Systematic Review and Meta-Analysis

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Psychological intervention and its immune effect in cancer patients

A meta-analysis

Ping Zhang, MM[a,b,c,d], Lin Mo, BD[a,*], Xia Li, MM[a,c,d], Qiyao Wang, MM[a,c,d]

Abstract

Objective: To determine whether psychological intervention (PI) changes the levels of immune indicators in cancer patients.

Methods: We conducted a systematic search published up to July 2018, followed by a manual search. Randomized controlled trials were included. Two reviewers independently screened and extracted data, which were analyzed using Review manager 5.3.

Results: Twenty-nine studies were included including four kinds of PI. Only stress management didn't result in immune changes; only cognitive behavior therapy affect NK cell activity. PI did not change immune indicators on cancer patients who completed therapy. Compared to patients not receiving PI, those received PI had significantly higher NK cell count and activity in whole blood; and serum levels of IL-2, IL-4, IFN-γ, IgA, and IgG. However, the differences in the serum levels of IL-6, IL-10, TNF-α, and IgM were not significant ($P > .05$), and the changes recorded for the $CD3^+$, $CD4^+$, and $CD8^+$ cell count, and $CD4^+/CD8^+$ ratios were inconsistent.

Conclusions: Although there are considerable evidences of PI's immune effect, but its magnitude was moderate. Therefore, it may be premature to conclude whether PI affects immunity of cancer patients. Further research is warranted, with special focus on the PI types and treatment methods.

Abbreviations: CBT = cognitive behavior therapy, CCT = Cochrane Collaboration's tool, CT = chemotherapy, HPA axis = hypothalamic–pituitary–adrenal axis, MT = mind–body therapy, PFs = psychological factors, pg/mL = picograms per milliliter, PI = psychological intervention, PNI = psychoneuroimmunology, PS = psychological support, RT = radiotherapy, SM = stress management, ST = surgical treatment.

Keywords: cancer, immune, intervention, meta-analysis, prognosis, psychology

1. Introduction

Cancer is an important public health concern worldwide. GLOBOCAN 2012 reported that there were 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide.[1] Traditional cancer treatments, such as surgery, chemotherapy, and radiotherapy, certainly affect the medical outcomes of cancer, but may not completely eradiate all types of cancers and always cause adverse effects. Therefore, enormous efforts are invested in exploring adjunctive interventions with minimal adverse effects in cancer patients.[2]

Etiological studies have shown that genetic, environmental, and socioeconomic factors are only partly responsible for the development and prognosis of cancer.[3] This has encouraged researchers to investigate the effect of psychological factors (PFs) on the initiation and prognosis of cancer.[4] As a result, several studies have been published on the interactions between cancer and psychological factors such as chronic stress, anxiety, distress, depression, and psycho-social support.[5] Although evidence of the positive influence of PFs in cancer survival is modest and findings are inconsistent, strong evidence has been obtained regarding the link between cancer progression and factors such as chronic stress, depression, and social isolation.[6] According to Straub and Yan, PFs (stress, anxiety, depression) affect the tumor microenvironment (peripheral immune cells and inflammatory processes) via the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, and non-adrenal stress hormones, which may alter disease prognosis.[7,8]

Many randomized controlled trails have examined the relationship between PFs and the immune system in cancer.[9,10] Most of these trials have focused on the effect of psychological intervention (PI) on immune function. These PIs mainly include cognitive behavior therapy (CBT), stress management (SM), mind–body therapy (MT), and psychological support (PS), while the immune indicators mostly involved are the counts of immune

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[a] Children's Hospital of Chongqing Medical University, Chongqing, [b] Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hubei, [c] China International Science and Technology Cooperation base of China Development and Critical Disorders, Chongqing Key Laboratory of Paediatric, [d] Ministry of Education Key Laboratory of Child Development and Disorder, Chongqing, China.

[*] Correspondence: Lin Mo, Children's Hospital of Chongqing Medical University, No 136 Zhongshan Road, Yuzhong District, Chongqing 400014, China (e-mail: molin999@126.com).

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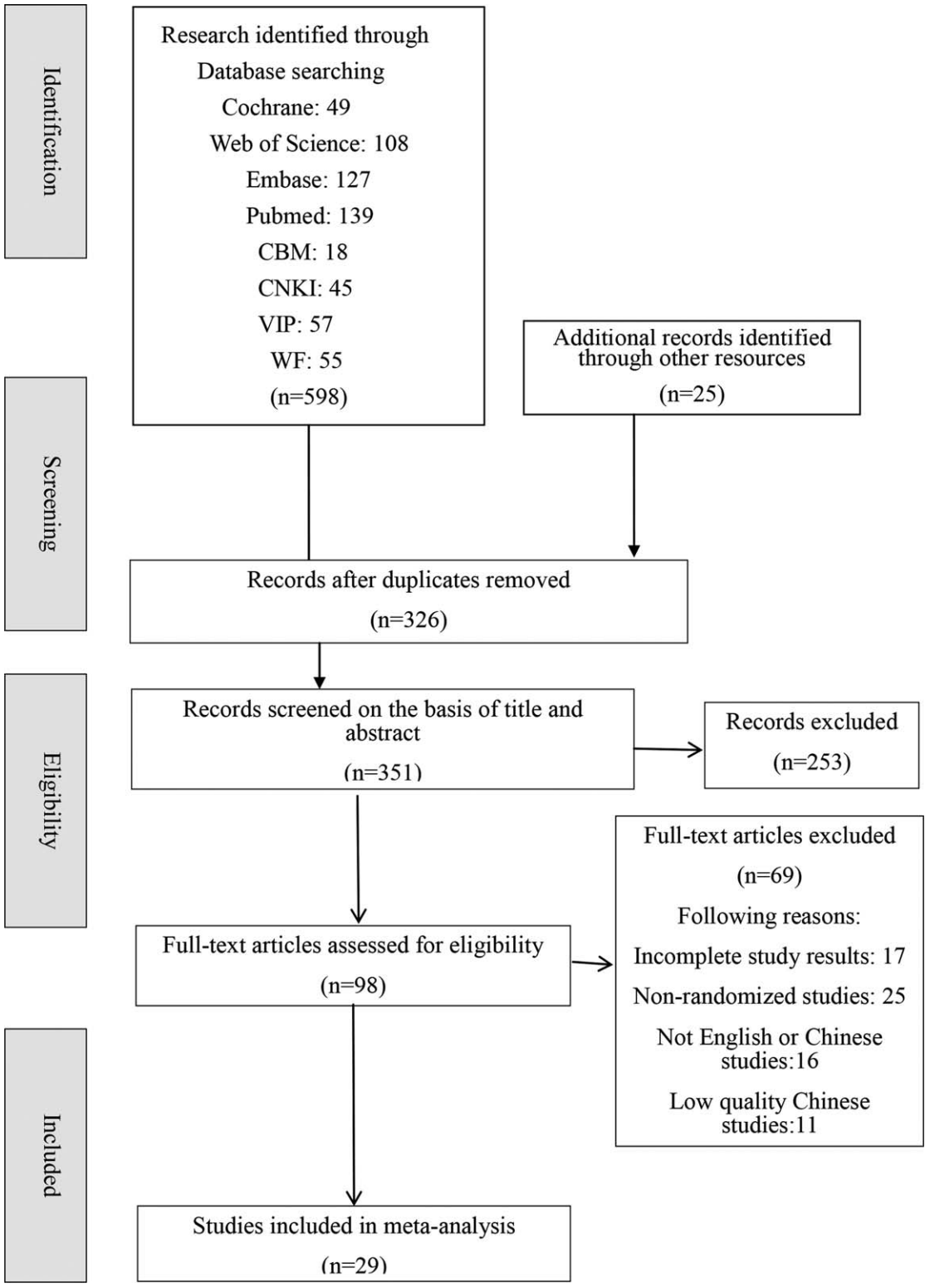

Figure 1. Flow chart of the study selection process.

cells, cytokines, and activity of NK cells. Although several meta-analyses have been conducted to collate the evidence regarding the effects of PI on immune response,[9,10] systematic analysis of the effects of different PIs at different stages in cancer treatment on immune function is generally lacking. In this study, we sought to analyze and compare the effect of various PIs administered at different stages of cancer treatment on immune response; we also aimed to evaluate the links between these changes and immune

Table 1

Characteristics of included studies.

Study/year	Patients	Intervention	Control	Outcomes	Study design
Bower et al (2015)[36]	Women; stages I–III breast cancer; completed therapy (except hormone therapy) at least 3 months; age $\leq$ 50 y	Mindfulness meditation, 2-h group sessions; 6 weeks (N=39)	Usual care (N=39)	IL-6	Two-armed randomized controlled
Reich et al (2014)[13]	Women; stages I–III breast cancer; completed treatment 2–12 weeks; mean age=58.2 years	Mindfulness-based stress reduction; 15–45 min daily; 6 weeks (N=17)	Usual care (N=24)	$CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, NK cell, IFN-γ, IL-4	Two-armed randomized controlled
Robins et al (2013)[37]	Women; stages I–III breast cancer; during chemotherapy; mean age=50 years	Psychoneuroimmunology-based stress management, 90 min in 1 week; 10 weeks (N=84)	Usual care (N=20)	IFN-γ	Two-armed randomized controlled
Lengacher et al (2008)[12]	Women; stages I–III breast cancer; mean age=58±9 years; completed treatment within the prior 18 months	Mindfulness-based stress reduction; 2-h sessions; 6 weeks, (N=40)	Usual care (N=42)	$CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, NK cell, IFN-γ, IL-4	Two-armed randomized controlled
Baker et al (2012)[17]	Women; stages 0–IIIa breast cancer; mean age: 52.3 years; after surgery with adjunctive therapy	Integrated support; a 2 days Haven Support Workshop, a maximum of 12 hour of therapy consultation time (N=6)	Usual care (N=6)	6 months after: peripheral blood mononuclear cells, NK CA	Randomized, controlled pilot feasibility
Cho et al (2011)[38]	Women; stages I–III breast cancer; mean age=49.4 years; completed chemotherapy and radiation therapy	Smile therapy; eight times, twice a week for 60 min per session (N=16)	Usual care (N=21)	Total T cell, T helper, T suppressor, Th/Ts ratio, Total B cell, NK cell	Pre-test-post-test randomized, controlled design
Cohen et al (2011)[20]	Men, early-stage prostate cancer; mean age=60.4 years; receive radical prostatectomy	Stress management; two 60- to 90-min individual sessions (N=38)	Usual care (N=44)	Two days after: peripheral blood mononuclear cells; IL-6, TNF-α	RCT
Eremin et al (2009)[39]	Women, large (>4 cm) or locally advanced (T3, T4, Tx, N2) breast cancer; mean age=49.9 years; received chemotherapy, surgery, and radiotherapy	Relaxation training and guide imagery; five individual live training sessions and regular home practice (N=40)	Usual care (N=40)	Natural killer (NK) and lymphokine activated killer (LAK); IL1b, IL2, IL4, IL6, and TNF-alph	Randomized, controlled, trial
Antoni et al (2009)[31]	Women; stages I–III breast cancer; mean age=47.5 years; 4–8 weeks after surgery	Cognitive behavior stress management; weekly 2 h sessions for 10 weeks (N=63)	Usual care (N=65)	6 or 12 months after: IL-2	Randomized, controlled, trial
McGregor et al (2009)[15]	Women, stages I–II breast cancer; mean age=47.5 years; in 4–8 weeks after surgery	Cognitive behavior stress management, 2-h structured group session; 10 weeks (N=18)	Usual care (N=11)	3 months after: $CD3^+$	randomized, controlled, trial
Ross et al (2009)[16]	Men/women; colorectal cancer I–V; mean age=68.5 years; undergoing abdominal surgery	Home PI; five times during the first 2–3 months, and repeated at approximately 4, 7, 11, 16, 24 months;10 times (N=125)	Usual care (N=124)	3 or 12 or 24 months after: $CD4^+$, $CD8^+$, NK cell	Randomized, controlled, trial
Lengacher et al (2008)[12]	Women, stage I or II breast cancer; 2–3 weeks before surgery; mean age=52.6 years	Guided imagery; 30-min sessions 3 times per week; (N=15)	Usual care (N=13)	1 months after: NK cytotoxicity cell, IL-2	An experimental randomized pre-test post-test design
Lindemalm et al (2008)[14]	Women, stages I–II breast cancer; mean age=61.1 years; received chemotherapy or radiotherapy	Support intervention; 4 days followed up 2 months after initial visit (N=21)	Usual care (N=20)	2,6,12 months after: NK cell; NK cytotoxicity cell	Randomized, controlled, trial
Savard et al (2005)[34]	Women; mostly stage I or II breast cancer; mean age=54.1 years; all therapy	Cognitive behavior therapy; 8-week (N=27)	Waiting-list control (N=30)	3 months after: $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, NK cell, IL-1beta, IFN-γ	Randomized, controlled, trial
Anderson et al (2004)[33]	Women, stage II or III breast cancer, surgically treated, awaiting adjuvant therapy; mean age=50.82 years	Psychological intervention; one session weekly for 1.5 h for 18 sessions; 4 months (N=114)	Usual care (N=113)	4 months after: NK cell, $CD3^+$,$CD4^+$, $CD8^+$; PHA; con A	Randomized, controlled, trial

(*continued*)

Table 1

(continued).

Study/year	Patients	Intervention	Control	Outcomes	Study design
Pompe et al (2001)[18]	Early-stage breast cancer either positive lymph nodes or distant metastases; after surgery; mean age = 58.8 years	Group psychotherapy; 2.5 h per session for 13 sessions over 3 months (N = 15)	Usual care (N = 16)	3 months after: $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, NK cell	Randomized, controlled, trial
Lekander et al (1997)[23]	Women; stages I–IV ovarian cancer; receive chemotherapy; mean age = 57 years	Relaxation therapy; 3 training sessions during 2 months for 30–45 min (N = 12)	Usual care (N = 10)	2 months after: NKCA	Randomized, controlled, trial
Zhou et al (2017)[40]	Men/women; stages I–III cervical cancer; mean age = 55 years; received only surgical therapy	Cognitive nursing; 1 session per day for 14 days (N = 60)	Usual care (N = 60)	14 days after: $CD3^+$, $CD4^+$, $CD8^+$	Randomized, controlled, trial; pre- and post-test design
Shen et al (2017)[35]	Men/women; stages I–III lung cancer, mean age = 50 years; received chemotherapy	Relaxation training for 30 min one day plus cognitive behavior therapy (N = 32)	Usual care (N = 32)	TNF-alph	
Dong et al (2016)[41]	Men/women; stages 0–IV cancer patients; mean age = 57.2 years; primary radiotherapy	Behavior relaxation training; cognitive therapy for two months (N = 30)	Usual care (N = 30)	2 months after: $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, NK cell	Randomized, controlled, trial; pre- and post-test design
Li et al (2016)[42]	Men/women, stage II or III gastric cancer; mean age = 57.89 years; only surgery	Psychosocial therapy, relaxation and meditation; 1 session per week for 3 months (N = 50)	Usual care (N = 50)	3 month after: $CD3^+$,$CD4^+$, $CD8^+$, $CD4^+/CD8^+$, NK cell, IgA, IgM, IgG	Randomized, controlled, trial; pre- and post-test design
Ren et al (2015)[43]	Men/women, stage II or III colorectal cancer;mean age = 54.5 years; receive radiotherapy	Psychological intervention; 50 min per session; 6 sessions (N = 30)	Usual care (N = 37)	1.5 months after: $CD4^+$, $CD8^+$, $CD4^+/CD8$	Randomized, controlled, trial; pre- and post-test design
Peng et al (2015)[44]	Men/women, stages III–IV lung cancer; mean age = 54.5 years; during therapy in hospital	Cognitive behavior therapy; 4 months (N = 30)	Usual care (N = 30)	4 months after: IL-2, IL-10, IL-12	Randomized, controlled, trial; pre- and post-test design
Zheng et al (2015)[45]	Men/women, all-stage esophageal cancer; mean age = 54 years; only surgery therapy	All-in—one nursing intervention usual; 8 days care (N = 52)	Usual care (N = 50)	8 days after: $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, IgA, IgM, IgG	Randomized, controlled, trial; pre- and post-test design
Guo et al (2015)[46]	Men/women; all stage rectal cancer; mean age = 61 years; only surgery therapy	Individuation psychological; 20–30 min/day for 1 month (N = 37)	Usual care (N = 37)	1 month after:$CD4^+$, $CD8^+$, $CD4^+/CD8^+$	Randomized, controlled, trial; pre- and post-test design
Chen et al (2013)[47]	Women; breast cancer, all stage; mean age = 45.4 years; only chemotherapy	Psychological intervention;1 h per session for relaxation and communication (N = 33)	Usual care (N = 33)	IL-2, IL-4, IFN-γ	
Han et al (2013)[48]	Women, stages I–II cervical carcinoma; mean age = 50 years only surgery therapy	Cognitive intervention; cognitive and relaxation training 2 times 1 day for 10 days (N = 30)	Usual care (N = 30)	10 days after: NKCA	Randomized, controlled, trial; pre- and post-test design
Zheng et al (2010)[45]	Men/women; stage II lung cancer; mean age = 52 years; preoperative	Synthesized psychology intervention; relaxation and spiritual healing during preoperative (N = 34)	Usual care (N = 28)	After surgery: $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD\ 8^+$	Randomized, controlled, trial; pre- and post-test design
Wang et al (2002)[22]	Men/women; lung or breast tumor, all stage; age >18 years; only chemotherapy	Psychological intervention; 1 per week during chemotherapy (N = 40)	Usual care (N = 40)	7 days after chemotherapy: NKCA, IgA, IgM, IgG	Randomized, controlled, trial; pre- and post-test design

Table 2

Publication bias and quality of included studies.

Study/year	Selective bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Quality rating
Bower et al (2015)[36]	N	N	N	N	N	N	High
Reich et al (2014)[13]	N	N	N	N	N	N	High
Robins et al (2013)[37]	N	N	N	N	N	N	High
Lengacher et al (2008)[12]	N	N	N	N	N	N	High
Baker et al (2012)[17]	N	N	N	N	N	N	High
Cho et al (2011)[38]	N	N	N	N	N	N	High
Cohen et al (2011)[20]	N	N	N	N	N	N	High
Eremin et al (2009)[39]	N	N	N	N	N	N	High
Antoni et al (2009)[31]	N	N	N	N	N	N	High
McGregor et al (2009)[15]	N	N	N	N	N	N	High
Ross et al (2009)[16]	N	N	N	N	N	N	High
Lengacher et al (2008)[12]	N	NC	NC	N	N	N	Moderate
Lindemalm et al (2008)[14]	N	NC	NC	N	N	N	Moderate
Savard et al (2005)[34]	N	N	NC	N	N	N	Moderate
Anderson et al (2004)[33]	N	NC	NC	N	N	N	Moderate
Pompe et al (2001)[18]	N	N	NC	N	N	N	Moderate
Lekander et al (1997)[23]	N	N	N	N	N	N	High
Zhou et al (2017)[40]	N	N	N	N	N	N	High
Shen et al (2017)[35]	N	N	NC	N	N	N	Moderate
Dong et al (2016)[41]	N	N	NC	N	N	N	Moderate
Li et al (2016)[42]	N	NC	N	N	N	N	High
Ren et al (2015)[43]	N	NC	NC	N	N	N	Moderate
Peng et al (2015)[44]	N	NC	NC	N	N	N	Moderate
Zheng et al (2015)[45]	N	N	NC	N	N	N	Moderate
Guo et al (2015)[46]	N	N	NC	N	N	N	Moderate
Chen et al (2013)[47]	N	NC	NC	N	N	N	Moderate
Han et al (2013)[48]	N	N	NC	N	N	N	Moderate
Zheng et al (2015)[45]	N	NC	N	N	N	N	High
Wang et al (2002)[22]	N	NC	NC	N	N	N	Moderate

N = no, NC = not clear, Y = yes.

Table 3

Effect sizes of PI on immune indicators according to PI types.

Outcome	Type of PI	E/C	MD[95%CI]	I^2 (%)	*P* value	k
CD3	CBT	140/140	0.06[0.04,0.08]	0	<.001	3
	SM	57/66	−0.01[−0.09,0.07]	0	.81	2
	MT	100/99	−0.06[−0.07,−0.05]	71	<.001	3
	PS	177/174	0.05[0.02,0.08]	0	<.001	3
CD4	CBT	135/130	0.1[0.07,0.12]	90	<.001	4
	SM	57/66	0.01[−0.01,0.12]	0	.85	2
	MT	84/78	0.07[0.06,0.09]	93	<.001	2
	PS	284/271	0.05[0.04,0.07]	76	<.001	4
CD8	CBT	146/146	0.02[0.0,0.03]	93	<.001	3
	SM	57/66	0.01[−0.05,0.06]	0	.77	2
	MT	100/99	−0.02[−0.03,−0.01]	25	<.001	3
	PS	284/271	−0.02[−0.04,−0.01]	80	<.001	6
CD4/CD8	SM	57/66	0.09[−0.48,0.66]	30	.76	2
	MT	100/99	0.09[0.02,0.17]	58	.001	3
	PS	126/125	0.43[0.34,0.52]	0	<.001	3
NK cell	CBT	57/60	0.03[0.03,0.04]	76	<.001	2
	SM	57/66	−0.01[−0.03,0.01]	0	.21	2
	MT	81/99	0.02[0.01,0.03]	56	<.001	3
	PS	151/149	0.02[0.00,0.03]	9	.03	4
NKCA	CBT	57/66	0.07[0.04,0.09]	88	<.001	2
	PS	50/49	0.86[−0.56,2.28]	0	.23	2

C = control group sample, CBT = cognitive behavior therapy, E = experiment group sample, k = number of studies, MD = mean difference, MT = mind–body therapy, NKCA = NK cell activity, PS = psychological support, SM = stress management.

response of cancer patients and possibly their prognosis. We believe that our findings would provide some insights into the psychoneuroimmunology of cancer.

2. Method

2.1. Inclusion and exclusion criteria

The protocol for the meta-analysis was developed in accordance with the PICOS approach. Studies were included in this analysis if they met the following criteria:

1. randomized controlled trials,
2. published in Chinese or English,
3. published before May 2018,
4. diagnosis of epithelial cancers established according to internationally accepted guidelines,
5. comparison of PI with usual care, and
6. outcomes recorded as post-treatment changes in immunological parameters.

Studies were excluded from the analysis if

1. they were not published in English or Chinese,
2. patients had any immunological or psychological diseases,
3. patients had received immune therapy for cancer or drugs for mental illness; and
4. the study design was other than randomized controlled trail.

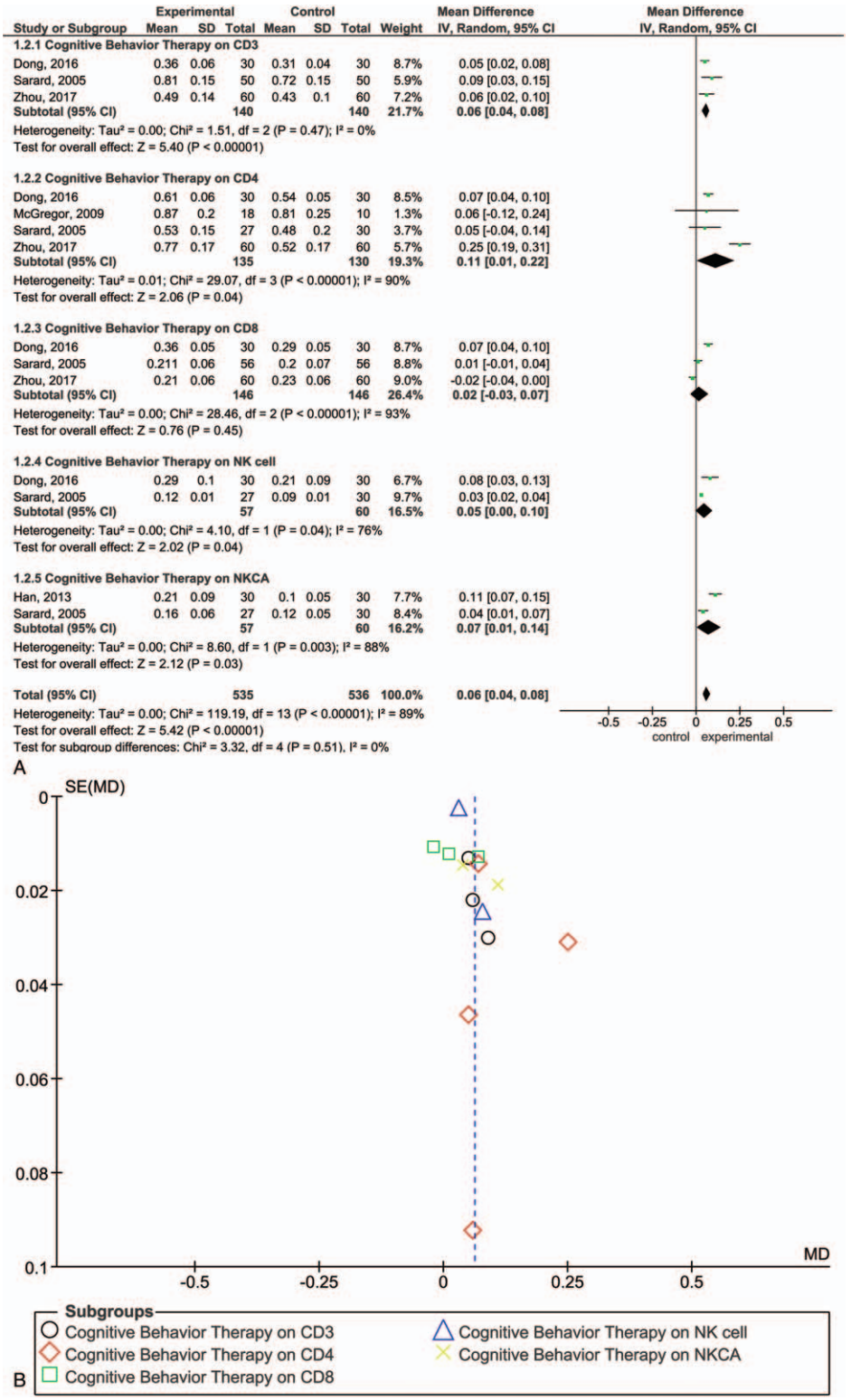

Figure 2. Meta-analysis forest map (A) and funnel plot (B) of the effect of cognitive behavior therapy on immune indicators in cancer patients.

The complete details about our study protocol are provided in the *About* pages at http://www.crd.york.ac.uk/ PROSPERO. The study is a meta-analysis which did not involve any interest of cancer patients, so the ethical review is not necessary.

2.2. Search strategy

A systematic computer-based literature search was conducted using relevant databases, including the Cochrane Library, EMBASE, PubMed, Web of Science, Chinese Biomedical

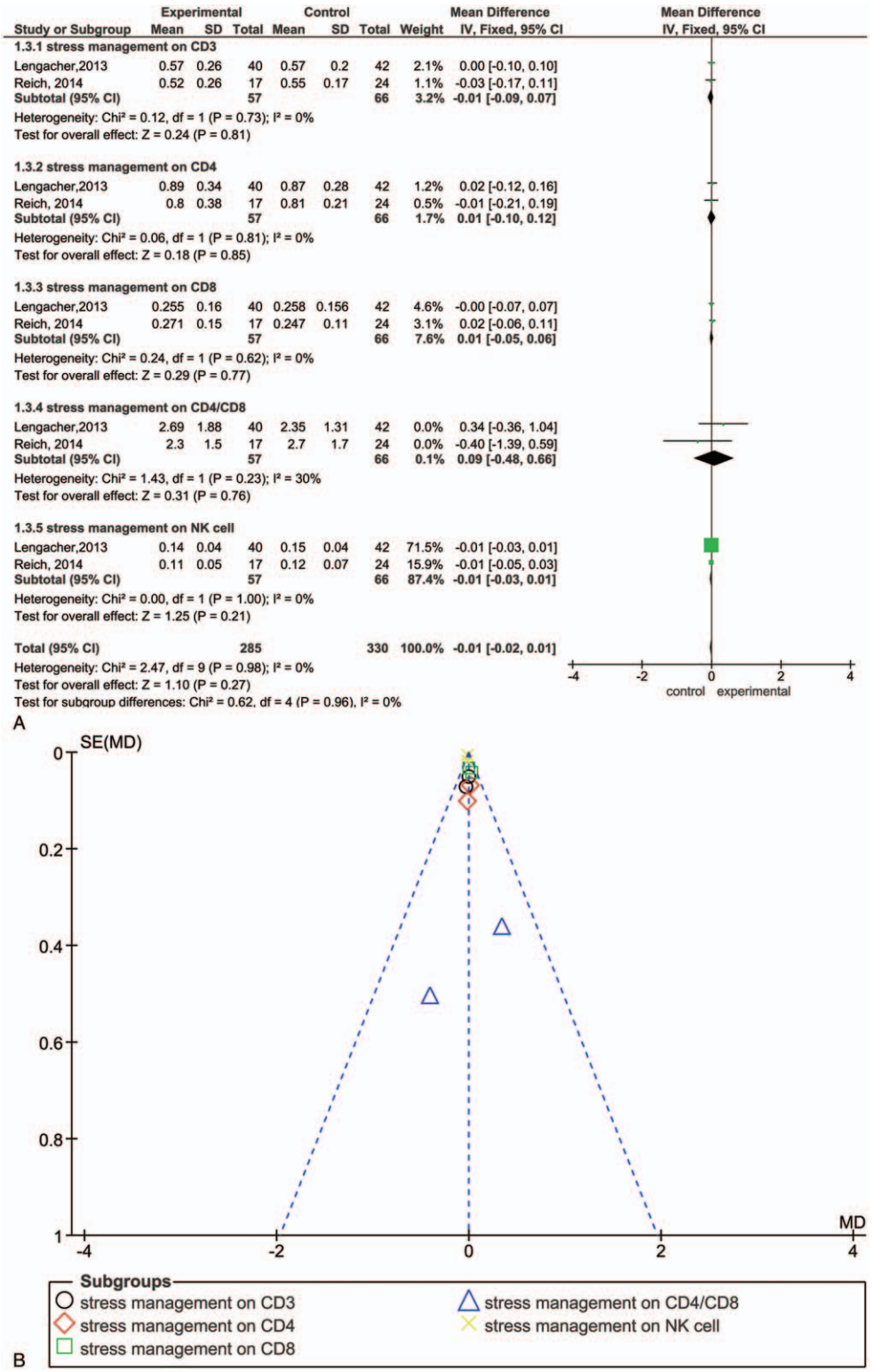

Figure 3. Meta-analysis forest map (A) and funnel plot (B) of the effect of stress management on immune indicators in cancer patients.

Literature Database, Chinese Journal Full-Text Database, VIP Database, and Wanfang Database. We used the following search terms: "cancer" or "tumor" or "tumors" or "tumours" or "carcinoma" or "neoplasm" or "neoplasms" or "oncology" or "oncological"; and "psychological" or "psychology" or "emotion" or "psychotherapy"; and "recovery" or "reduce" or "therapy" or " treatment" or "therapeutical" or "support" or "counsel"; and "immune" or "immunology"; and "immunological" and "random controlled trials" or "random."

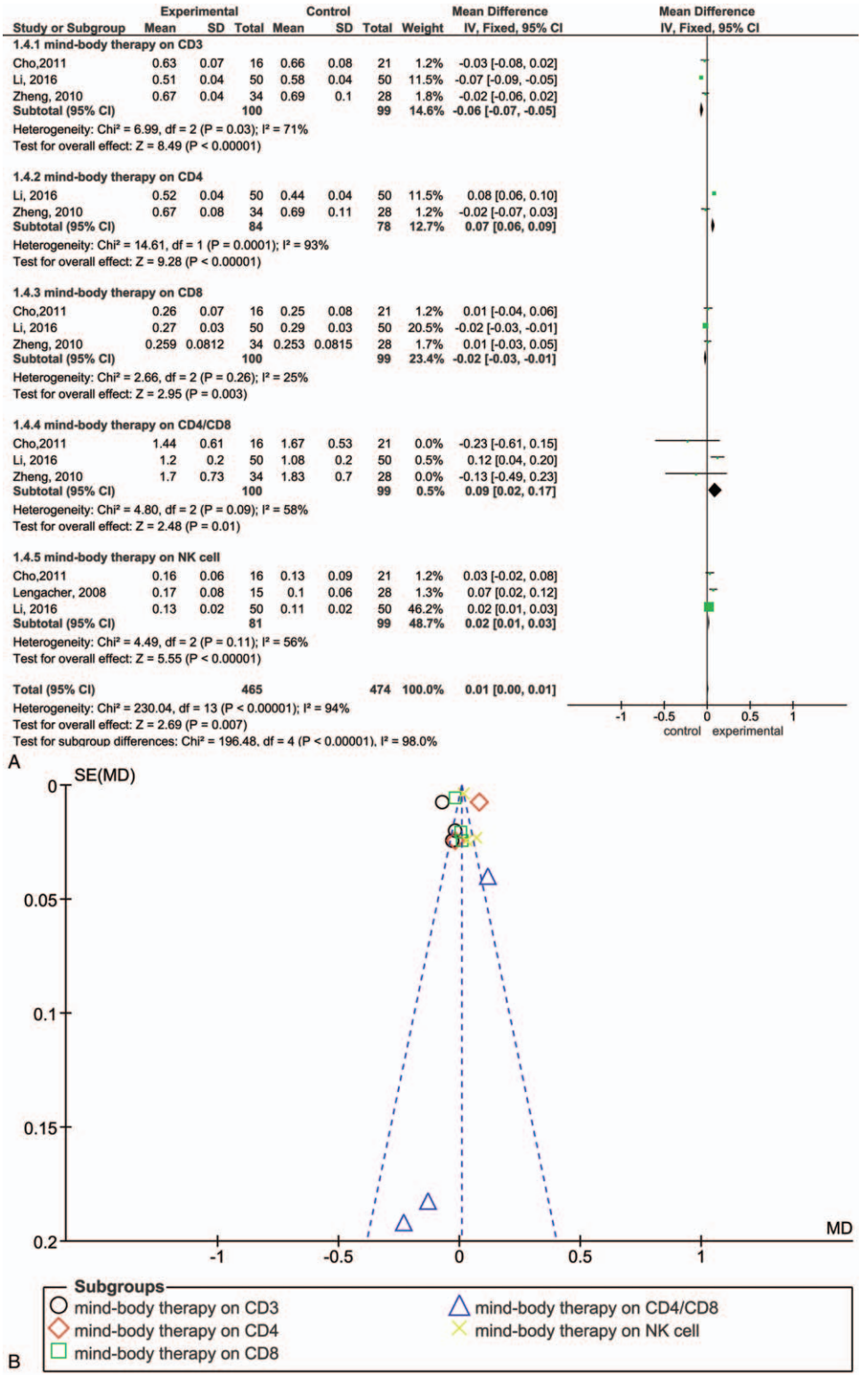

Figure 4. Meta-analysis forest map (A) and funnel plot (B) of the effect of mind-body therapy on immune indicators in cancer patients.

2.3. Study selection and data extraction

After eliminating duplicates using EndNote X7, the title, keywords, abstracts, and contents of all the articles retrieved were independently screened by two reviewers to check if they met the inclusion criteria. If there was any disagreement or doubt about potentially relevant articles, three reviewers jointly decided whether or not the study should be included in this review. Two independent reviewers extracted the data from each study,

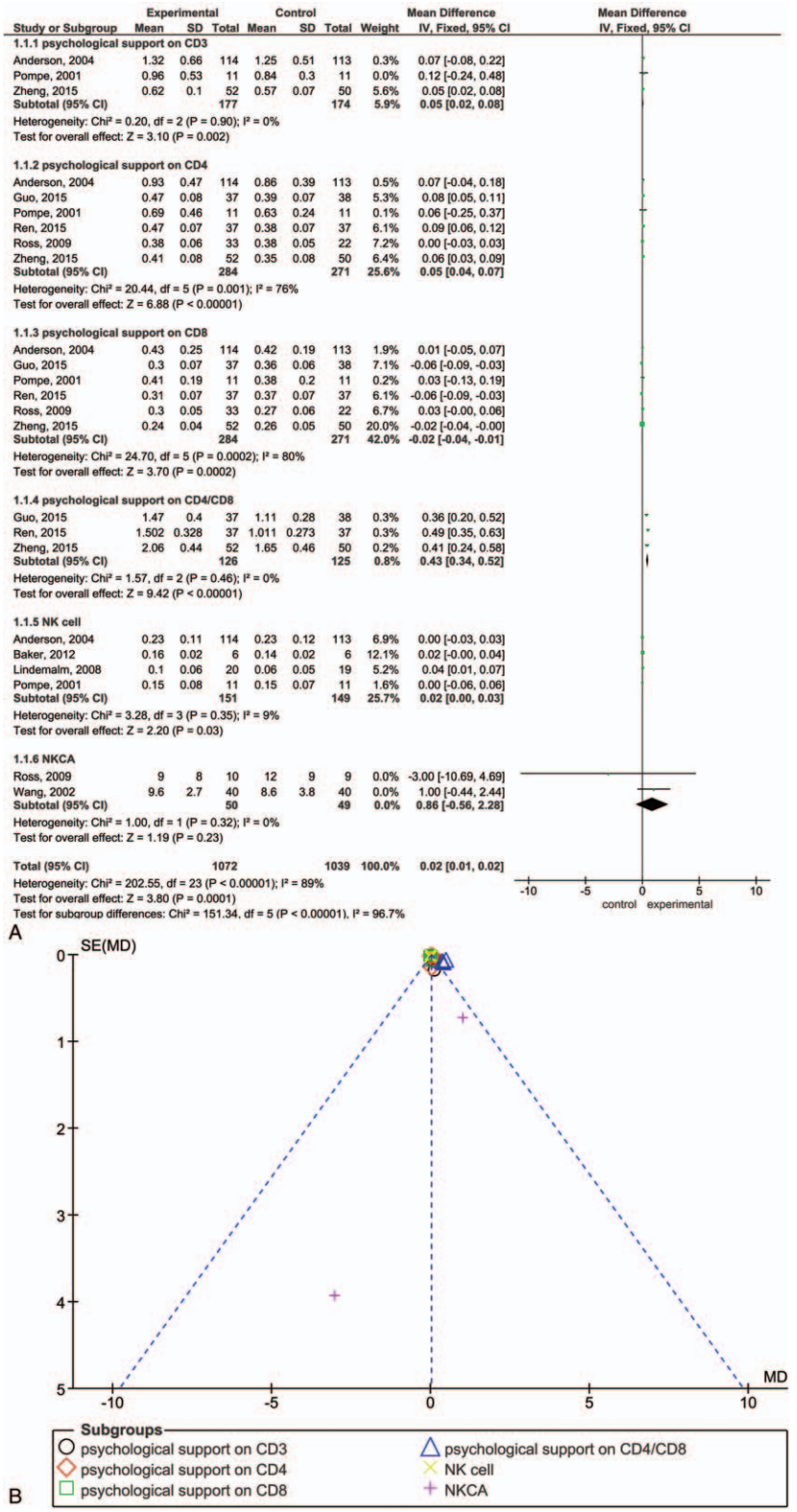

Figure 5. Meta-analysis forest map (A) and funnel plot (B) of the effect of psychological support on immune indicators in cancer patients.

including authors, year of publication, type and stage of cancer, size of sample, mean patient age, intervention method, type of adjuvant treatment, duration of intervention, and immune outcome.

2.4. Data analysis/synthesis

We used Review Manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom) for the meta-analysis. Since the parameters for the measurement of immune status were continuous data, the

Table 4

Effect sizes of PI on immune indicators according to treatment types.

Outcome	Treatment	E/C	MD[95%CI]	I^2 (%)	*P* value	k
CD3	ST	321/312	0.08[0.05,0.10]	89	<.001	6
	CDT	57/66	0.01[−0.01,0.12]	0	.85	2
CD4	ST	409/382	0.02[0.01,0.03]	74	<.001	9
	RT	67/67	0.07[0.05,0.09]	73	<.001	2
	CDT	73/87	−0.03[−0.07,0.00]	0	.05	3
CD8	ST	391/372	−0.02[−0.03,−0.01]	65	<.001	8
	RT	67/67	0.03[0.08,0.23]	98	<.001	2
	CDT	73/87	−0.00[−0.03,0.03]	0	.98	3
CD4/CD8	ST	173/166	0.19[0.13,0.25]	82	<.001	4
	RT	67/67	0.16[0.08,0.23]	97	<.001	2
	CDT	73/87	−0.13[−0.45,0.18]	12	.40	3
NK cell	ST	223/224	0.02[0.01,0.03]	39	<.001	5
	AT	53/55	0.03[0.02,0.03]	0	<.001	3
	CDT	48/73	0.02[−0.00,0.05]	0	.80	3
NKCA	CT	52/50	0.93[−0.53,2.36]	0	.20	2

C = control group sample, CDT = completed therapy, CT = chemotherapy, E = experiment group sample, k = number of studies, MD = mean difference, NKCA = NK cell activity, RT = radiotherapy, ST = surgery therapy.

mean and standard deviation were used to collate the results of the studies. Heterogeneity was tested for all combined results by means of a Q statistic (calculated using a chi-square test), and inconsistency was calculated using an I^2 index to determine the impact of heterogeneity. The presence of significant heterogeneity suggests diversity in the various characteristics of the studies, including stage of disease, age, diagnosis, gender, setting, intervention time, and type of assay. When the heterogeneity test was not statistically significant ($I^2 < 60\%$, $P > .05$), a fixed model was used; otherwise, a random effect model or subgroup analysis was used. However, when the heterogeneity of a subgroup analysis was still high ($I^2 > 60\%$, $P < .05$), the random effect model was used.

2.5. Literature quality analysis

Two independent reviewers assessed the internal validity of the studies using Cochrane Collaboration's tool (CCT) for assessing risk of bias Any disagreements were resolved by consultation with a third reviewer. The CCT[11] is an effective instrument for the evaluation of the internal validity of randomized controlled trials. The quality of a study was classified as strong, moderate, or weak on the basis of the following six domains:

1. selection bias: random sequence generation and allocation concealment;
2. performance bias: blinding of participants and personnel;
3. detection bias: blinding of outcome assessment;
4. attrition bias: incomplete outcome data;
5. reporting bias: selective outcome reporting; and
6. other bias.

If the study was without bias, it was considered to be of high quality; if there was some literature bias, it was deemed to be of moderate quality; and if there was evidence of all types of bias, the study was classified as being of poor quality.

3. Results

3.1. Study selection

After removal of duplicates using EndNote X7, and screened for title and their data abstracted by the inclusion criteria, 29 publications were finally included in this review (Fig. 1).

Study characteristics, publication bias, and quality of studies

Twenty-nine studies were included in the meta-analysis, including 17 English studies and 12 Chinese studies. In all studies, the cytokine concentrations were reported in picograms per milliliter (pg/mL). The type of intervention varied across the studies: 7 trails used cognitive behavior therapy; 4 utilized stress management; 8 employed mind-body therapy; and the remaining 10 trails adopted psychological supports. The trials also differed in terms of the cancer treatment period during which PI was administered. In four of the studies, patients received PI after completing therapy; in 6, during chemotherapy (CT); in 3, during radiotherapy (RT); in 12, during surgical treatment (ST); and in 4, during adjunctive (multiple) therapy. Among the included studies, 15 provided data on breast cancer. The characteristics of the 29 included studies are summarized in Table 1.

Fifteen of these studies were of high quality, while 14 were of moderate quality. All the included studies reported random sequence generation using methods such as random numbers table, coin tossing, and dice throwing, and they provided complete data and results. Nine studies did not provide details regarding allocation concealment, while 14 studies did not provide a clear description about the blinding of the outcome assessment. Data on publication bias and quality of the studies included are detailed in Table 2.

3.2. Meta-analysis results

3.2.1. The effect of different PI approaches on immune cells.

Compared with the control group, the SM group did not show any significant differences in $CD3^+$ cell, $CD4^+$ cell, and $CD8^+$ cell counts; $CD4^+/CD8^+$ ratio; or NK cell count ($P > .05$), although significant changes were noted in the CBT group, MT group, and PS group ($P < .05$). Compared with MT and PS, the CBT group showed the highest magnitude of immune effect, and only the CBT group showed changes in NK cell activity (Table 3, Figs. 2–5).

3.2.2. The influence of PI on immune cells over various cancer treatment periods. Patients who received PI after cancer treatment completion or during CT did not exhibit changes in the counts of any immune indicators, as compared to the control

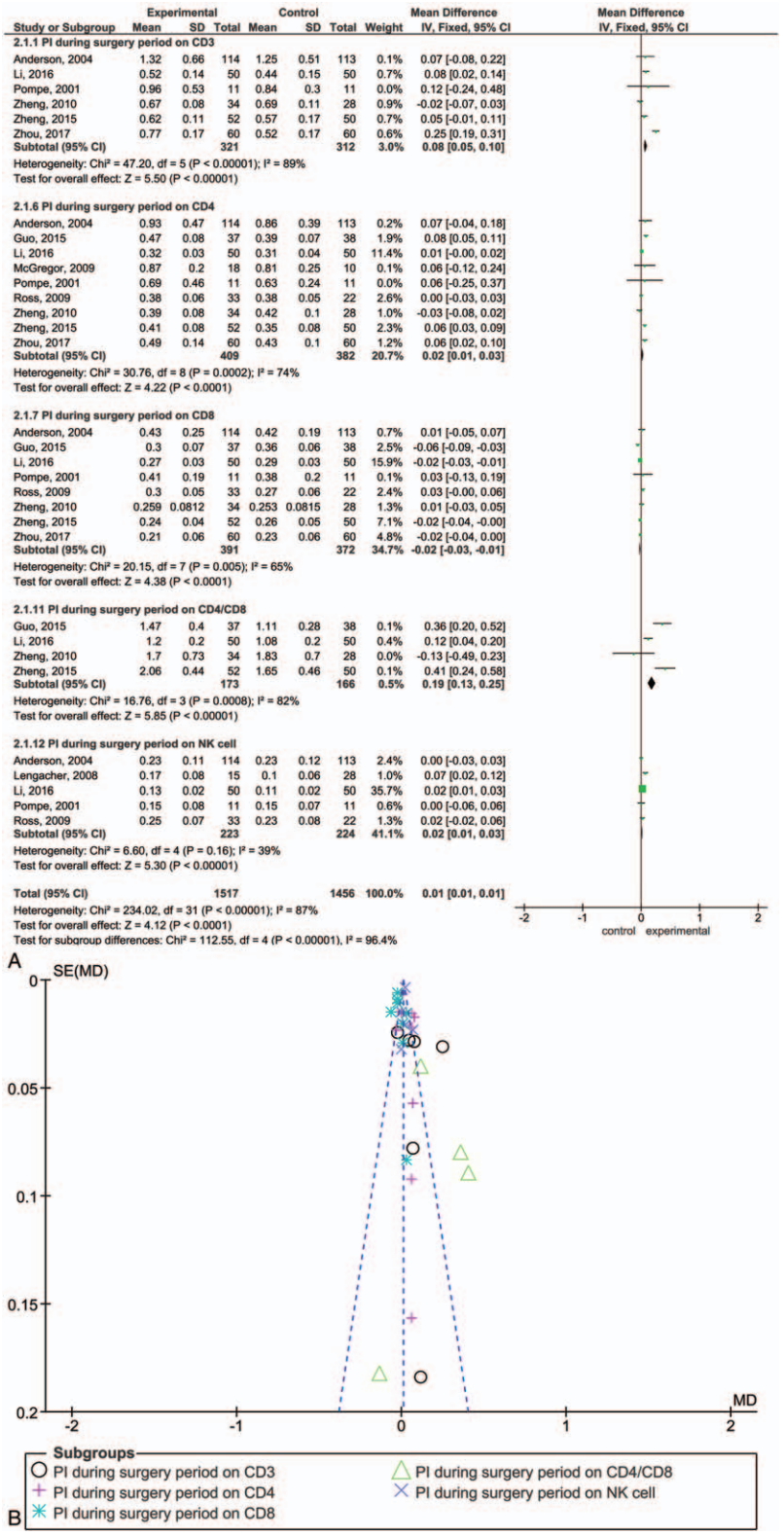

Figure 6. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI during surgery period on immune indicators in cancer patients.

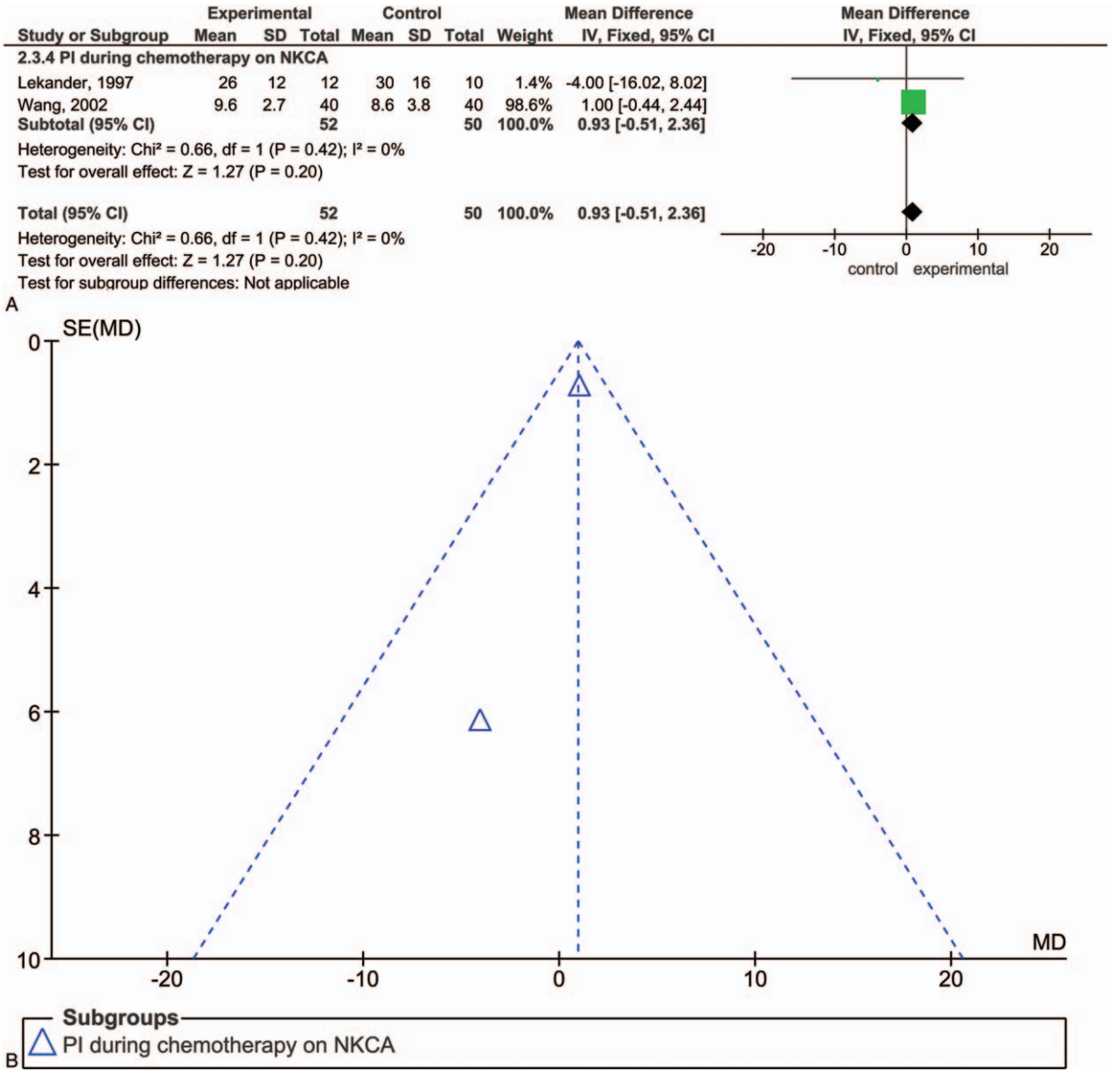

Figure 7. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI during chemotherapy period on immune indicators in cancer patients.

group ($P > .05$). However, the counts of $CD3^+$ cell, $CD4^+$ cell, and $CD8^+$ cell counts; $CD4^+/CD8^+$ ratio, and NK cell count of patients receiving PI during ST, RT, or adjunctive therapy were significantly different compared with the control group($P < .05$, Table 4, Figs. 6–10)

3.2.3. The influence of PI on immune cells in breast cancer patients. Since many of the included studies focused on the effect of PI in breast cancer patients, we conducted a subgroup analysis for breast cancer patients. The $CD3^+$ cell count, $CD4^+/CD8^+$ ratio, and NK cell count in breast cancer patients were significant higher in the PI group than in the control group ($P > .05$), but there were no differences in the $CD4^+$ cell and $CD8^+$ cell count between the two groups ($P > .05$, Table 5, Fig. 11).

3.2.4. The effect of PI on immune cytokines. Compared to patients not receiving PI, those who received PI had significantly higher serum levels of IL-2, IL-4, IFN-γ, lgA, and lgG. However, the differences in the serum levels of IL-6, IL-10, TNF-α, and IgM were not significant ($P > .05$, Fig. 12).

3.2.5. Meta-analysis of heterogeneity. Although we performed a subgroup meta-analysis according to the different PI methods employed, different stages of treatment during which PI was administered, and some of the cancer types, there still exist some heterogeneity. The source of heterogeneity may be attributed to sample size, intervention dosage, cancer stages, and patient characteristics.

4. Discussion

4.1. Different immune effect of different PIs

Although there are many factors that affect cancer patient immunity, studies on psychoneuroimmunology (PNI) have

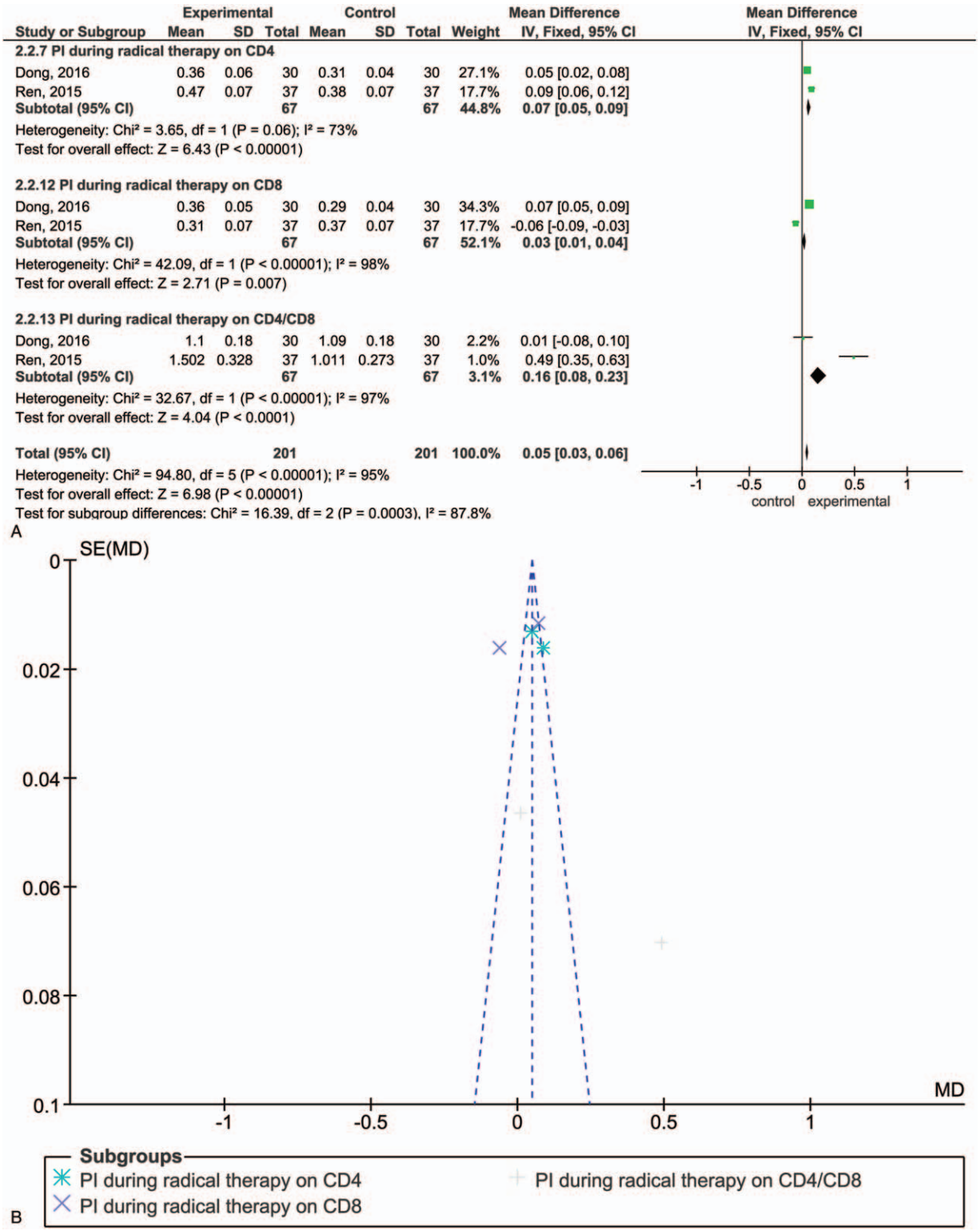

Figure 8. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI during radiotherapy period on immune indicators in cancer patients.

proven that immunomodulation through stressors is a reliable and replicable phenomenon.[7,10] The results of our meta-analysis suggest that no significant immune changes were obtained through SM. To our knowledge, SM is an effective stress-reducing PI. However, the degree of cancer patient participation, compliance, and individual stress levels influences its efficacy; moreover, none of the studies that focused on SM took this point into consideration, and SM intervention showed no significant psychological effect as compared to control analogues.[12,13] To the best of our knowledge, the

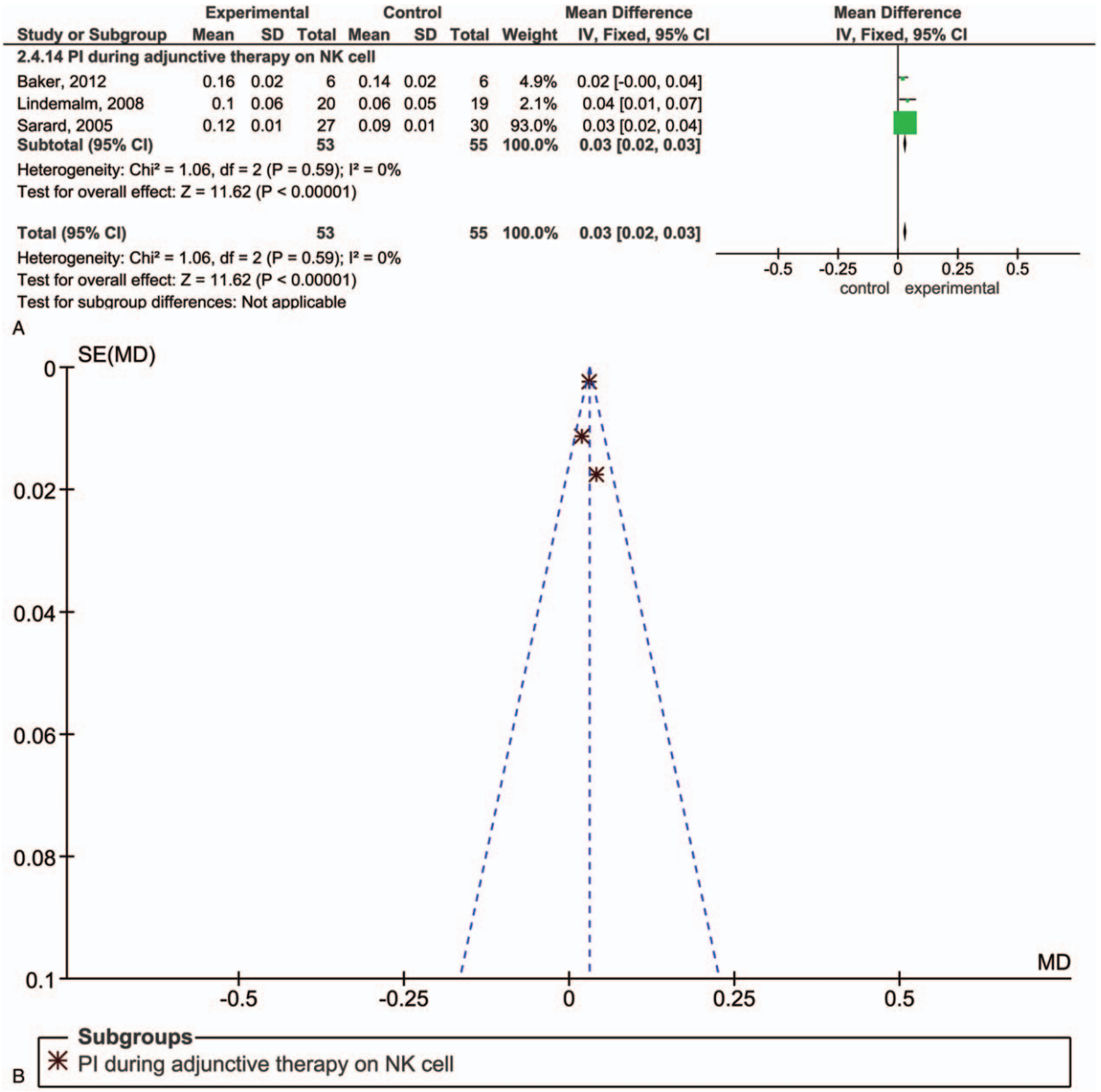

Figure 9. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI during adjunctive therapy period on immune indicators in cancer patients.

effect of PI on the immune response may be associated with improvements in psychological emotions, hypothalamic–pituitary–adrenal axis (HPA axis), and the sympathetic nervous system. The reason for the nonsignificant immune effect of SM might be the ineffective nature of the PI or low level of emotion distress.[14–16] The other PI-mediated immune responses may likely be attributed to psychological stress-reduction.[17,18] CBT appears to be the best therapeutic strategy for reducing stress and negative emotions.[19] Working through stressful experiences can change a person's individual appraisal of subsequent stressors from a sense of threat to a sense of challenge. Perception of a potential stressor as a challenge may lead to changes and support improved immune function.[15] Therefore, the magnitude of CBT influence on the immune response is greater than that of the other three PIs.

4.2. PI immune influence over cancer treatment progression

Because cancer patients might receive psychopharmacological treatment and anti-cancer therapy may affect immune cells, we conducted a subgroup analysis on various therapies. Our meta-analysis revealed that PI intervention changed the concentration of T and NK cells in cancer patients when administered during ST, RT, and adjunctive therapy ($P < .05$), but not after completion of the cancer treatment ($P > .05$). There were no significant differences in the activity levels of the NK cells between the PI group in the chemotherapy and the control groups. We believe that cancer treatment may affect the concentration of immune cells. Lengacher et al showed that compared to T cells, NK cells were more susceptible to suppression during cancer treatment.[12] However, studies still indicate that PI can result in

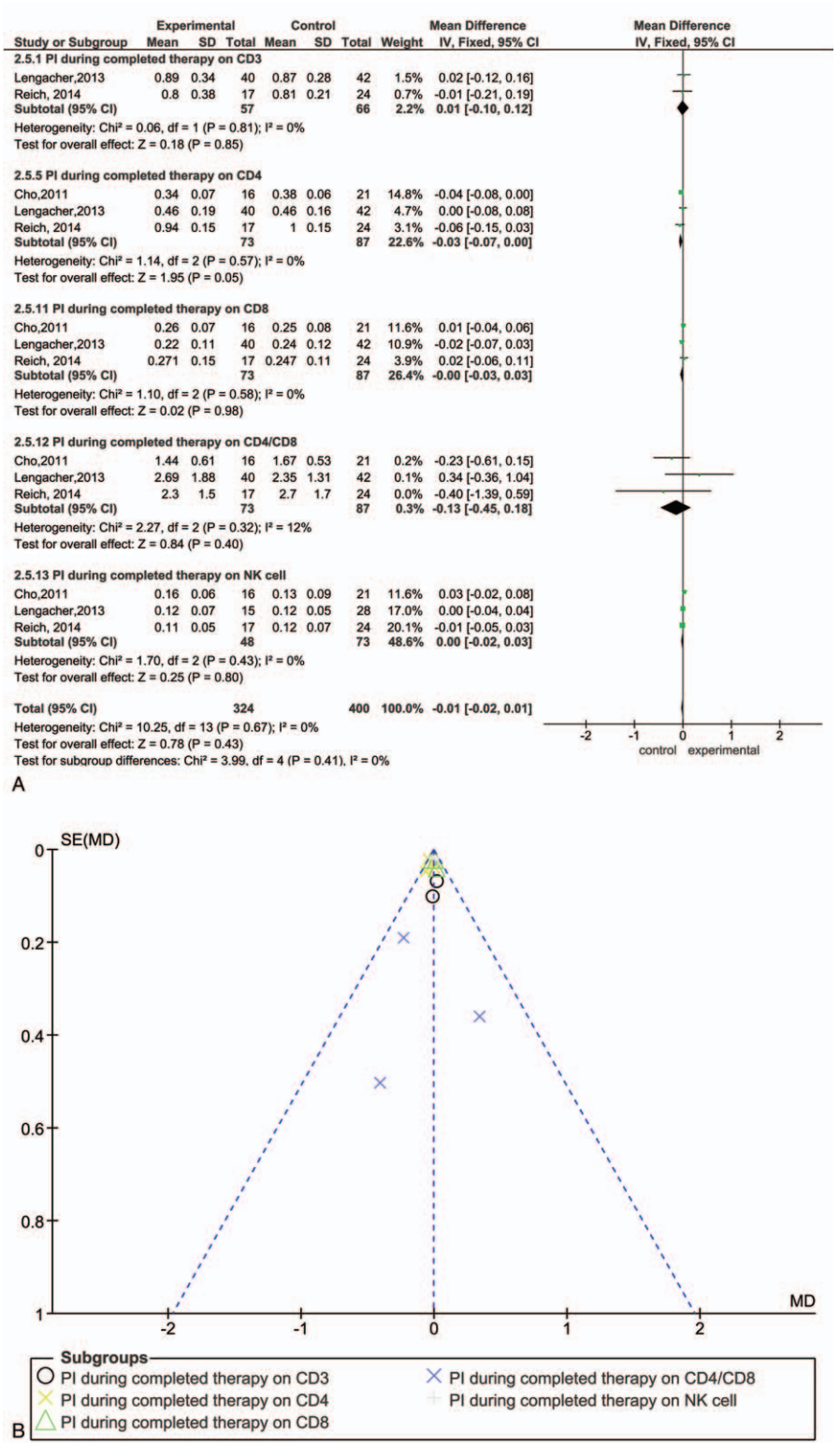

Figure 10. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI during completed therapy period on immune indicators in cancer patients.

changes in the levels of some immune indicators in cancer patients during different treatment periods.[12,13,15,17,20] Wang et al have shown that NK cell activity is associated with the severity of anxiety and depression in cancer patients and that the degree of psychological recovery might affect NK cell activity.[21,22] However, studies on PI during chemotherapy did not indicate any psychological changes after intervention.[22,23] The lack of significant changes in NK cell activity during CT may be due to unclear psychological PI or immunosuppression effects caused by CT.

Table 5

Effect sizes of PI on immune indicators in breast cancer.

Outcome	E/C	MD[95%CI]	I^2 (%)	*P* value	k
CD3	250/250	0.07[0.03,0.12]	0	.003	6
CD4	225/241	−0.01[−0.05,0.02]	14	.47	6
CD8	254/267	0.01[−0.01,0.03]	0	.83	6
CD4/CD8	73/87	0.21[0.12,0.31]	73	<.001	3
NK cell	266/294	0.03[0.02,0.03]	54	<.001	9

C = control group sample, E = experiment group sample, k = number of studies, MD = mean difference.

4.3. The Immune response to PI in breast cancer patients

Our meta-analysis consistently showed that PI can change the $CD3^+$ cell count, $CD4^+/CD8^+$ratio, and NK cells in breast cancer patients ($P < .05$), but not the $CD4^+$ cell and $CD8^+$cell counts ($P > .05$). $CD3^+$ cells could positively promote and enhance the immune response.[24] When the concentrations of $CD3^+$ cells and $CD4^+/CD8^+$ increase in breast cancer patients, relapse or metastasis may occur, leading to poor prognoses.[25] Therefore, PI may be beneficial to the prognosis of breast cancer patients.

4.4. Post-PI influence on immune indicator levels and/or activity and ultimate cancer prognosis.

With respect to the immune response trends, we found that there was an increase or decrease in the T-cells counts, but consistent increases in the NK cell count and activity were observed ($P < .05$). Four of the 10 studies on NK cells confirmed that PI can improve the NK cell content in cancer patients. Likewise, the overall meta-analysis revealed an increase in NK cell count. Three of five studies on NK cell activity indicated that PI may promote the activity of these cells and the overall meta-analysis revealed an increase in NK cell activity. NK cells, which are members of the innate immune cells family,[26] are the first line of defence against tumors and infection, assuming the function of immune surveillance cancer cells direct killing.[26] NK cell activity can control the growth and spread of pathogens and tumors, both of which play an active immune-monitoring role in controlling the occurrence and metastasis of primary tumors.[26] The concentration and activity of NK cells in cancer patients are generally low[27]; however, increases in their numbers have a positive influence in terms of enhancing immune surveillance and tumor occurrence prevention, and metastasis.[28] Therefore, increases in NK cell count and NK cell activity could have a positive influence on the immune function and, ultimately the prognosis of cancer patients.

Three of the five studies on IL-2 showed that PI can increase IL-2 concentration and the overall meta-analysis revealed an increase in IL-2 levels. Two of the four studies on IL-4 confirmed that IL-4 content increased significantly after PI and the overall meta-analysis showed an increase in the IL-2 level. Three of the six studies on IFN-γ proved that PI can increase IFN-γ levels, and the overall meta-analysis revealed an increase in the level of IFN-γ. IL-2 and IFN-γ can significantly induce NK cells to produce and enhance antitumor activity,[29] and low concentration of these cells in cervical cancer has been shown to predict severe disease.[30] IL-4 has the effect of inhibiting the growth of breast tumors.[31] Therefore, the increase in the content of IL-2, IL-4, and IFN-γ may have a positive effect on the immune function and prognosis of cancer patients. Two of the three studies on immunoglobulins confirmed that PI could increase the content of IgA and IgG. The immunoglobulin content reduces in patients with worsening, progressive cancer, and poor prognosis.[32] The increase in the concentrations of immunoglobulins may have some beneficial effect in the prognosis of cancer patients.

Further investigations are necessary to determine the mechanism and stability of the immune effect of PI.

Recent studies show that the immune effect of PI may be related to the neuroendocrine changes caused by cognitive changes and improvement in the patient's psychological state.[33–35] However, our subgroup meta-analysis revealed that SM and PI administered after the completion of the cancer therapy or during CT did not bring about any change in the levels of the immune indicators in cancer patients. The stability of the immune effect of PI may also be influenced by intervention-related factors such as PI duration time,[9,10] content of PI,[12,31] and effect of PI[16] as well as the cancer stage, the type of adjuvant treatment,[20] the severity of psychological stress disorder,[14–16,33] the degree of PI participation,[31] and ability for recovery from immunosuppression.[14] There is also some evidence on the interactions between PI and immune indicators, but the psychoneuroimmunology mechanism underpinning the influence of PI on the immune system still remains unclear and further investigations are necessary to elucidate these.

5. Limitations

This study has some limitations. Most of the papers retrieved by our search were of moderate quality, and most of the enrolled cancer patients in the included studies were female. Furthermore, due to the lack of studies focusing on similar patient groups, subgroup analyses based on the duration of PI or immune function indicators could not be performed in this study. Another point worth mentioning is that the plausible ability of cancer cells evading detection by the immune system makes it difficult to conclusively define the benefits of PI on an individual's immune response.

6. Conclusion

There is some evidence that supports the benefits of PI on some immune indicators and these immune changes benefit the overall immune function in cancer patients, and possibly their prognosis. However, the definitive influence of PI remains vague and cannot be conclusively defined in terms of immune function and prognosis in cancer patients. Moreover, further research is necessary to examine the individual influence of various PI types against different cancer treatments.

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Author contributions

Conceptualization: Xia Li, Qiyao Wang.
Data curation: Ping Zhang, Xia Li, Qiyao Wang.
Formal analysis: Ping Zhang, Xia Li, Qiyao Wang.
Investigation: Ping Zhang, Xia Li, Qiyao Wang.
Writing – original draft: Ping Zhang.
Writing – review & editing: Mo Lin.

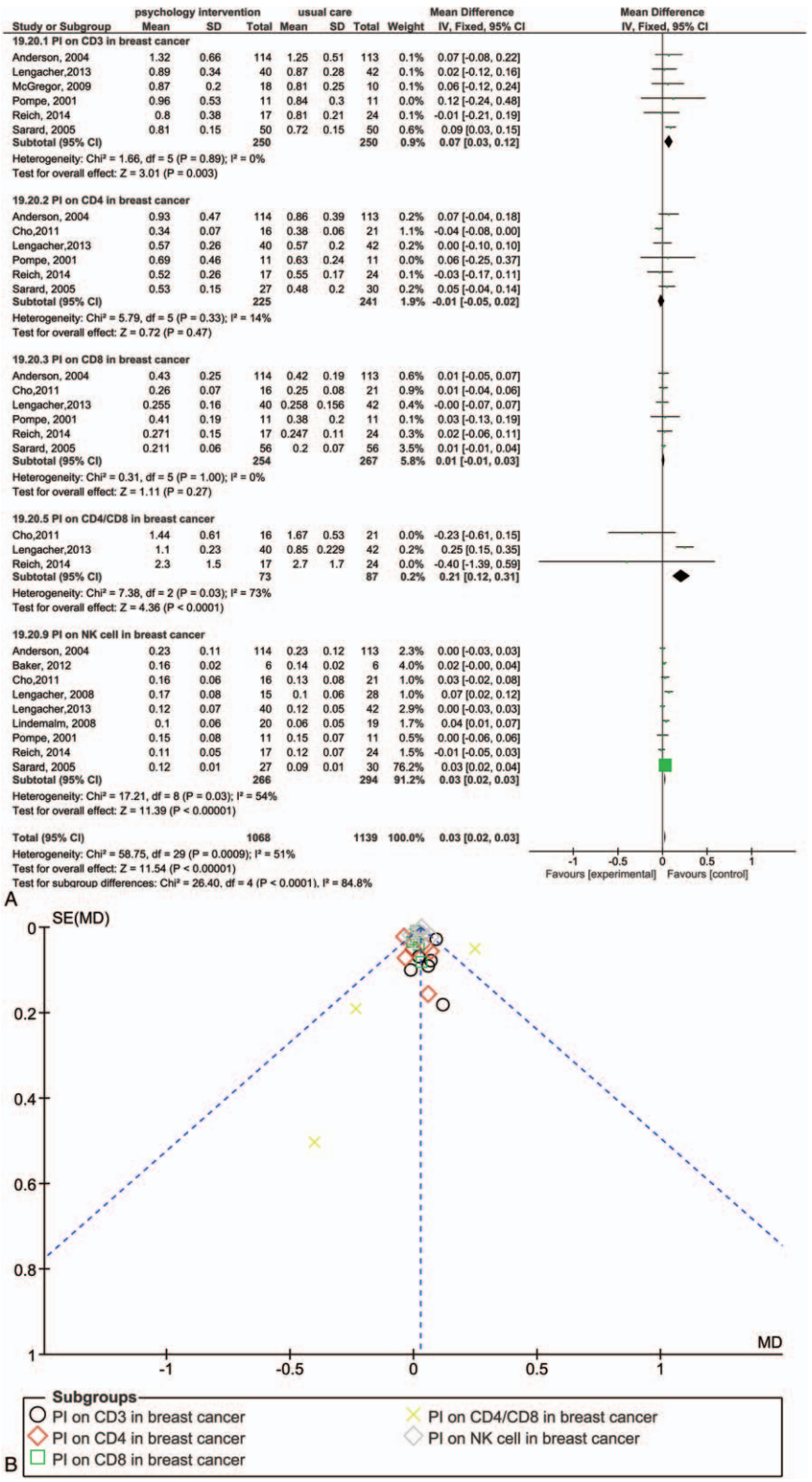

Figure 11. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI on immune indicators in breast cancer patients.

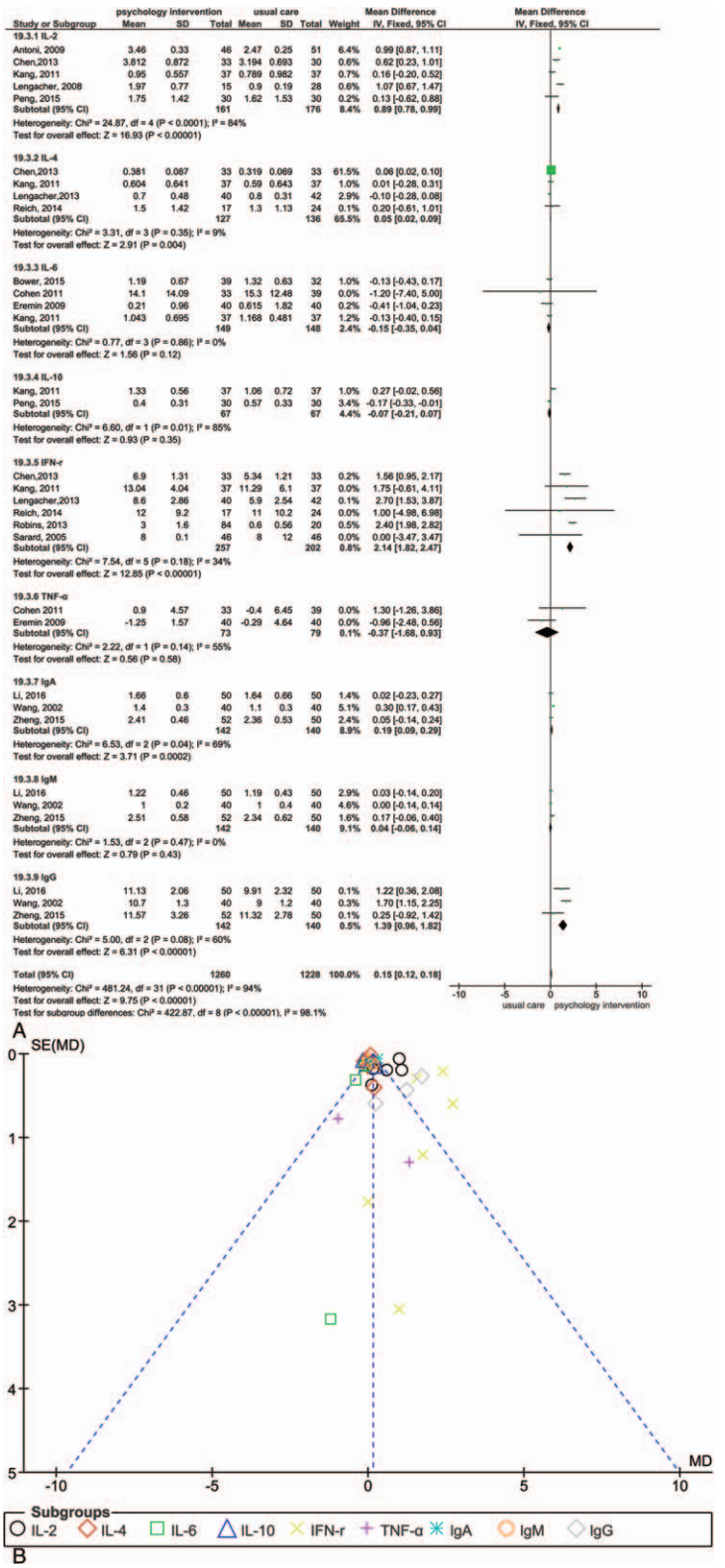

Figure 12. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI on cytokines and immunoglobulins in cancer patients.

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