of Controlled Trials (January 2004–April 2015). References of included articles were also screened to identify additional eligible trials. The search algorithm included the following medical subject headings and keywords: (neoplasm OR cancer OR carcinoma) AND (psychotherapy OR psychosocial OR group therapy OR social work OR psychiatric OR counseling OR psychological techniques OR psychoanalytic interpretation OR mental health services).

Inclusion criteria

Articles were eligible for inclusion if they (I) involved an RCT study design; (II) included adult cancer patients; (III) compared one or more groups receiving a psychosocial intervention to a control group receiving an alternate intervention; or no intervention; (IV) provided relevant survival outcomes and/or Kaplan-Meier survival curves. Authors of studies without Kaplan-Meier survival curves and no relevant data were contacted to obtain available survival data. Studies were excluded if they were duplicates, non-English studies, non-original studies, non-clinical trials, case reports or small case series (<5 patients).

Study selection

Two reviewers (WW Fu and A Agarwal) independently screened studies identified for inclusion and determined

study eligibility. Disagreements were resolved by consultation from a third opinion (M Popovic).

Data collection and statistical analysis

Data were systematically extracted and tabulated in a standardized database. Extracted variables included the number of patients randomized to intervention or control groups, type of cancer, type of intervention, duration of follow-up, and survival rates at one, two, and four years. Whenever possible, the raw value for the survival rate was recorded. When these rates were unavailable, overall survival rates were estimated from survival curves. To compute survival rates, the cumulative survival was identified at one, two, and four years, and multiplied by the number of patients randomized to each group to estimate the number of survivors.

Pooled treatment effects on survival were compared between intervention and control groups for all cancer patients. A subgroup analysis for primary breast cancer patient-specific trials was conducted as previous studies have shown that these patients live longer compared to cancer patients with metastatic disease from other primary sites (20). Additional subgroup analyses comparing group and individually-delivered psychosocial interventions were conducted, given substantial controversy in the literature regarding their relative survival benefits (30). Tests of statistical heterogeneity using the I² statistic were applied to assess the extent of observed variability in results between trials.

Risk of bias was assessed using the Cochrane risk of bias tool (32). The tool evaluates methodological quality of the trials based on random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. We evaluated incomplete outcome data by determining the number of patients excluded due to loss at follow-up or missing patient data. Trials were assessed as low risk of attrition bias if less than 20% of patient data were excluded and if similar proportions were excluded from both arms.

Data from each trial were pooled and analyzed using Review Manager (version 5.3) by the Cochrane Collaboration (Oxford, England). The random effects model was applied using the Mantel-Haenszel method to generate risk ratios (RR) estimates with their accompanying 95% confidence intervals (CI).

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Results

Literature search

As shown in *Figure 1*, the search strategy identified a total of 5,080 articles, of which 14 trials were eligible for further review. Among the 14 trials, one of the trials was excluded because it was missing extractable survivable data. Overall, 13 trials met the final inclusion criteria and were included in the meta-analysis (23,27-31,33-39). *Table 1* lists studies that exclusively examined patients with breast cancer. *Table 2* lists studies that examined patients with other types of cancer or a combination of cancers.

Study characteristics

The thirteen included trials contained a total of 2,632 patients, with 1,362 patients randomized to the intervention group and 1,270 patients to the control cohort. Six studies exclusively examined breast cancer patients (23,29,31,33,35,36). Two other trials studied patients with a variety of cancer types including nasopharyngeal, gynecological, breast, lung, colon, and others (27,30). The remaining five trials included patients with cutaneous melanoma (34), esophageal carcinoma (28), colorectal cancer (37), gastrointestinal cancer (38), and hepatobiliary carcinoma (39). Studies were conducted in five countries-specifically, the United States (23,30,31,36,39), Denmark (29,34,37), Australia (33,35), China (27,28), and Germany (38). The intervention arm received psychosocial interventions including CBT (30), small group psychoeducation (34), psychotherapy (23), psychosocial visits (37), or a combination of interventions (27-29,31,33,35,36,38,39). Control arms received usual care (30,38,39), no intervention (28,29,34,37), radiotherapy only (27) relaxation therapy only (33,35), assessment only (23,31) or education only (36). In total, eight of the trials involved group-delivered interventions (23,27,29,31,33-36) while five trials (23,28,30,37-39) involved individuallydelivered interventions. One- and two-year survival data was available in all thirteen trials (23,27-31,33-39) and four-year survival data was available in twelve trials (23,28-31,33-39).

Risk of bias assessment

Table 3 reports risk of bias assessments for each trial. All studies demonstrate adequate random sequence generation. However, seven trials had unclear or missing classifications



Figure 1 Article retrieval for systematic reviews and meta-analysis flow of information diagram for included studies.

regarding allocation concealment (23,28,30,33,34,36,38). Due to the nature of the interventions, blinding was not applicable in any of the studies (23,27-31,33-39). With respect to incomplete outcome data, ten of the studies (23,27-29,31,33,36-39) were classified as low risk and the remaining three (27,34,35) were deemed high risk for attrition bias. Selective reporting of outcomes was not found to be a source of bias; all trials reported relevant survival outcomes as described in their methods (23,27-31,33-39). Finally, four trials were assessed with unclear or high risk for other biases (27-29,37); two studies had small sample sizes as a potential source of sampling bias (28,31), and two other studies reported differences in patient baseline characteristics between intervention and control groups (29,37).

Comparison of survival outcomes between psychosocial intervention and control groups

Among all cancer patients, there was a statistically significant improvement in overall survival favouring the

psychosocial intervention group at one year (RR =0.82; 95% CI, 0.67–1.00; P=0.04; *Figure 2A*) and two years (RR =0.86; 95% CI, 0.78–0.95, P=0.003; *Figure 2B*) but no significant difference at four years (RR =0.94; 95% CI, 0.85–1.04, P=0.24; *Figure 2C*). The test for statistical heterogeneity was not significant at one, two, or four years (P=0.20, 0.62, and 0.12, respectively).

In breast cancer-only trials, there was a significant improvement in overall survival at one year favoring the psychosocial intervention group (RR =0.59; 95% CI, 0.42–0.82; P=0.002; *Figure 3A*) but no significant difference at two (RR =0.82; 95% CI, 0.67–1.02, P=0.07; *Figure 3B*) or four years (RR =0.95; 95% CI, 0.73–1.23; P=0.68; *Figure 3C*). The test for statistical heterogeneity was not significant at one, two, or four years (P=0.97, 0.68, and 0.06, respectively).

Comparison of group- and individually-delivered Interventions

Among group-delivered intervention trials, there was a

Table 1 Recent rando	nized controlled trials e	examining psychosocial	intervention for survival prolongation in only p	oatients with breast can	cer	
Trial (authors, year	Number of patients,				Duration of	Group or
published), study	l = intervention,	cancer types	Intervention	Control	follow-up on	individual
location	C = control	arru stage			survival	intervention
Kissane <i>et al.</i> ,	l: n=154, C: n=149	Early-stage breast	1.5 hours of weekly CEGT for 20 weeks	Three relaxation	5 years	Group
2004 (33),		cancer, stages l	plus three 1 hour relaxation classes	classes alone		
Melbourne, Australia		and II				
Kissane <i>et al.</i> ,	l: n=147, C: n=80	Metastatic breast	1.5 hours of weekly supportive expressive	Three relaxation	6 years	Group
2007 (35),		cancer, stages I–IV	group therapy over one year plus three	classes alone		
Melbourne, Australia			1 hour relaxation classes			
Spiegel <i>et al.</i> ,	l: n=62*, C: n=56	Metastatic breast	1.5 hours of weekly supportive-expressive	Education alone	14 years	Group
2007 (36), California,		cancer, unspecified	group therapy for 1 year plus education			
NSA		stages				
Andersen <i>et al.</i> ,	l: n=114, C: n=113	Breast cancer,	1.5 hours of weekly supportive-expressive	Assessment alone	14 years	Group
2008 (23), Ohio, USA		stages II-III	group therapy plus assessment for 1 year			
Andersen <i>et al.</i> ,	l: n=29, C: n=33	Breast cancer,	1.5 hours of sessions for improving	Assessment alone	5 years	Group
2010 (31), Ohio, USA		stages II-III	relaxation, stress coping, health behaviors,			
			social support, and adherence to treatment			
Boesen <i>et al.</i> ,	l: n=89, C: n=97	Breast cancer,	12 hours of psychoeducation over 2 weeks	No psychoeducation	5 years	Group
2011 (29), Denmark		stages I-III	plus 8 sessions of group therapy each	or group therapy		
			2.5 hours over 8 weeks			
*, Spiegel et al. repor	ted total intervention [64] and control [61] s	ample sizes, but only used 62 and 56, respe	ctively, in their Kapla	n-Meier survival	graph. CEGT,

2 5 2 2) 2 2 cognitive-existential group therapy. Ň 22.

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Table 2 Randomized	studies examining psycho	social intervention for surviva	ll prolongation in patients with other ty	pes of cancer or a com	bination of cance	S
Trial (first author,	Total number of patients				Duration of	Group or
year published),	I = intervention,	Cancer types and stage	Intervention	Control	follow-up on	individual
study location	C = control				survival	intervention
Boesen <i>et al.</i> , 2007 (34), Denmark	l: n=128, C: n=130	Cutaneous malignant melanoma, T1–4, N1-2-2 M0	2 hour weekly sessions of group psychoeducation for 6 weeks	No group psychoeducation	6 years	Group
Küchler <i>et al.</i> , 2007 (38), Hamburg, Germany	l: n=136*, C: n=135	Gastrointestinal cancer, unspecified stages	Psychotherapeutic support during hospital stay (median length of stay was 22 days) versus standard care alone	Standard care alone	10 years	Individual
Ross <i>et al.</i> , 2009 (37), Denmark	l: n=125, C: n=124	Colorectal cancer, unspecified stages	10 home psychosocial visits, each 1.5 hours over 2 years	No psychosocial visits	9.5 years	Individual
Choi <i>et al.</i> , 2012 (30), Ohio, Michigan, Connecticut, USA	, l: n=118, C: n=119	Breast, lung, colon, and other cancers, unspecified stages	4 classes of CBT over 20 weeks	Usual care alone	6 years	Individual
Guo <i>et al.</i> , 2013 (27), Guangxi, China	l: n=89, C: n=89	Nasopharyngeal, breast, gynecological, lung, and other cancers, unspecified stages	8-12 hours of psychoeducation, CBT, supportive-expressive therapy plus radiotherapy over 4 weeks	Radiotherapy alone	2 years	Group
Zhang e <i>t al.</i> , 2013 (28), China	l: n=27, C: n=28	Esophageal carcinoma, stages I–III	1-hour sessions of comprehensive supportive care every other day for 3 weeks	No comprehensive supportive care	4 years	Individual
Steel <i>et al.,</i> 2016 (39), Pittsburgh, USA	l: n=144, C: n=117	Advanced hepatobiliary carcinoma, primarily stage IV	Web-based collaborative care: CBT and/or pharmacological treatment, variable treatment period	Usual care alone	4 years	Individual
*, Kuchler <i>et al.</i> used original intervention <i>i</i>	d a cross-over design w and control group sampl	/here patients had the oppo e sizes (136 and 135, respe	ortunity to cross to an alternate grou	p if they requested a sier survival graph. co	l change. We us gnitive-behavior	ed the study's al therapy.

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Table 3 Assess	ment of risk of blas u	sing Cochrane i	isk of blas	tool			
Reference	Random sequence	Allocation	Blinding	Incomplete outcome	Selective	Other	Description of
Telefence	generation	concealment	Dimaing	data addressed	reporting	biases	other biases
Andersen	Low	Unclear	Low	Low	Low	Low	
<i>et al.</i> , 2008 (23	3)						
Andersen	Low	Unclear	Low	Low	Low	High	Small sample size
<i>et al.</i> , 2010 (31)						
Boesen et al.,	Low	Unclear	Low	High	Low	Low	
2007 (34)							
Boesen et al.,	Low	Low	Low	Low	Low	Unclear	Intervention group had
2011 (29)							significantly larger tumors
							than control group
Choi <i>et al.</i> ,	Low	Unclear	Low	High	Low	Low	
2012 (30)							
Guo <i>et al.</i> ,	Low	Low	Low	Low	Low	Low	
2013 (27)							
Kissane et al.,	Low	Unclear	Low	Low	Low	Low	
2004 (33)							
Kissane et al.,	Low	Low	Low	High	Low	Low	
2007 (35)							
Küchler et al.,	Low	Unclear	Low	Low	Low	Low	
2007 (38)							
Ross et al.,	Low	Low	Low	Low	Low	Unclear	Control group had
2009 (37)							significantly higher daily
							consumption of tobacco
							than intervention group
Spiegel et al.,	Low	Unclear	Low	Low	Low	Low	
2007 (36)							
Steel et al.,	Low	Low	Low	Low	Low	Low	
2016 (39)							
Zhang et al.,	Low	Unclear	Low	Low	Low	High	Small sample size
2013 (28)							

significant improvement in overall survival at one-year favoring the psychosocial intervention group (RR =0.57; 95% CI, 0.41-0.79; P=0.0008; Figure 4A), but no difference at two years (RR =0.84; 95% CI, 0.68-1.02; P=0.08; Figure 4B) or four years (RR =0.94; 95% CI, 0.75-1.20; P=0.64; Figure 4C). The test for statistical heterogeneity was not significant at one, two, or four years (P=0.75, 0.69, and 0.10, respectively).

In contrast, among individually-delivered trials, there was no significant difference in overall survival between intervention and control groups at one year (RR =0.92; 95% CI, 0.79–1.08; P=0.32; Figure 5A), two years (RR =0.87; 95% CI, 0.75-1.00; P=0.05; Figure 5B), or four years (RR =0.93; 95% CI, 0.84-1.04; P=0.21; Figure 5C). The test for statistical heterogeneity was not significant at one, two, or four years (P=0.37, 0.28, and 0.23, respectively).

Discussion

The survival benefit of psychosocial interventions in RCTs of cancer patients remains controversial. Previous metaanalyses by Chow et al. (20) and Smedslund and Ringdal (21) failed to detect a significant difference in overall survival rates between intervention and control groups. Chow

A One Year	Interven	ntion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Andersen 2008	1	114	2	113	0.7%	0.50 [0.05, 5.39]	
Andersen 2010	3	29	7	33	2.3%	0.49 [0.14, 1.71]	
Boesen 2007	1	128	0	130	0.4%	3.05 [0.13, 74.10]	
Boesen 2011	1	89	1	97	0.5%	1.09 [0.07, 17.17]	
Choi 2012	25	118	25	119	11.4%	1.01 [0.62, 1.65]	
Guo 2013	1	89	7	89	0.9%	0.14 [0.02, 1.14]	
Kissane 2004	0	154	0	149		Not estimable	
Kissane 2007	35	147	31	80	15.2%	0.61 [0.41, 0.92]	
Kuchler 2007	53	136	67	135	23.1%	0.79 [0.60, 1.03]	
Ross 2009	25	125	19	124	9.9%	1.31 [0.76, 2.25]	+
Spiegel 2007	8	62	15	56	5.5%	0.48 [0.22, 1.05]	
Steel 2016	84	144	71	117	28.7%	0.96 [0.79, 1.18]	+
Zhang 2013	2	27	5	28	1.5%	0.41 [0.09, 1.96]	
Total (95% CI)		1362		1270	100.0%	0.82 [0.67, 1.00]	•
Total events	239		250				
Heterogeneity: Tau ² =	0.02; Chi ²	= 14.73	, df = 11 (P = 0.2	20); l² = 25	5%	
Test for overall effect: 2	Z = 2.01 (F	P = 0.04)				Eavours [intervention] Eavours [control]

B Two Year	Interver	ntion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Andersen 2008	1	114	3	113	0.2%	0.33 [0.03, 3.13]	
Andersen 2010	6	29	14	33	1.5%	0.49 [0.22, 1.10]	
Boesen 2007	2	128	4	130	0.3%	0.51 [0.09, 2.72]	
Boesen 2011	3	89	1	97	0.2%	3.27 [0.35, 30.86]	
Choi 2012	37	118	42	119	7.5%	0.89 [0.62, 1.27]	
Guo 2013	15	89	14	89	2.2%	1.07 [0.55, 2.09]	
Kissane 2004	3	154	3	149	0.4%	0.97 [0.20, 4.72]	
Kissane 2007	70	147	44	80	14.4%	0.87 [0.67, 1.12]	
Kuchler 2007	66	136	90	135	22.2%	0.73 [0.59, 0.90]	-
Ross 2009	39	125	35	124	6.7%	1.11 [0.75, 1.62]	-
Spiegel 2007	23	62	26	56	5.3%	0.80 [0.52, 1.23]	
Steel 2016	96	144	84	117	37.4%	0.93 [0.79, 1.09]	=
Zhang 2013	7	27	10	28	1.5%	0.73 [0.32, 1.63]	
Total (95% CI)		1362		1270	100.0%	0.86 [0.78, 0.95]	•
Total events	368		370				
Heterogeneity: Tau ² =	0.00; Chi ²	= 9.98,	df = 12 (F	P = 0.62	2); I ² = 0%		
Test for overall effect:	Z = 2.96 (F	P = 0.00	3)				Favours [intervention] Favours [control]

C Four Year	Interver	ntion	Contr	ol		Risk Ratio	Risk Rati	D
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random,	95% CI
Andersen 2008	5	114	10	113	0.9%	0.50 [0.17, 1.40]		
Andersen 2010	15	29	27	33	5.6%	0.63 [0.43, 0.93]		
Boesen 2007	7	128	8	130	1.0%	0.89 [0.33, 2.38]		
Boesen 2011	5	89	1	97	0.2%	5.45 [0.65, 45.75]		<u> </u>
Choi 2012	50	118	58	119	9.3%	0.87 [0.66, 1.15]		
Kissane 2004	18	154	12	149	2.0%	1.45 [0.72, 2.91]		_
Kissane 2007	114	147	62	80	18.9%	1.00 [0.86, 1.16]	+	
Kuchler 2007	90	136	108	135	18.9%	0.83 [0.71, 0.96]	-	
Ross 2009	59	125	52	124	9.4%	1.13 [0.85, 1.49]		
Spiegel 2007	39	62	33	56	8.8%	1.07 [0.80, 1.43]	+	
Steel 2016	118	144	97	117	22.6%	0.99 [0.88, 1.11]	+	
Zhang 2013	10	27	12	28	2.3%	0.86 [0.45, 1.66]		
Total (95% CI)		1273		1181	100.0%	0.94 [0.85, 1.04]	•	
Total events	530		480					
Heterogeneity: Tau ² =	0.01; Chi ²	= 16.68	, df = 11 (P = 0.1	2); I ² = 34	1%		40 400
Test for overall effect:	Z = 1.16 (F	P = 0.24)		,		0.01 0.1 1	10 100
	•						ravous [intervention] rav	



A One Year								
	Interven	ition	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
Andersen 2008	1	114	2	113	2.0%	0.50 [0.05, 5.39]		
Andersen 2010	3	29	7	33	7.0%	0.49 [0.14, 1.71]		
Boesen 2011	1	89	1	97	1.5%	1.09 [0.07, 17.17]		
Guo 2013	1	19	1	22	1.5%	1.16 [0.08, 17.28]		
Kissane 2004	0	154	0	149		Not estimable	_	
Kissane 2007	35	147	31	80	69.7%	0.61 [0.41, 0.92]		
Spiegel 2007	8	62	15	56	18.4%	0.48 [0.22, 1.05]		
Total (95% CI)		614		550	100.0%	0.59 [0.42, 0.82]	•	
Total events	49		57					
Heterogeneity: Tau ² =	0.00; Chi²	= 0.84, c	df = 5 (P :	= 0.97)	; l² = 0%			
Test for overall effect: 2	Z = 3.14 (F	P = 0.002	2)				0.01 0.1 1 10 Eavours [intervention] Eavours [control]	100
			,				Favours [intervention] Favours [control]	
B Two Year	Interve	ntion	Cont	rol		Pick Patio	Pick Patio	
Study or Subaroup	Events	Total	Events	Total	Weight	M-H Random 95% C	M-H Random 95% Cl	
Andersen 2008	1	11/	2	113	0.9%			
Anderson 2010	6	20	14	22	6.6%	0.33 [0.03, 3.13]		
Roccon 2011	3	20	14	07	0.0%	3 27 [0 25 30 86]		
Guo 2012	2	10	ו 2	31	1 20/	1 16 [0 19 7 45]		
Guo 2013 Kiasana 2004	2	154	2	140	1.0 /0			
Kissane 2004	3 70	154	3	149	1.0%	0.97 [0.20, 4.72]	-	
Rissarie 2007	70	147	44	00 50	04.7 %	0.07 [0.07, 1.12]		
Spiegei 2007	23	62	20	50	23.9%	0.60 [0.52, 1.23]	-	
Total (95% CI)		614		550	100.0%	0.82 [0.67, 1.02]	•	
Total events	108		93					
Heterogeneity: Tau ² =	0.00; Chi ²	= 4.01,	df = 6 (P	= 0.68); I² = 0%			100
Test for overall effect:	Z = 1.80 (I	P = 0.07)				Favours [intervention] Favours [control]	100
	Interve	ntion	Cont	rol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% CI	
Andersen 2008	5	114	10	113	5.4%	0.50 [0.17, 1.40]		
Andersen 2010	15	29	27	33	21.1%	0.63 [0.43, 0.93]		
Boesen 2011	5	89	1	97	1.4%	5.45 [0.65, 45.75]		—
Kissane 2004	18	154	12	149	10.3%	1.45 [0.72, 2.91]	+	
Kissane 2007	114	147	62	80	35.2%	1.00 [0.86, 1.16]	*	
Spiegel 2007	39	62	33	56	26.5%	1.07 [0.80, 1.43]		
Total (95% CI)		595		528	100.0%	0.95 [0.73, 1.23]		
Total events	196		145					
Heterogeneity: Tau ² =	0.04; Chi ² 7 = 0.41 (P = 10.75	5, df = 5 (l	P = 0.0	6); I² = 53°	%	0.01 0.1 1 10	100
	- 5.71(. 0.00	· /				⊢avours [intervention] Favours [control]	

Figure 3 Psychosocial intervention versus control for breast cancer with overall mortality at: (A) one year (n=799), (B) two years (n=1,102), (C) four years (n=1,061).

et al. (20) examined eight RCTs between 1996 and 2002 and found no statistically significant difference in one- and four-year survival (RR =0.94; 95% CI, 0.72–1.22; P=0.6) and (RR =0.93; 95% CI, 0.77–1.13; P=0.5), respectively. Subgroup analysis of four trials containing 511 patients with breast cancer also showed no survival difference at one and four years (RR =0.87; 95% CI, 0.67–1.14; P=0.3) and (RR =0.91; 95% CI, 0.76–1.10; P=0.3), respectively. Smedslund *et al.* (21) studied 13 articles published between 1989 and 2003 and similarly reported no survival advantage of psychosocial interventions (hazard ratio =0.77; 95% CI, 0.56–1.06; P=0.1). More recently, Xia *et al.* (22) compared survival rates at one, two, four, and six years with a total of fifteen RCTs, and only reported a significant survival benefit for the psychosocial intervention group at two years of follow-up (RR =0.85; 95% CI, 0.75–0.96; P=0.01). However, subgroup analysis of articles studying interventions with at least 30 hours of treatment revealed a survival advantage at one and two years (RR =0.69; 95% CI, 0.55–0.87; P=0.002) and (RR =0.82; 95% CI, 0.71–0.95;

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A One Year	Interven	tion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Andersen 2008	1	114	2	113	1.9%	0.50 [0.05, 5.39]	· · · ·
Andersen 2010	3	29	7	33	6.9%	0.49 [0.14, 1.71]	
Boesen 2007	1	128	0	130	1.1%	3.05 [0.13, 74.10]	
Boesen 2011	1	89	1	97	1.4%	1.09 [0.07, 17.17]	
Guo 2013	1	89	7	89	2.5%	0.14 [0.02, 1.14]	
Kissane 2004	0	154	0	149		Not estimable	
Kissane 2007	35	147	31	80	68.2%	0.61 [0.41, 0.92]	
Spiegel 2007	8	62	15	56	18.0%	0.48 [0.22, 1.05]	
Total (95% CI)		812		747	100.0%	0.57 [0.41, 0.79]	•
Total events	50		63				
Heterogeneity: Tau ² = (0.00; Chi² :	= 3.42, (df = 6 (P =	= 0.75)	; l² = 0%		
Test for overall effect: 2	z = 3.34 (P	= 0.00) (80	,			0.01 0.1 1 10 100
B Two Year							
o	Interver	ition	Conti	ol T		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Iotal	Events	Iotal	weight	M-H, Random, 95% Cl	I M-H, Random, 95% CI
Andersen 2008	1	114	3	113	0.8%	0.33 [0.03, 3.13]	· · · · · · · · · · · · · · · · · · ·
Andersen 2010	6	29	14	33	6.0%	0.49 [0.22, 1.10]	
Boesen 2007	2	128	4	130	1.4%	0.51 [0.09, 2.72]	
Boesen 2011	3	89	1	97	0.8%	3.27 [0.35, 30.86]	
Guo 2013	15	89	14	89	9.0%	1.07 [0.55, 2.09]	
Kissane 2004	3	154	3	149	1.6%	0.97 [0.20, 4.72]	
Kissane 2007	70	147	44	80	58.7%	0.87 [0.67, 1.12]	
Spiegel 2007	23	62	26	56	21.7%	0.80 [0.52, 1.23]	
Total (95% CI)		812		747	100.0%	0.84 [0.68, 1.02]	•
Total events	123		109				
Heterogeneity: Tau ² =	0.00; Chi ²	= 4.77,	df = 7 (P	= 0.69)	; l² = 0%		
Test for overall effect:	Z = 1.76 (F	P = 0.08)				Eavours [intervention] Eavours [control]
C Four Year							
	Interve	ntion	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Tota	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Andersen 2008	5	114	10	113	4.5%	0.50 [0.17, 1.40]	
Andersen 2010	15	29	27	33	19.5%	0.63 [0.43, 0.93]	
Boesen 2007	7	128	8	130	5.0%	0.89 [0.33, 2.38]	
Boesen 2011	5	89	1	97	1.2%	5.45 [0.65, 45.75]	
Kissane 2004	18	154	12	149	9.0%	1.45 [0.72, 2.91]	+
Kissane 2007	114	147	62	80	35.5%	1.00 [0.86, 1.16]	+

Spiegel 2007 39 33 56 25.3% 1.07 [0.80, 1.43] 62 Total (95% CI) 658 100.0% 0.94 [0.75, 1.20] 723 Total events 203 153 Heterogeneity: Tau² = 0.04; Chi² = 10.77, df = 6 (P = 0.10); l² = 44% 0.01 0.1 10 Test for overall effect: Z = 0.47 (P = 0.64) Favours [intervention] Favours [control]

Figure 4 Group-delivered psychosocial intervention versus control for all cancer with overall mortality at: (A) one year (n=1,150), (B) two years (n=1,453), (C) four years (n=1,319).

P=0.007), respectively.

The present study examined thirteen RCTs and compared pooled treatment effects on one, two and fouryear survival. In contrast to previous studies, the present study showed that psychosocial interventions conferred a short-term survival benefit at one and two years of followup in the main analysis. The subgroup analysis of breast cancer showed that psychosocial interventions only had

a survival benefit at one year. These discrepancies can be explained by differences in the time period, geographical location, patient characteristics, types of psychosocial interventions, and a relatively small number of studies.

The present study also found that there was no significant survival difference at four years after the intervention, a finding that is consistent with previous meta-analyses (20-22). There are several potential explanations for

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, i filst fear	Interver	ntion	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Choi 2012	25	118	25	119	9.9%	1.01 [0.62, 1.65]	
Kuchler 2007	53	136	67	135	30.3%	0.79 [0.60, 1.03]	-8-
Ross 2009	25	125	19	124	8.2%	1.31 [0.76, 2.25]	+
Steel 2016	84	144	71	117	50.6%	0.96 [0.79, 1.18]	#
Zhang 2013	2	27	5	28	1.0%	0.41 [0.09, 1.96]	
Total (95% CI)		550		523	100.0%	0.92 [0.79, 1.08]	•
Total events	189		187				
Heterogeneity: Tau ² =	0.00; Chi ²	= 4.24,	df = 4 (P	= 0.37)	; l² = 6%		
Test for overall effect:	Z = 0.99 (F	> = 0.32	:)				Favours [intervention] Favours [control]
B Two Year							

B Hile Ical	Interver	ntion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Choi 2012	37	118	42	119	13.2%	0.89 [0.62, 1.27]	
Kuchler 2007	66	136	90	135	30.3%	0.73 [0.59, 0.90]	-
Ross 2009	39	125	35	124	11.9%	1.11 [0.75, 1.62]	
Steel 2016	96	144	84	117	41.6%	0.93 [0.79, 1.09]	•
Zhang 2013	7	27	10	28	3.0%	0.73 [0.32, 1.63]	
Total (95% CI)		550		523	100.0%	0.87 [0.75, 1.00]	•
Total events	245		261				
Heterogeneity: Tau ² = (0.01; Chi ²	= 5.09,	df = 4 (P	= 0.28)	; I² = 21%		
Test for overall effect: 2	z = 1.94 (F	P = 0.05)				Favours [intervention] Favours [control]

C Four Year	Interver	tion	Contr	ol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl	
Choi 2012	50	118	58	119	12.6%	0.87 [0.66, 1.15]		
Kuchler 2007	90	136	108	135	31.2%	0.83 [0.71, 0.96]	-	
Ross 2009	59	125	52	124	12.8%	1.13 [0.85, 1.49]		
Steel 2016	118	144	97	117	40.6%	0.99 [0.88, 1.11]	•	
Zhang 2013	10	27	12	28	2.7%	0.86 [0.45, 1.66]		
Total (95% CI)		550		523	100.0%	0.93 [0.84, 1.04]	•	
Total events	327		327					
Heterogeneity: Tau ² =	0.00; Chi ²	= 5.64,	df = 4 (P	= 0.23)	; I² = 29%			100
Test for overall effect:	Z = 1.26 (F	P = 0.21)				Favours [intervention] Favours [control]	100

Figure 5 Individually-delivered psychosocial intervention versus control for all cancer with overall mortality at: (A) one year (n=817), (B) two years (n=817), (C) four years (n=817).

the lack of statistical significance in the 4-year survival endpoint. First, nearly all of the psychosocial interventions in the included studies lasted one year or less; therefore, the benefits of these interventions may have diminished after the treatment period (23,27-31,34,35,38). Second, contamination bias may exist as patients are often disappointed when they are assigned to the control group and may actively seek psychosocial interventions outside of the trial. This would effectively dilute the impact of psychosocial interventions between the intervention and control groups. In fact, Spiegel *et al.* (36) found that 43% of control group patients actively joined other social cancer support groups. Subgroup analyses were also performed to compare survival outcomes between group- and individuallydelivered psychosocial interventions. Group-delivered therapies are generally considered more effective than individually-delivered interventions for treating depressive and anxiety symptoms (40-42). Furthermore, studies (43,44) have shown that group-delivered interventions may also be more time-and-cost-efficient than individuallydelivered interventions, although the literature is still unclear about which type of therapy is more beneficial for survival outcomes (42). The subgroup analysis found that group-delivered interventions have a significant short-term survival benefit, while individually-delivered interventions show no significant survival benefit.

The present study is subject to certain limitations. The systematic search yielded only 13 relevant clinical trials in the past 10 years, highlighting the paucity of research in this area and the need for additional studies. Furthermore, while statistical heterogeneity was absent, inter-study clinical heterogeneity was more apparent as there were different types of interventions and diverse patient populations (23,30,38). Statistical heterogeneity refers to variability in the intervention effects from the evaluated studies, while clinical heterogeneity refers to variability in the participants, interventions, and outcomes of the evaluated studies. In this meta-analysis, clinical heterogeneity represented a major challenge in terms of synthesizing meaningful conclusions based on pooled analysis. For instance, the present study included trials that examined a variety of psychosocial interventions, including individually-delivered cognitive behavioral therapies (30,34), group supportive-expressive therapies (36,37), and various combinations of psychoeducational and group cognitive therapies (29). In addition, the patients in these trials were characterized by different cancer sites or variable stages of cancer which may have influenced how they responded to the interventions and thus produced biased survival outcomes. For example, Küchler et al. (38) suggested that metastatic or advanced cancer patients may have progressed too far in their disease for psychotherapeutic treatments to yield a substantial impact on survival outcomes relative to patients with early stage disease.

However, because these diverse patient populations were often lumped together in trials and analyzed aggregately in their survival outcomes, it was difficult to isolate the impact of individual cancer stages or cancer sites on survival.

Furthermore, this meta-analysis only incorporated RCTs to minimize differences in baseline demographics between comparators. However, two included RCTs reported variations in patient baseline characteristics which may have influenced the results (29,37). For instance, Ross *et al.* (37) reported that patients in the control group had a significantly higher daily consumption of tobacco than patients in the intervention group, while Boesen *et al.* (29) indicated that women in the intervention group had significantly larger tumours than those in the control group.

Kissane *et al.* (35) also suggested that psychosocial interventions may not appeal to all patients, especially to those who are more distressed or overburdened with treatment complications. These patients are more likely to be forced to delay or withdraw from psychosocial treatments, thereby limiting their participation in these studies and creating a biased sample. On the other hand, patients with lower levels of distress may feel less burdened and more likely to participate in psychosocial interventions. This may have been the case in two studies (29,34) where patients reported relatively low levels of baseline distress. Boesen *et al.* (29) reasoned that these patients had less room for psychological improvement (i.e., "ceiling effect") and thus were less sensitive in showing survival improvements. Moreover, data from different studies were pooled irrespective of whether survival was collected as an a priori or post-hoc outcome. Publication bias may be further introduced due to studies that were unpublished because of negative findings or because they were rejected for publication.

While some critics have argued against the efficacy of psychosocial intervention as well as the investment of resources towards a large-scale RCT examining survival outcomes, severe limitations in sample size and betweenstudy heterogeneity among previously-conducted RCTs highlight the need for additional studies with larger, more homogenous patient populations and study characteristics, and examination of long-term outcomes (45).

Conclusions

This meta-analysis of the recent literature demonstrates a significant survival benefit of psychosocial interventions among cancer patients at one and two years following intervention, but a non-significant survival difference at four years relative to controls. Future studies with larger sample sizes, longer follow-up and more homogenous protocols and study populations are needed to validate these results and clarify the long-term survival benefit of these interventions. More comprehensive analyses are also warranted to elucidate differences in outcomes between group- and individually-delivered interventions. Until larger, more comprehensive studies are available to dispute the efficacy of psychosocial interventions, these interventions should continue to be considered in the management of cancer patients given their potential survival benefit. Importantly, clinicians should recognize that long-term treatment may be needed to confer sustained improvement in survival outcomes.

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Footnote

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