Psychological intervention and its immune effect in cancer patients

A meta-analysis

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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 (<i>P</i> >.05), and the changes recorded for the CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> cell count, and CD4<sup>+</sup>/CD8<sup>+</sup> 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, PIs = 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 eradicate 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 trials 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 most involved are the counts of immune...
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,\textsuperscript{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
| Study/year | Patients | Intervention | Control | Outcomes | Study design |
|-----------|----------|--------------|---------|----------|--------------|
| Bower et al (2015) | Women; stages I-III breast cancer; completed therapy (except hormone therapy) at least 3 months; age < 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) | Women; stages I-III breast cancer; completed 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 (2014) | 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) | IRF-γ | Two-armed randomized controlled |
| Lengacher et al (2008) | Women; stages I-III breast cancer; mean age = 58 ± 5 years; completed treatment 2-12 weeks; mean age = 58 years | Mindfulness-based stress reduction; 2-h sessions; 6 weeks, (N = 15) | Usual care (N = 42) | CD3+, CD4+, CD8+, CD4+/CD8+, NK cell, IFN-γ, IL-4 | Two-armed randomized controlled |
| Baker et al (2012) | Women; stages 0-II breast cancer; mean age = 52.3 years; after surgery | Integrated support; a 2 days Haven Support Workshop, a maximum of 12 hours of therapy consultation time (N = 6) | Waiting-list control (N = 6) | 6 months after: peripheral blood mononuclear cells, NK CA | Randomized, controlled pilot feasibility |
| Cho et al (2011) | Women; stages I-III breast cancer; mean age = 50 ± 9 years; completed | Smile therapy; eight times, twice a week for 60 min per session | Usual care (N = 21) | Total T cell, T helper, T suppressor, Th/Th ratio, Total B cell, NK cell | Pre-test-post-test randomized, controlled design |
| Cohen et al (2011) | Men, early-stage prostate cancer; mean age = 60.4 years; received radical prostatectomy | Stress management; two 60- to 90-min individual sessions (N = 39) | Usual care (N = 44) | Two days after: peripheral blood mononuclear cells; IL-6, TNF-α | RCT |
| Eremin et al (2009) | 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-α | Randomized, controlled trial |
| Antoni et al (2009) | Women; stages I-II 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) | 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) | Men/women; colorectal cancer I-IV; mean age = 68.5 years; undergoing abdominal surgery | Home 24; 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) | 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 month after: NK cytotoxicity cell, IL-2 | An experimental randomized pre-test-post-test design |
| Lindemalm et al (2008) | 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 cells | Randomized, controlled trial |
| Savard et al (2005) | Women; mostly stage I or II breast cancer; mean age = 54.1 years; all therapy | Cognitive behavior therapy; 8-week | Waiting-list control (N = 30) | 3 months after: CD3+, CD4+, CD8+, CD4+/CD8+, NK cell, IL-10, IFN-γ | Randomized, controlled trial |
| Anderson et al (2004) | 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 |
| Study/year               | Patients                                                                 | Intervention                                                                 | Control                        | Outcomes                                      | Study design      |
|-------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------|-------------------|
| Pompe et al (2001)[18]  | Women; stages I–IV ovarian cancer; mean age = 57.2 years; primary radiotherapy | Relaxation therapy; 3 training sessions during 2 months for 30-45 min (N = 12) | Usual care (N = 10)            | 2 months after: NCA                          | Randomized, controlled, trial |
| Zhou et al (2017)[40]   | Women; stages I–III uterine cancer; mean age = 56 years; received 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 |
| Sheng et al (2017)[23]  | 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-alpha                                    | Randomized, controlled, trial |
| Dong et al (2016)[41]   | Men/women; stages I–IV cancer patients; mean age = 54.5 years; receive chemotherapy during hospital | Behavior relaxation training; 1 session per day for 2 months (N = 50)          | Usual care (N = 50)            | 2 months after: CD3+, CD4+, CD8+             | Randomized, controlled, trial |
| Li et al (2016)[42]     | Men/women, stage II or III gynecologic cancer; mean age = 57.89 years; only surgery | Psychological therapy, relaxation and meditation; 1 session per week for 3 months (N = 50) | Usual care (N = 50)            | 3 months after: CD3+, CD4+, CD8+, CD4+/CD8+, NK cell | Randomized, controlled, trial |
| Peng et al (2015)[43]   | Men/women; stages II–IV lung cancer; mean age = 54.5 years; receive chemotherapy | Psychological intervention; 50 min per session; 6 sessions (N = 30)            | Usual care (N = 30)            | 1.5 months after: CD4+, CD8+, CD4+/CD8     | Randomized, controlled, trial |
| Zheng et al (2015)[44]  | 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, NK cell, IgA, IgM, IgG | Randomized, controlled, trial |
| Guo et al (2015)[45]    | Men/women; all stages colorectal cancer; mean age = 61 years; only surgery therapy | Psychological intervention; 20–30 min/day for 1 month (N = 37)                | Usual care (N = 37)            | 1 month after: CD4+, CD8+, CD4+/CD8          | Randomized, controlled, trial |
| Chen et al (2013)[46]   | 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                            | Randomized, controlled, trial |
| Han et al (2013)[47]    | Women, stages I–II cervical carcinoma; mean age = 50 years only surgery therapy | Cognitive intervention; 12 h per day for 10 days (N = 30)                     | Usual care (N = 30)            | 10 days after: NKCA                          | Randomized, controlled, trial |
| Zheng et al (2010)[48]  | Men/women; stage II lung cancer; mean age = 52 years; preoperative  | Synthesized psychological intervention; relaxation and spiritual healing during preoperative (N = 34) | Usual care (N = 28)            | After surgery: CD3+, CD4+, CD8+, CD4+/CD8+ 8 | Randomized, controlled, trial |
| Wang et al (2002)[49]   | Men/women; lung or breast tumors, 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 |
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.

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### 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)[32] | 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 |
| Erennin et al (2009)[39] | N | N | N | N | N | N | High |
| Antoni et al (2009)[21] | N | N | N | N | N | N | High |
| McGregor et al (2009)[15] | N | N | N | N | N | N | High |
| Ross et al (2009)[40] | N | N | N | N | N | N | High |
| Lengacher et al (2008)[32] | N | NC | NC | N | N | N | Moderate |
| Lindermalm et al (2008)[14] | N | NC | NC | N | N | N | Moderate |
| Anderson et al (2004)[43] | N | NC | NC | N | N | N | Moderate |
| Pompe et al (2001)[30] | N | N | NC | N | N | N | Moderate |
| Leukander et al (1997)[22] | N | N | N | N | N | N | High |
| Zhou et al (2017)[35] | N | N | N | N | N | N | High |
| Shem et al (2017)[25] | N | N | N | N | N | N | Moderate |
| Dong et al (2016)[11] | N | N | N | N | N | N | Moderate |
| Li et al (2016)[40] | N | NC | N | N | N | N | High |
| Ren et al (2015)[34] | N | NC | NC | N | N | N | Moderate |
| Peng et al (2015)[34] | N | NC | NC | N | N | N | Moderate |
| Zheng et al (2015)[45] | N | N | NC | N | N | N | Moderate |
| Chen et al (2013)[25] | N | NC | NC | N | N | N | Moderate |
| Han et al (2013)[46] | N | NC | NC | N | N | N | Moderate |
| Zhou et al (2017)[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] | f2 (%) | 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 | 0.10[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[0.02,0.03] | 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 | 57/66 | 0.03[0.03,0.04] | 76 | <.001 | 2 |
| SM | 57/66 | -0.01[-0.03,0.00] | 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.
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
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 3. Meta-analysis forest map (A) and funnel plot (B) of the effect of stress management 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,
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
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.
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 significantly higher in the PI group than in the control group (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, IgA, and IgG. 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
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 influence 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 8. Meta-analysis forest map (A) and funnel plot (B) of the effect of PI during radiotherapy 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. The other PI-mediated immune responses may likely be attributed to psychological stress-reduction. CBT appears to be the best therapeutic strategy for reducing stress and negative emotions. 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. 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. However, studies still indicate that PI can result in
changes in the levels of some immune indicators in cancer patients during different treatment periods.\cite{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.\cite{21,22} However, studies on PI during chemotherapy did not indicate any psychological changes after intervention.\cite{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) | t (%) | P value | k  |
|------------------|-----|-----------|-------|---------|----|
| CD4+             |     | 0.070(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 prognosis.^[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 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,^[26] are the first line of defence against tumors and infection, assuming the function of immune surveillance cancer cells direct killing.^[27] 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.^[24] 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,^[28] 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 of 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

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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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