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The relationship between psychosocial factors and biomarkers in cancer patients: A systematic review of the literature

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ABSTRACT

Purpose: This review measured the relationships between psychosocial factors and biomarkers in cancer research setting in order to summarize their relationship. It may help to clarify the roles of psychosocial factors and biomarkers in cancer treatment, provide information for developing interventions, and contribute to personalized medicine.

Methods: A total of 4 databases were searched and 2151 articles were screened. Thirty eligible articles were captured including 2093 cancer patients with 11 different kinds of tumor.

Results: Totally 10 groups of biomarkers, 7 positive and 7 negative psychosocial factors were identified. Higher scores of positive psychosocial factors and lower scores of negative psychosocial factors were associated with biomarkers indicating good clinical results. Tumor types can affect the significance of results. Interactions among psychosocial factors may influence the main effect of the targeted psychosocial factors. Biomarkers in reviewed studies were immune response-related biomarkers.

Conclusions: The identified psychosocial factors may provide information for intervention development to increase the quality of life of cancer patients during their cancer treatment and promote better clinical outcomes. When investigating the relationship between psychosocial factors and biomarkers, the tumor type and interaction among psychosocial factors should be noted.

1. Introduction

The term 'psychoneuroimmunology' (PNI) was coined in the 1960s to describe the link between psychosocial factors and health consequences (Solomon and Moos, 1964). Before this concept arose, studies on the interrelationship between psychology and medicine were less likely to involve each other (Arden-Close et al., 2008). Multidisciplinary teams of researchers in different fields began to investigate the relationship between the mind and the human body (Yan, 2011). A large number of researchers examined the relationship between psychosocial factors and diseases like cancer, infectious disease and human immunodeficiency virus (HIV), and found clinically significant results (Kiecolt-Glaser et al., 2002b).

Among all these conditions, cancer has received a lot of attention due to its high incidence and mortality rate. Many of the current studies in the cancer setting are based on the theory that stress can influence the development and progression of cancer (Straub and Cutolo, 2018). However, there is disagreement on the process from stress to cancer, that is whether stress results in cancer via immunosuppression or through proinflammatory factors. Regardless, stress has been assessed as an important factor related to cancer in previous research. Molecular studies have revealed that chronic stress can shorten the length of telomeres, which in turn is associated with hematologic malignancies (Biegler et al., 2012). Among patients of chronic lymphocytic leukemia, stress was found to heighten the level of biomarkers related to disease progression (Andersen et al., 2018). An intervention study conducted by McGregor demonstrates the emotional benefits and improvement in immune function after breast cancer patients receive stress management intervention (McGregor et al., 2004).

Besides stress, other psychosocial factors have also been examined in the cancer research setting, like wellbeing (Jutagir et al., 2017), social isolation (Lutgendorf et al., 2011b) and fatigue (Bower et al., 2018a). These studies provide the evidence to support the influence of psychosocial factors on biomarkers of cancer progression and health status. Integrating psychosocial research into biological and clinical studies has become the key model of investigating human disease (Alford, 2007). Realizing individual differences in treatment and providing patient-centered medicine is the central theme of personalized medicine, and different personal interpretations and responses may contribute to various health consequences like cancer (Yan, 2011).

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Therefore, understanding the interaction of psychosocial factors and biomarkers can contribute to identifying the specific psychosocial factors that influence clinical results, and developing effective interventions and therapies for cancer patients (Yan, 2018).

However, the currently available studies vary in terms of which psychosocial factors and biomarkers they assess. Also, the tumor types and cancer stages investigated differ. Although many empirical studies have been conducted to explore the relationship between psychosocial factors and biomarkers among cancer patients, few studies synthesize the interactions among psychosocial factors, biomarkers and cancer. Little is known about different impacts of psychosocial factors on biomarkers in various cancers. Understanding what psychosocial factors can influence biomarkers among cancer patients can help researchers develop interventions in different stages of treatment (Straub and Cutolo, 2018). Such interventions, if effective, may increase cancer patients' quality of life, delay cancer progression via reducing inflammatory processes, as well as achieve favorable prognosis (Moraes et al., 2018). This systematic review aims to investigate what psychosocial factors and biomarkers were measured in previous studies, and how these psychosocial factors associate with biomarkers among cancer patients. Therefore, this study summarizes the relationship between different psychosocial factors and biomarkers in various cancer research settings in order to clarify the role of psychosocial factors and biomarkers in cancer treatment, provide information for developing interventions, and contribute to the development of personalized medicine.

2. Materials and methods

2.1. Literature search strategy

A total of 4 databases were searched – Medline, PsycINFO, Embase and Medline epub ahead of print and in-process & other non-indexed citations. In order to capture psychosocial factors and biomarkers investigated in cancer research setting, as well as their association, search terms were developed from the following perspectives: psychosocial factors (e.g., "Psychological/"), biomarkers of cancer patients (e.g., "biomarker*.mp.") and cancer research setting (e.g., "9. cancer.mp. or exp Neoplasms/"). No year limitation was set, and all articles were included updated to December 2018. The search strings are listed in Table 1. The identified articles were exported to EndNote X9 for management.

2.2. Article selection criteria

Articles were eligible for initial review if they met the following criteria:

(1) Measured psychosocial factors of patients AND
(2) Measured biomarkers of participants AND
(3) Assessed the relationship between psychosocial factors and biomarkers in the cancer setting AND
(4) Primary research published in English

Studies were excluded if they only mentioned the psychosocial factors and biomarkers without assessing them. Reviews, conference abstracts, books, editorials and dissertations were excluded.

2.3. Data extraction

Both qualitative and quantitative studies were included if they meet the selection criteria. A total of 2151 articles were identified and imported into EndNote for further screening. After removing 295 duplicates, 1856 articles were screened by title and abstract according to the pre-determined inclusion criteria stated above. These criteria were reconciled by two reviewers (LC and BM) and used as a guideline for screening. It yielded 32 articles for full-text review and 3 of them were excluded later because the participants were caregivers instead of cancer patients. Another 3 articles were excluded because no psychosocial factors were measured. In addition, references of eligible articles were searched, and 4 additional articles were identified. Therefore, the review captures 30 articles. The data extraction process is summarized in Fig. 1.

Table 1
Search strings.

Medline	PsycINFO	Embase	Medline Epub
1 .Psychological/or Stress, Psychological/, Posttraumatic Growth, Psychological/or Adaptation, Psychological/or Psychological Tests/or Resilience	1 psychological.mp. [mp = title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	1 psychological.mp. or psychological adjustment/or psychological well-being/ or psychological aspect/or psychological resilience/	1 psycho*.mp.
2 "Quality of Life"/or Psychosocial Support Systems/	2 exp "RESILIENCE (PSYCHOLOGICAL)"/or exp PSYCHOLOGICAL CONSEQUENCE/or exp PSYCHOLOGICAL STRESS/or exp PSYCHOLOGICAL NEEDS/	2 psychosocial.mp. or psychosocial care/	2 anxiety.mp.
3 biomarker*.mp. or Biomarkers/or Biomarkers, Tumor/	3 exp Psychosocial Factors/	3 social support/	3 depress*.mp.
4 Psychoneuroimmunilogy/	4 exp POST-TRAUMATIC STRESS/or exp PSYCHOLOGICAL STRESS/or exp CHRONIC STRESS/or exp STRESS/	4 coping behavior/	4 cancer.mp. or Neoplasms/
5 Mind-body interaction*.mp.	5 biomarker*.mp	5 adaptive behavior/	5 .carcinoma.mp.
6 cancer.mp. or Neoplasms/	6 exp PSYCHONEUROIMMUNOLOGY/	6 cancer.mp. or malignant neoplasm/	6 tumor.mp.
7 . tumor*.mp.	7 mind-body interaction*.mp.	7 tumor*.mp.	7 leukemia*.mp.
8 .leukemia*.mp.	8 exp Biopsychosocial Approach/or biobehavioral.mp.	8 exp psycho-oncology/or oncology/	8 lympho*.mp.
9 lympho*.mp.	9 cancer.mp. or exp Neoplasms/	9 leukemia*.mp.	9 biomarker*.mp.
10 Carcinoma/or carcinoma.mp.	10 LEUKEMIAS/or leukemia*.mp.	10 lympho*.mp.	10 1 OR 2 OR 3
11 Cancer patient*. mp.	11 Neoplasms/or lympho*.mp. or exp Oncology/	11 carcinoma.mp. or carcinoma/	11 4 OR 5 OR 6 OR 7 OR 8
12 Oncology.mp.	12 carcinoma.mp.	12 cancer patient/	12 9 AND 10 AND 11
13 1 OR 2	13 lympho*.mp.	13 biomarker*.mp. or biological marker/	
14 3 OR 4 OR 5	14 exp Neoplasms/or exp Oncology/or exp "Blood and Lymphatic Disorders"/or exp Leukemias/or hematology.mp.	14 psychoneuroimmunology/	
15 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	15 (1 OR 2 OR 3 OR 4) AND (5 OR 6 OR 7 OR 8) AND (9 OR 10 OR 11 OR 12 OR 13 OR 14)	15 mind-body interaction*.mp.	
16 13 AND 14 AND 15		16 1 OR 2 OR 3 OR 4 OR 5	
		17 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	
		18 13 OR 14 OR 15	
		19 16 AND 17 AND 18	
Results: 29	Results: 381	Results: 683	Results: 158

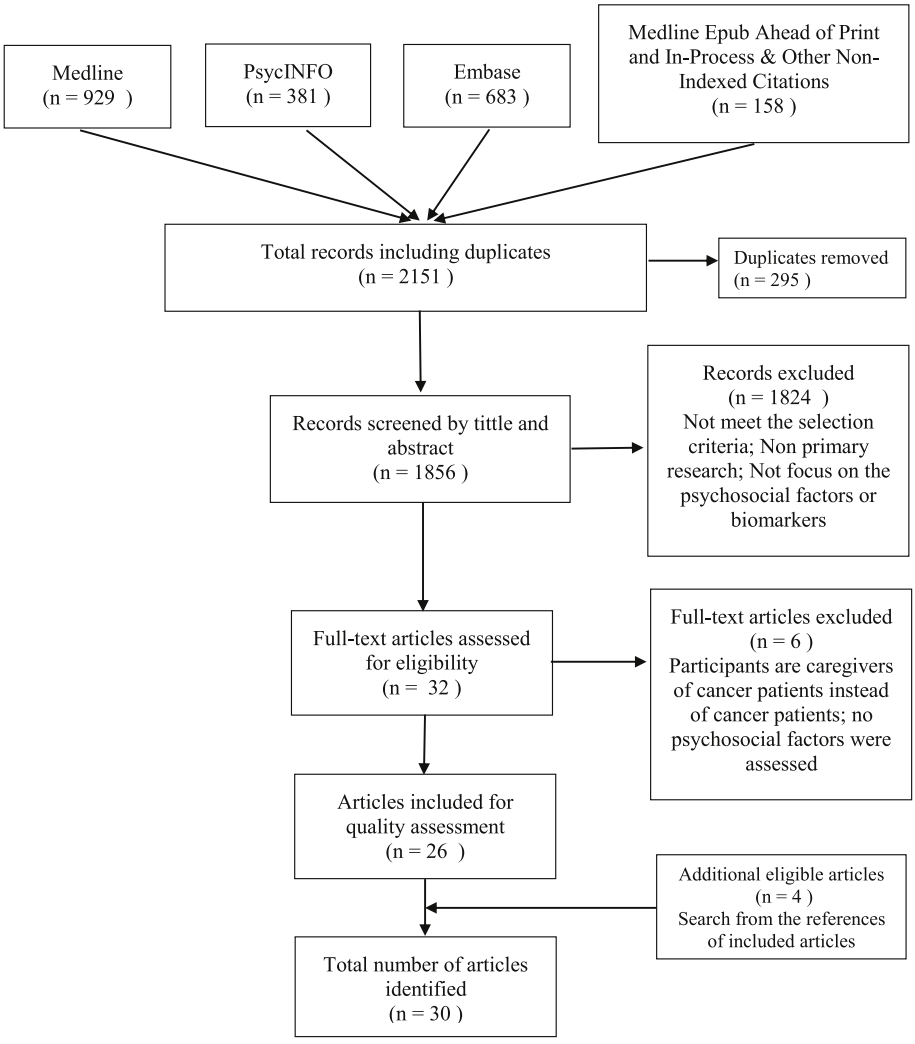

Fig. 1. A PRISMA flow diagram displaying the selection process.

2.4. Critical appraisal

The articles included were assessed by using Standard Quality Assessment Criteria (Kmet et al., 2004). The 'Checklist for assessing the quality of quantitative studies' included in the Standard Quality Assessment Criteria were used (Kmet et al., 2004), because all the articles met the selection criteria were quantitative studies. Each study was appraised according to the 14 criteria in the checklist. The study would score 2 if it fully met the specific criterion and would score 1 if it partially met the criterion. A study not meeting the specific criteria, would score 0. Items not applicable were marked as "N/A". The summary score was calculated according to the manual. Two reviewers (LC and BM) independently assessed the quality of the final set of included articles. Inter-rater reliability was calculated using an intraclass correlation coefficient.

3. Results

The review identified 30 articles examining the relationship between psychosocial factors and biomarkers in cancer patients. All the articles included are quantitative studies. The majority of the studies were conducted in the United States (n = 27, 90.0%), the other studies were conducted in China (n = 1, 3.3%), Canada (n = 1, 3.3%) and Brazil (n = 1, 3.3%). Most studies are cross-sectional studies (n = 20, 66.7%). Other study designs include longitudinal studies (n = 7, 23.3%) and intervention study (n = 3, 10.0%).

3.1. Study participants

A total of 2093 patients with different tumor types were captured in this review. The most frequent tumor types were breast cancer (n = 1284, 61.3%) and ovarian cancer (n = 269, 12.9%). The other tumor types are shown in Table 2. Among the 30 studies, patients from 14 (46.7%) studies had early or middle stage cancer. Patients in 6 studies had advanced-stage cancer while 5 studies recruited patients with mixed cancer stages. Five studies did not report the cancer stage of patients (Table 2). The ages of patients ranged from 18 to 75.

3.2. Critical appraisal

Two reviewers (LC and BM) independently appraised the quality of the finally identified articles according to the manual of Standard Quality Assessment Criteria (Kmet et al., 2004). The manual suggests various cut-off points and shows they are relatively robust. A liberal cut-off point of .55 (range from .55 to .75) was selected for article inclusion. No articles were excluded after the quality assessment. Summary scores of each article and inter-rater reliability were calculated using intraclass correlation coefficient (ICC). The agreement of the two reviewers was excellent (ICC = 0.87, $p < .001$).

3.3. Positive psychosocial factors and biomarkers

Positive psychosocial factors in this review refer to factors where

Table 2
Characteristics of cancer patients in included articles.

Category	n (Patients)	%
Tumor type		
Breast cancer	1284	61.3
Ovarian cancer	269	12.9
Renal cell carcinoma	138	6.6
Prostate cancer	127	6.1
Chronic lymphocytic leukemia	96	4.6
Head and neck squamous cell carcinoma	93	4.4
Lung cancer	76	3.6
Cervical cancer	30	1.4
Gastrointestinal cancer	23	1.1
Endometrial cancer	9	0.4
Fallopian tube cancer	1	0.1
Cancer stage	n (Studies)	
Early or middle stage	14	46.7
Advanced stage	6	20.0
Mixed cancer stage	5	16.7
Not report	5	16.7
Study origin		
United States	27	90.0
China	1	3.3
Canada	1	3.3
Brazil	1	3.3
Study design		
Cross-sectional study	20	66.7
Longitudinal study	7	23.3
Intervention study	3	10.0

higher scores are related to better clinical outcomes. A total of 7 positive psychosocial factors were identified in this review (Table 3).

Among the 30 included articles, two studies assessed well-being. Well-being in these two studies was divided into social well-being, emotional well-being, physical well-being, and functional well-being. One study reported a negative relationship between social well-being and leukocyte pro-inflammatory, pro-metastatic gene expression in early- and middle-stage breast cancer patients (Jutagir et al., 2017). Another study that investigated emotional well-being, physical well-being, and functional well-being did not find an association between three kinds of well-being and leukocyte gene expression in mixed-stage breast cancer (Kang et al., 2012a).

Social support was assessed by 6 studies. Negative relationships between social support and cytokine (interleukin 6) were reported by two studies in gynecologic cancer (Costanzo et al., 2005; Lutgendorf et al., 2000). Lutgendorf found a negative link between social support and exosome and tumor norepinephrine (NE) in ovarian cancer patients (Lutgendorf et al., 2011b, 2018). The association between social support and hemoglobin was also examined in advanced-stage cancer patients with renal cell carcinoma (Prinsloo et al., 2015). Social support was positively associated with the level of hemoglobin.

Quality of life was investigated in 4 studies. No relationship was found between quality of life and telomere length in patients with early- and middle-stage cervical cancer (Biegler et al., 2012). Similarly, Kang did not find an association between quality of life and biomarker – leukocyte count – in mixed-stage breast cancer patients (Kang et al., 2012a). The other two studies reported an association between quality of life and cytokines. Higher quality of life is associated with higher levels of tumor necrosis factor alpha (TNF-α) (Blomberg et al., 2009) in breast cancer and lower levels of interleukin 6 (IL-6) in ovarian cancer (Costanzo et al., 2005).

Only one study investigated vigor as an independent variable and reported a positive relationship between vigor and enzyme activity – that is glutathione peroxidase 1 (GPx1) activity (Bayer et al., 2015).

McGregor revealed that the posttraumatic growth was related to lymphocyte proliferation in early- and middle-stage breast cancer patients (McGregor et al., 2004). This positive change was also found to be associated with a steeper diurnal cortisol slope, which indicates healthy status in breast cancer patients (Diaz et al., 2014).

Positive mood is assessed in three studies. Two of them assessed early- and middle-stage breast cancer patients. The higher level of positive mood was associated with higher level of interleukin 12 (IL-12), interferon gamma (IFN-γ) and C-creative protein (CRP), and negatively related to levels of soluble receptor for tumor necrosis factor type II (sTNF-RII) (Blomberg et al., 2009; Moreno et al., 2016). Prinsloo measured the link between positive mood, on the one hand, and hemoglobin and albumin, on the other hand, and reported positive relationships between them (Prinsloo et al., 2015).

Coping approach was assessed by only two studies by Hoyt and his colleagues. Their studies were conducted in prostate cancer patients. One study (Hoyt et al., 2014) divided the coping approach into approach-oriented coping and avoidance-oriented coping. No significant relationship was identified between approach-oriented coping and cortisol slopes. In the other study conducted by Hoys and his colleagues, two strategies of emotional approach coping were investigated (Hoyt et al., 2013). Higher scores for emotional processing strategy were related to lower levels of IL-6, sTNF-RII, and CRP, while higher scores for emotional expression were related to higher level of sTNF-RII.

3.4. Negative psychosocial factors and biomarkers (Table 3)

Negative psychosocial factors in this review refer to factors where higher scores are associated with poor health outcomes. A total of 8 negative psychosocial factors were identified in this review (Table 3). Among these factors, childhood adversity was assessed by one study and selected as an indicator of fatigue trajectory. There was no association between childhood adversity and biomarkers. Hence, childhood adversity was not considered a negative psychosocial factor. Seven negative psychosocial factors are discussed in this review.

Psychological distress was assessed in 7 studies, and only one study found a link between increased psychological distress and increased telomere length in early- and middle-stage cervical cancer patients (Biegler et al., 2012). Four studies assessed the association between psychological distress, on the one hand, and cytokines, hormone and lymphocyte proliferation, on the other. No significant relationships between them were found. That is, psychological distress did not correlate with TNF-α, IL-6, interleukin 1 beta (IL-1β), IL-12, IFN-γ (Cash et al., 2015; Lutgendorf et al., 2000), cortisol changes (Cruess et al., 2000) and lymphocyte proliferation (McGregor et al., 2004). Andersen and Lutgendorf controlled psychological distress as covariate and did not examine the relationship between psychological distress and biomarkers (Andersen et al., 2010; Lutgendorf et al., 2011a).

Perceived stress was investigated in 5 studies. Two studies reported negative relationships between perceived stress and leukocyte count (Kang et al., 2012a) and hemoglobin (Prinsloo et al., 2015) in breast cancer and renal cancer patients respectively. Andersen reported a positive relationship between perceived stress and levels of TNF-α, interleukin 16 (IL-16), and chemokine (C–C motif) ligand 3 (CCL3). However, no association with a proliferation-inducing ligand (APRIL), B-cell activating factor (BAFF), IL-6, interleukin 10 (IL-10), or vascular endothelial growth factor (VEGF) was found in this study (Andersen et al., 2018). Similarly, no association with tumor, ascites, or plasma NE was found among ovarian cancer patients in Lutgendorf's study (Lutgendorf et al., 2011a). One study (Andersen et al., 2017) did not examine the link between perceived stress and biomarkers – natural killer cell cytotoxicity (NKCC).

Depressive symptoms or depression is the most frequently assessed factor in previous studies. It has been assessed in 15 studies. However, five of them selected depressive symptoms as covariates and did not investigate their association with biomarkers (Bower et al., 2009, 2018b; Collado-Hidalgo et al., 2006, 2008; Jutagir et al., 2017). Depressive symptoms were found to be negatively associated with NKCC (Andersen et al., 2017), cortisol (Du et al., 2013), leukocyte count (Kang et al., 2012a), interleukin 4 (IL-4), interleukin 17 (IL-17) (Li

Table 3
The relationships of psychosocial factors and biomarkers.

Author and year	Study design	Psychosocial factors	Biomarkers	Tumor type	Relationships
Positive factors					
Jutagir et al. (2017)	Cross-sectional study	Social Well-being	Leukocyte pro-inflammatory and pro-metastatic gene expression	Breast cancer	Negative association
Kang et al., 2012a,b	Cross-sectional study	Emotional well-being, physical well-being, and functional well-being	Leukocyte gene expression	Breast cancer	Non-significant relationships
Andersen et al. (2010)	Intervention	Social support	Immune indices higher (NKCC)	Breast cancer	Positive association
Costanzo et al. (2005)	Cross-sectional study	Social support	IL-6	Ovarian cancer	Negative association
Lutgendorf et al. (2000)	Cross-sectional study	Social support	IL-6	Endometrial cancer, cervical cancer, ovarian cancer, fallopian tube cancer	Negative association
Lutgendorf et al. (2018)	Cross-sectional study	Social support	Exosome	Ovarian cancer	Negative association
Lutgendorf et al., 2011a,b	Cross-sectional study	Social support	Higher tumor NE	Ovarian cancer	Negative association
Prinsloo et al. (2015)	Cross-sectional study	Social support	Haemoglobin	Renal cell carcinoma	Positive association
Biegler et al. (2012)	Longitudinal study	Quality of life	Telomere length	Cervical cancer	Non-significant relationships
Blomberg et al. (2009)	Cross-sectional study	Quality of life	Th1 cytokine, tumor necrosis factor-alpha (TNF-α)	Breast cancer	Positive association
Costanzo et al. (2005)	Cross-sectional study	Quality of life	IL-6	Ovarian cancer	Negative association
Kang et al., 2012a,b	Cross-sectional study	Quality of life	Leukocyte count	Breast cancer	Non-significant relationships
Bayer et al. (2015)	Cross-sectional study	Vigour	GPx1 activity	Ovarian cancer	Positive association
Diaz et al. (2014)	Cross-sectional study	Positive change (posttraumatic growth)	Diurnal salivary cortisol slope (normal)	Breast cancer	Positive association
McGregor et al. (2004)	Intervention	Positive change	Lymphocyte proliferation	Breast cancer	Positive association
Blomberg et al. (2009)	Cross-sectional study	Positive mood	IL-12 and IFN-γ	Breast cancer	Positive association
Moreno et al. (2016)	Longitudinal study	Positive affect	sTNF-RII	Breast cancer	Negative association
Moreno et al. (2016)	Longitudinal study	Positive affect	CRP	Breast cancer	Positive association
Prinsloo et al. (2015)	Cross-sectional study	Positive affect	Haemoglobin and albumin	Renal cell carcinoma	Positive association
Hoyt et al. (2014)	Cross-sectional study	Approach-oriented coping	Salivary cortisol slopes	Prostate cancer	Non-significant relationships
Negative factors					
Biegler et al. (2012)	Longitudinal study	Psychological distress	Telomere length	Cervical cancer	Positive association
Cash et al. (2015)	Cross-sectional study	Psychological distress	TNF-α, IL-6, IL-1β, IL-12, IFN-γ	Breast cancer	Non-significant relationships
Cruess et al. (2000)	Intervention	Psychological distress	Serum cortisol	Breast cancer	Non-significant relationships
Lutgendorf et al. (2000)	Cross-sectional study	Psychological distress	IL-6	Endometrial cancer, Cervical cancer, ovarian cancer, fallopian tube cancer	Non-significant relationships
McGregor et al. (2004)	Intervention	Psychological distress	Lymphocyte proliferation	Breast cancer	Non-significant relationships
Andersen et al. (2018)	Cross-sectional study	Perceived stress	TNF-α, IL-16, and CCL3	Chronic lymphocytic leukemia (CLL)	Positive association
Andersen et al. (2018)	Cross-sectional study	Perceived stress	APRIL, BAFF, IL-6, IL-10, or VEGF	Chronic lymphocytic leukemia (CLL)	Non-significant relationships
Kang et al., 2012a,b	Cross-sectional study	Perceived stress	Leukocyte count	Breast cancer	Negative association
Lutgendorf et al., 2011a,b	Cross-sectional study	Perceived stress	Tumor, ascites, or plasma NE	Ovarian cancer	Non-significant relationships
Prinsloo et al. (2015)	Cross-sectional study	Perceived stress	Haemoglobin	Renal cell carcinoma	Negative association
Bayer et al. (2015)	Cross-sectional study	Fatigue	GPx1 activity	Ovarian cancer	Negative association
Bower et al. (2009)	Longitudinal study	Fatigue	Serum CRP and IL-1 receptor antagonist	Breast cancer and prostate cancer	Positive association
Bower et al. (2009)	Longitudinal study	Fatigue	Serum IL-1β and IL-6	Breast cancer and prostate cancer	Non-significant relationships
Bower et al., 2018a,b	Longitudinal study	Fatigue	sTNF-RII	Breast cancer	Positive association
Bower et al., 2005	Cross-sectional study	Fatigue	Salivary cortisol slope (flatter)	Breast cancer	Negative association
Collado-Hidalgo et al. (2008)	Cross-sectional study	Fatigue	Cytokine gene (IL1B genotype)	Breast cancer	Positive association
Costanzo et al. (2005)	Cross-sectional study	Fatigue	IL-6	Ovarian cancer	Positive association

(*continued on next page*)

Table 3 (*continued*)

Author and year	Study design	Psychosocial factors	Biomarkers	Tumor type	Relationships
Hoyt et al. (2014)	Longitudinal study	Coping approach (avoidance-oriented coping)	Salivary cortisol slopes (flatter)	Prostate cancer	Negative association
Hoyt et al. (2013)	Longitudinal study	Coping approach (emotional processing)	IL-6, sTNF-RII, and CRP	Prostate cancer	Negative association
Hoyt et al. (2013)	Longitudinal study	Coping approach (emotional expression)	sTNF-RII	Prostate cancer	Positive association
Bastos et al. (2018)	Cross-sectional study	Anxiety	NE and E	Oral SCC, oropharyngeal SCC and leukoplakia	Positive association
Blomberg et al., 2009	Cross-sectional study	Anxiety	IL-2	Breast cancer	Negative association
Cash et al. (2015)	Cross-sectional study	Anxiety	TNF-α, IL-6, IL-1β, IL-12, IFN-γ	Breast cancer	Non-significant relationships
Costanzo et al. (2005)	Cross-sectional study	Anxiety	IL-6	Ovarian cancer	Non-significant relationships
Du et al. (2013)	Cross-sectional study	Anxiety	TNF-α, salivary cortisol, IL-6	Lung cancer	Non-significant relationships
Lutgendorf et al., 2008a,b	Cross-sectional study	Anxiety	IFN-γ	Ovarian cancer	Negative association
Blomberg et al. (2009)	Cross-sectional study	Anger	TNF-α	Breast cancer	Negative association
Bayer et al. (2015)	Cross-sectional study	Depressed mood	MnSOD activity	Ovarian cancer	Positive association
Andersen et al. (2017)	Cross-sectional study	Depressive symptoms	NKCC	Breast cancer	Negative association
Bouchard et al. (2016)	Cross-sectional study	Depressive symptoms	IL-1β and TNF-α	Breast cancer	Positive association
Costanzo et al. (2005)	Cross-sectional study	Depressive symptoms	IL-6	Ovarian cancer	Non-significant relationships
Du et al. (2013)	Cross-sectional study	Depressive symptoms	IL-6 and TNF-α	Lung cancer	Positive association
Du et al. (2013)	Cross-sectional study	Depressive symptoms	Salivary cortisol	Lung cancer	Negative association
Kang et al., 2012a,b	Cross-sectional study	Depressive symptoms	Leukocyte count	Breast cancer	Negative association
Li et al. (2017)	Cross-sectional study	Depressive symptoms	IL-4 and IL-17	Gastrointestinal clinics, Lung cancer	Negative association
Lutgendorf et al., 2011a,b	Cross-sectional study	Depressive symptoms	Plasma NE	Ovarian cancer	Non-significant relationships
Lutgendorf et al., 2008a,b	Cross-sectional study	Depressive symptoms	IFN-γ	Ovarian cancer	Negative association
Prinsloo et al. (2015)	Cross-sectional study	Depressive symptoms	Haemoglobin Albumin	Renal cell carcinoma	Negative association
Prinsloo et al. (2015)	Cross-sectional study	Depressive symptoms	Alkaline	Renal cell carcinoma	Positive association

Abbreviations: IL-6 = interleukin 6; TNF-α = tumor necrosis factor alpha; IL-1RA = interleukin 1 receptor antagonist; sTNF-RII = soluble receptor for tumor necrosis factor type II; IL-1β = interleukin 1 beta; IFN-γ = interferon gamma; IL-2 = interleukin 2; IL-4 = interleukin 4; IL-12 = interleukin 12; IL-10 = interleukin 10; IL-16 = interleukin 16; VEGF = vascular endothelial growth factor; BAFF = B-cell activating factor; CCL3 = chemokine (C–C motif) ligand 3; APRIL = a proliferation-inducing ligand; NE = norepinephrine; E = epinephrine; CRP = C-creative protein; NKCC = natural killer cell cytotoxicity; MnSOD = manganese superoxide dismutase; GPx1 = glutathione peroxidase 1; RNA = ribonucleic acid; DNA = deoxyribonucleic acid; PBMC = peripheral blood mononuclear cell.

et al., 2017), IFN-γ (Lutgendorf et al., 2008a), hemoglobin and albumin (Prinsloo et al., 2015). Positive relationships were reported in 4 studies. Higher levels of depressive symptoms correlated with higher level of manganese superoxide dismutase (MnSOD) activity (Bayer et al., 2015), IL-1β, TNF-α (Bouchard et al., 2016; Du et al., 2013), IL-6 (Du et al., 2013) and alkaline (Prinsloo et al., 2015). However, results are inconsistent. The level of IL-6 did not correlate with depressive symptoms in ovarian cancer patients (Costanzo et al., 2005). The depressive symptoms were also not found to be correlated with tumor, ascites or plasma NE (Lutgendorf and Sood, 2011).

Fatigue is another factor that many studies have examined. Increased fatigue was reported to have positive correlations with serum CRP, IL-1 receptor antagonist (IL-1RA) (Bower et al., 2009), sTNF-RII (Bower et al., 2018b), interleukin 1 beta (IL1B) genotype (Collado-Hidalgo et al., 2008), and IL-6 (Costanzo et al., 2005). Different results were also reported in Bower's study (Bower et al., 2009). These authors found no association between IL-6 and fatigue, nor was serum IL-1β correlated with fatigue in breast cancer patients and prostate cancer patients. In addition, Bower and her colleagues reported that the more fatigue patients felt, the flatter their cortisol slope was. The other three studies assessed fatigue as covariate and did not examine the relationship between fatigue and biomarkers (Bouchard et al., 2016; Kang et al., 2012b; Moreno et al., 2016).

A total of 8 studies assessed anxiety. Three of them did not find significant correlations between anxiety and cortisol and five kind of cytokines – TNF-α, IL-6, IL-1β, IL-12, and IFN-γ (Cash et al., 2015; Costanzo et al., 2005; Du et al., 2013). Lutgendorf reported different results after assessing the level of IFN-γ in advanced stage ovarian cancer patients (Lutgendorf et al., 2008a). It was negatively correlated with patients' anxiety level. Another kind of cytokine – interleukin 2 (IL-2) – was assessed by Blomberg (Blomberg et al., 2009). A negative relationship was reported between IL-2 level and anxiety (Blomberg et al., 2009), while a positive relationship was reported between NE, epinephrine (E) level and anxiety (Bastos et al., 2018). Two studies did not directly investigate the association between anxiety and biomarkers (Bayer et al., 2015; Kang et al., 2012a).

Though anger was examined as a psychosocial factor by three studies, two of them did not assess the correlation between anger and biomarkers directly (Bayer et al., 2015; Kang et al., 2012a). The other study indicated that a higher level of anger was associated with lower level of TNF-α (Blomberg et al., 2009).

Only one study measured coping approach as a psychosocial factor. Avoidance-oriented coping as one of coping approaches, was negatively associated with cortisol slope in prostate cancer patients (Hoyt et al., 2014). That is, the more avoidance-oriented coping approach patients used, the flatter cortisol slopes they had. This may result in poor clinical outcomes.

4. Discussion

In order to clarify the relationship between different psychosocial factors and various biomarkers in the cancer research setting, a systematic review was carried out. This review identified 14 psychosocial factors and 10 groups of biomarkers that were assessed. A total of 30 studies including 2093 cancer patients were reviewed.

According to all the studies reviewed, there is an agreement that higher scores of positive psychosocial factors are associated with biomarkers indicating more satisfactory clinical results and survival in cancer patients with different tumor types. By contrast, higher scores of negative psychosocial factors are associated with biomarkers indicating worse health outcomes and prognosis in various kinds of cancer patients.

Despite this agreement, the relationships between specific psychosocial factors and biomarkers are inconsistent. Among the 14 psychosocial factors, depressive symptoms were the most frequently assessed due to its close relationship with medication adherence (Bright et al., 2018; Sabiston et al., 2018) and cancer survival (Zimmaro et al., 2018). Depressive symptoms were identified to have a positive association with pro-inflammatory cytokines (Bouchard et al., 2016; Du et al., 2013) and negative relationship with anti-inflammatory cytokines (Li et al., 2017). But inconsistent results were reported by Costanzo (Costanzo et al., 2005) suggesting that the depressive symptoms were not associated with pro-inflammatory cytokines (IL-6) in ovarian cancer patients while a positive relationship was found in lung cancer patients in Du's study (Du et al., 2013).

Similarly, inconsistent results were also identified when investigating the association between fatigue and anxiety, on the one hand, and biomarkers on the other. Fatigue and anxiety were the second most frequently assessed psychosocial factors in the included articles. Higher level of fatigue was associated with higher level of IL-6 in ovarian cancer patients, while no relationship was found in breast cancer patients and prostate cancer patients (Bower et al., 2009; Costanzo et al., 2005). Also, anxiety level was negatively correlated with IFN-γ level in ovarian cancer patients. However, no association was found in breast cancer patients (Cash et al., 2015; Lutgendorf et al., 2008b). Overall the results identified in this review were either statistically significant in the predicted direction or they were non-significant. Most likely, this pattern of results is due to small sample sizes of the non-significant studies and hence limited statistically power (Type II error). No contradictory results were identified. According to the reviewed studies, the inconsistent results may be caused by different tumor types. Significance may vary in cancer patients with different cancer types even if the same psychosocial factors and biomarkers are assessed. Thus, it appears important to consider tumor type, when discuss the relationship between psychosocial factors and biomarkers in cancer patients.

When considering which psychosocial factors should be assessed, it is important to note and control the potential interactions among psychosocial factors. Taking depressive symptoms as an example, several studies (Bower et al., 2009, 2018b; Collado-Hidalgo et al., 2008) controlled depressive symptoms as a covariate when investigating the relationship between fatigue and inflammatory cytokines. Since inflammatory cytokines are implicated in fatigue and depression in cancer research setting (Lutgendorf et al., 2010), the interrelationship among fatigue, depressive symptoms and cytokines can influence the main effect of fatigue on cytokines level. Therefore, in order to have a better understanding of the main effect of a specific psychosocial factor, the psychosocial factors which interact with this target factor should be determined and controlled.

With regard to biomarkers in included articles, inflammatory cytokines are the most frequently studied biomarkers. Actually, cytokines were widely studied in cancer immunotherapy over the past three decades (García-Martínez et al., 2018). They can activate a cancer patient's immune system and are a key contributor to clinical cancer research (Conlon et al., 2019). A 5.5-year follow-up study (Il'yasova et al., 2005) revealed an impact of cytokines on progression of lung cancer, breast cancer and colorectal cancer. Actually, not only inflammatory cytokines, the other biomarkers identified in this review are related to immune response. The immune system can recognize and eliminate cancer in human body (Topalian et al., 2015). The choice of immune response-related biomarkers in previous studies is possibly related to the fact that they have a close relationship with cancer development, but also that these biomarkers are associated with psychosocial factors (Kiecolt-Glaser et al., 2002a). Therefore, assessing the immune-related biomarkers may be a good trajectory to investigate the relationship between psychosocial factors and biomarkers in the cancer research setting.

5. Limitations

Some limitations should be born in mind when drawing conclusions. Firstly, only English language published articles were analyzed. Results

from articles in other languages were excluded, which may contain useful information. Second, most studies were from breast cancer patients. As was mentioned above, the relationship between psychosocial factors and biomarkers can vary in cancer patients with different tumor types. Therefore, the results from this review may be biased because many studies assessed breast and ovarian cancer patients. Men were also underrepresented, thus limiting generalizability to men. Third, all the studies included in this review used self-report scales to measure psychosocial factors. Acquiescence bias of participants' responses may exist in primary studies which can lead to significant relationships or non-significant relationships between psychosocial factors and biomarkers.

6. Implications

Studies with patients with different types of cancer are needed since the present data mostly come from breast and ovarian cancer patients. Future studies should include a broader range of cancer types, such as lymphoma. Only when more types of cancer and more male patients included, will studies capture a comprehensive view of relationship between psychosocial factors and biomarkers. Besides, future studies may note that when discussing the association between psychosocial factors and biomarkers, the tumor type should be considered since the associations can vary in cancer patients with different tumor types. Additionally, the interaction among different psychosocial factors can also influence the main effect of the target psychosocial factor. Therefore, it is better to control for untargeted psychosocial factors statistically. Lastly, besides self-report scales, different kinds of measurements like health professional assessment can be used when assessing psychological factors in order to decrease bias of self-reported data.

7. Conclusions

In this systematic review, 7 positive and 7 negative psychosocial factors were identified, and associations between these psychosocial factors and biomarkers were summarized in the cancer research setting. Decreasing depressive symptoms, as well as decreasing levels of perceived distress, fatigue, anxiety, anger and use of avoidant coping are related with biomarkers that help achieve good prognosis, progression, and even survival. By contrast, increased levels of social support, positive changes, positive mood, quality of life, well-being and vigor are associated with biomarkers that contribute to good health results. These synthesised results may help researchers to determine the psychosocial factors that can benefit cancer patients and develop interventions addressing deficits in these psychosocial factors in order to increase their life-of-quality during cancer treatment and promote clinical outcomes. Several implications were also provided for future studies.

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