THE RELATIONSHIP BETWEEN CYTOKINES AND SYMPTOMS IN PEOPLE WITH INCURABLE CANCER: A SYSTEMATIC REVIEW

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Authors: Rebekah Patton*[a], Robert Paval*[b], James J McDonald [c], Duncan Brown [a], Iain J Gallagher [b], Richard JE Skipworth [d], Donald C McMillan [e], Ross D Dolan [e], Marie Fallon [a, f], Barry JA Laird [a, f].

Affiliations:

[a] St Columba's Hospice, Edinburgh, UK

[b] Faculty of Health Sciences & Sport, University of Stirling, Stirling, UK

[c] Ninewells Hospital, Dundee, UK

[d] Department of Clinical Surgery, Royal Infirmary, Edinburgh, UK

[e] Academic Unit of Surgery, School of Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK

[f] Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh UK

*Joint First Authors

Corresponding Author: Dr Rebekah Patton, St Columba's Hospice, Edinburgh, EH5 3RW. Email: rpatton@stcolumbashospice.org.uk T: 0044 131 551 1381

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CONTENTS

ABSTRACT

Background: Development and spread of cancer is linked to the inflammatory response, in which cytokines serve a key role. The inflammatory response may also form the basis for symptoms of cancer. This systematic review examines the relationship between cytokines and symptoms in incurable cancer.

Methods: MEDLINE, EMBASE, Cochrane Library, CINAHL, Web of Science and PsycINFO databases were searched for studies from January 2004 to January 2020.

Results:

Twenty studies were selected (n=1,806 patients, 119 controls). Symptoms studied included depression, fatigue, pain, and loss of appetite. Nine studies examined patients with a specified tumour type, the remainder included patients with a mix of tumour types. Thirty-one cytokines were examined; multiple associations between cytokines and symptoms were described, supporting the hypothesis that cytokines may have a key role in symptom generation.

Conclusion:

Symptoms of incurable cancer are associated with circulating cytokines. Further study is required to characterise these relationships, and to explore their therapeutic potential.

Key Words: Cytokines, Palliative Medicine, Symptoms, Systemic Inflammatory Response, Cancer

Corresponding Author: Dr Rebekah Patton, St Columba's Hospice, Edinburgh, EH5 3RW. Email: rpatton@stcolumbashospice.org.uk T: 0044 131 551 1381

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1. INTRODUCTION

The systemic inflammatory response (SIR) is inextricably linked to cancer and its progression [1]. Many cancers arise from sites where there is chronic inflammation or irritation. Once cancer is established changes in the tumour microenvironment which are largely promoted by immune and inflammatory cells, facilitate tumour survival and spread [2]. The SIR is regulated through a complex and vast network of cytokine messengers [3]. Cytokines are small proteins which are secreted by many cell types. In health, pro-inflammatory and anti-inflammatory cytokines are closely balanced and work to promote wound healing and tissue homeostasis. As cancer progresses this equilibrium is disrupted resulting in a dysfunctional state of both immune stimulation and immune suppression [4]. As the understanding of this process has advanced there now exists growing evidence that the same altered immune state which drives cancer progression also influences the development of symptoms such as fatigue, depression and pain [5].

This relationship has been explored by Laird and co-workers who reported a link between routine biomarkers of the SIR such as C-reactive protein (CRP) and patient reported outcome measures of quality of life in people with cancer [6,7]. This would suggest that inflammation is responsible for multiple symptoms. It must be noted however, that biomarkers assessed to date including CRP are largely surrogates of the inflammatory process.

The hypothesis that cytokine networks may be involved in the aetiology of cancer related symptoms has its foundation in work examining 'sickness behaviour' in non-malignant conditions. Sickness behaviour is a set of adaptive physiological and behavioural responses to peripheral infection or injury which include fever, pain, fatigue, reduced physical activity and cognitive impairment [8]. Three main cytokines have been linked with sickness behaviour in diseases which involve systemic inflammation namely IL-6, IL-1β and TNF-α [9]. Accordingly, use of anti-TNF therapies in inflammatory diseases such as rheumatoid arthritis and psoriasis have shown significant rapid improvements in health related quality of life on initiation of therapy [10]. These results provide a basis for further exploration of the role of cytokines in cancer symptoms and potential therapeutic targets.

Multiple cytokines have been found in raised levels in the serum of patients with cancer including the interleukins – (notably IL-2, 6, 10, 12 and 18), TNF- α and Transforming Growth Factor- β (TGF- β) [11]. Several studies have assessed the association between one or more of these cytokines and symptoms in specific cancer sites for example: increased levels of IL-6, IL-8 and TNF-α have been associated with sickness symptoms such as pain, nausea and lack of energy in women with breast cancer and with anxiety and depression in patients with colorectal cancer [12,13]. In patients with ovarian cancer, levels of IL-6 have also been linked to sleep disturbance and fatigue [14]. When it comes to incurable cancer the associations between cytokines and symptoms are inconsistently reported. This may be due to methodological differences in symptom recording, sensitivity of cytokine assay used and cross-sectional design of studies [15].

Symptom management and control is imperative in people with incurable cancer where multiple co-occurring symptoms have a significant effect on quality of life and daily function [16,17]. Maintaining and improving quality of life in these patients is a therapeutic priority where potential for prolongation of survival is reduced. There is an urgent need to explore the inflammatory model of symptom generation and propagation in this group in order to identify specific targets which may have therapeutic utility. To date, a comprehensive critique of studies linking the SIR and symptoms of incurable cancer has not been undertaken.

Therefore, the aim of this systematic review was to examine the relationship between circulating levels of cytokines and symptoms in people living with incurable cancer.

2. METHODS

The principal aim of this systematic review was to describe the associations between symptoms and levels of circulating cytokine proteins in patients with incurable cancer. This was carried out by an extensive literature search to identify studies dated from January 2004 to January 2020. The last literature search was conducted on the 6th of January 2020. The search was carried out using key terms which were selected based upon preliminary searches, scanning of existing studies and advice from a specialist librarian. Search terms included individual symptoms – i.e. ‘depression’, ‘fatigue’, ‘pain’ and

common cytokine classes – i.e. ‘interleukin’, ‘interferon.’ Detailed search strategies are outlined in appendix A.

The following databases were comprehensively searched: MEDLINE, EMBASE, Cochrane Library, CINAHL, Web of Science and PsycINFO. The PROSPERO database (international database of prospectively registered systematic reviews in health and social care) was searched beforehand to ensure a previous systematic review in this area had not been performed. Ethical approval was not required for this systematic review. Please note that in this current review we have not examined the potential role of cytokines in cancer cachexia and anorexia, however a review examining these specifically is in preparation.

2.1 Eligibility Criteria

Eligible studies met the following criteria: written in English, studies which examined adults with incurable cancer (defined as metastatic cancer [histological, radiological or cytological evidence] or locally advanced cancer being treated with palliative intent), studies which assessed symptoms using a validated symptom measure (defined as a patient-reported tool which has been validated in a population with cancer) and studies which measured one or more circulating cytokine protein (defined as per paper reporting and corroborated by RP).

Exclusion criteria included: studies in which the symptom being examined was attributed directly to cancer treatment (i.e. oxaliplatin-induced neuropathy, bone pain due to anti-cancer therapy or radiotherapy-related fatigue), studies which included patients who were cancer survivors or healthy caregivers, studies which included patients with both curable and incurable cancer, studies that reported symptom measures and cytokine levels as outcome measures for a clinical trial (with no association made between the two) and studies which were reviews, protocols, case reports and conference abstracts.

2.2 Appraisal

Titles of retrieved studies were screened for relevance by RP. Studies which were not available in English, animal studies, and studies which did not include patients with cancer were excluded.

Studies which were selected on the basis of title then underwent independent abstract review by RP and RDP. Abstract review was conducted using the exclusion criteria detailed above.

Studies which were identified as eligible during abstract screening were then independently reviewed in full by RP and RDP using the criteria detailed above. Any disagreements on final inclusion in the review were settled by an independent third party.

Quality assessment of eligible studies was carried out using a modified Downs and Black Checklist (MDBC) [18]. The Downs and Black Checklist is a 27-item tool which can be used to evaluate the quality of both randomised and non-randomised studies. For the purposes of this review, the checklist was modified to produce a ten-item quality assessment guide with three sections: reporting, internal validity/bias, and external validity. Studies were reviewed by RP, RDP and JM. Each study was assigned a final quality rating ranging from 0-10. Scores 0-4 were considered low quality, 5-7 moderate quality and 8-10 high quality. A consort diagram was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram of literature search process

3. RESULTS

The literature review process is shown in **Figure 1**. The following numbers of studies were retrieved from the electronic databases: Medline=1302; EMBASE=2089; Cochrane=418; CINAHL=597; Web

of Science=1324; PsycINFO=110. Following removal of duplicates 5202 studies were screened for eligibility by title. Of these, 1264 were eligible for abstract screening. Nine hundred and forty-two were then excluded on review of the abstract, leaving 322 studies for full text review, with 20 studies meeting the eligibility criteria for this review.

At the abstract screening stage, the most common reasons for exclusion were: studies including animals, studies including symptoms that were directly attributed to anti-cancer treatment, and studies which were reviews or conference abstracts. At the full text screening stage the most common reason for exclusion was studies that included patients with both curable and incurable cancer. Such studies had no subgroup analysis in the results section making it impossible to draw conclusions regarding the patients with incurable cancer.

A summary of eligible studies is presented in **Table 1.** In total 1,806 patients with incurable cancer and 119 controls were included. Most studies (16) employed a cross-sectional design.

Table 1. Summary of Eligible Studies in Alphabetical Order of First Author Surname						
Reference	**Setting**	**Country**	**Type of Cancer**	**Number of Participants**	**Current Treatment**	**Modified Downs and Black Score**
Breitbart et al. (2014)	Outpatient Oncology	USA	Advanced Pancreatic Cancer	Cancer=43 Controls=32	Gemcitabine Based Chemotherapy	7
de Raaf et al. (2012)	Inpatient/Outpatient Palliative Care	Netherlands	Metastatic Cancer-Multiple Sites	Cancer=45 Controls=47	Nil	8
Heitzer et al. (2012)	Inpatient Oncology	Austria	Metastatic Cancer-Multiple Sites	Cancer= 38 Controls= 20	Nil	7
Inagaki et al. (2008)	Outpatient Palliative Care	Japan	Metastatic Cancer-Multiple Sites	46	Nil	10
Inagaki et al. (2013)	Outpatient Palliative Care	Japan	Metastatic Cancer-Multiple Sites	112	Nil	10
Jacobs et al. (2017)	Outpatient Oncology	USA	Advanced NSCLC	50	Nil	8
Jacobson et al. (2008)	Inpatient Palliative care	USA	Metastatic Cancer-Multiple Sites	73	NR	8

Jehn et al. (2010)	Inpatient Oncology	Germany	Stage IV Cancer- Multiple Sites	114	Chemotherapy	8
Jehn et al. (2012)	Outpatient Chemotherapy	Germany	Metastatic Breast Cancer	70	Chemotherapy	8
Jehn et al. (2015)	Inpatient Oncology	Germany	Metastatic Cancer – Multiple Sites	59	Chemotherapy	8
Kao et al. (2013)	NR	Australia	Inoperable Pleural Mesothelioma	63	Nil	7
Kwak et al. (2012)	Palliative Care	Korea	Metastatic Cancer- Multiple Sites	114	Nil	8
Kwekkeboom et al. (2018)	Outpatient Oncology	USA	Metastatic Cancer- Multiple Sites	155	Nil/Cytotoxic Targeted Therapy/ Chemotherapy	8
Liu et al. (2018)	NR	China	Advanced Lung Cancer- Mixed Histology	Cancer= 92 Controls= 20	NR	5
Paulsen et al. (2017)	NR	Norway	Metastatic Cancer- Multiple Sites	49	Nil/Chemotherapy/Hormonal Therapy	6

Rich et al. (2005)	Outpatient Chemotherapy	France	Metastatic Colorectal Cancer	80	Nil- Pre Chemotherapy	10
Rodrigues et al. (2016)	NR	Brazil	Metastatic Cancer- Multiple Sites	51	Nil/ Palliative Radiotherapy	8
Scheede-Bergdahl et al. (2012)	Outpatient and Inpatient Oncology	Canada	Inoperable Gastrointestinal or NSCLC	83	Palliative Radiotherapy/ Chemotherapy	7
Starkweather et al. (2014)	Inpatient Surgery	USA	Grade III/IV Astrocytoma	22	Nil- Pre Surgery	6
Thomsen et al. (2017)	Outpatient Chemotherapy	Norway	Metastatic Colorectal Cancer	447	Nil- Pre Phase III Trial	9

3.1 Quality Assessment

Thirteen studies were considered to be of high quality (Scoring 8-10 on the MDBC) while the remainder were considered to be of moderate quality (scoring 5-7 on the MDBC). The most common reason that studies were awarded a lower score for quality was lack of external validity. Indeed, few studies explained how the population was selected from the source population.

When examining the quality of the included studies, several factors were considered. One of these factors was the use of medications which are known moderators of inflammation inclusive of steroids, non-steroidal anti-inflammatory medications, anti-depressants and opioids. These medications were variably included in this set of studies- nine studies did not exclude any of these medications, 11 studies excluded one or more. Another confounding factor was patients receiving chemotherapy or palliative radiotherapy the inclusion of these patients was also variable, information on which studies included patients currently receiving cancer treatment is available in **Table 1**. Another factor was patients with co-existent inflammatory or auto-immune illnesses which may influence cytokine measures- only two studies explicitly excluded people with these conditions. It has also been well established that cytokine levels can show a diurnal variation [40]. Therefore, the time of day of blood sampling was important to consider when comparing results. The window for blood sampling was specified in 12 studies. Nine studies had a morning sampling window. Seven of these specified a one to four hour window and two had an unspecified 'morning' window. Two studies had a seven hour sampling window between 10:30 and 17:30; one study had a 14:00 to 17:00 sampling window; and eight studies did not specify when samples were taken. Only two studies specified that samples had been taken when participants were fasted. Further information regarding sample time, assay method used, and sample type are available in **Table 2.**

Table 2. Details of Assay Methods and Nature of Samples Used in Eligible Studies						
Reference	**Nature of Blood Sample**	**Time of Day Sample Acquired**	**Fasted**	**Assay Method**	**Assay Sensitivity Reported**	**Lowest Detection Limit Reported**
Breitbart et al. (2014)	Serum	14:00-17:00	NR	Multiplex Electro-Chemiluminescent Immunoassay	No	No
de Raaf et al. (2012)	Plasma	08:00-12:00	NR	Enzyme Linked Immunosorbent Assay (ELISA) (IL-1ra) Cytometric Bead Arrays (IL-6, IL-8-)	No	Yes
Heitzer et al. (2012)	Serum	NR	NR	ELISA	No	No
Inagaki et al. (2008)	Plasma	10:30-17:30	NR	ELISA	Yes	No
Inagaki et al. (2013)	Serum	10:30-17:30	NR	Multiplex Electro-Chemiluminescent Immunoassay	No	Yes IL-6 only
Jacobs et al. (2017)	Serum	NR	NR	Multiplex Electro-Chemiluminescent Immunoassay (IL-1ß, IL-6, TNF-α), ELISA (TGF-α)	No	Yes
Jacobson et al. (2008)	Plasma	07:30-08:30	NR	ELISA	No	No
Jehn et al. (2010)	Plasma	08:00	NR	Solid-Phase Chemiluminescent Immunoassay	Yes	No
Jehn et al. (2012)	Plasma	10:00	NR	Solid-Phase Chemiluminescent Immunoassay	Yes	No
Jehn et al. (2015)	Plasma	10:00	NR	Solid-Phase Chemiluminescent Immunoassay	Yes	Yes
Kao et al. (2013)	Serum	NR	NR	ELISA	No	No
Kwak et al. (2012)	Plasma	09:00-11:00	NR	Multiplex Bead Array Assay	Yes	No
Kwekkeboom et al. (2018)	Plasma	NR	NR	Multiplex Electro-Chemiluminescent Immunoassay	No	Yes

Liu et al. (2018)	Serum	‘morning’	Yes	ELISA	No	No
Paulsen et al. (2017)	Serum	NR	NR	Multiplex Bead Array Assay	No	No
Rich et al. (2005)	Serum	08:00	NR	ELISA	No	No
Rodrigues et al. (2016)	NS	‘morning’	NR	NR	No	No
Scheede-Bergdahl et al. (2012)	Plasma	NR	yes	Multiplex Bead Array Assay	No	No
Starkweather et al. (2014)	Serum	NR	NR	ELISA	Yes	No
Thomsen et al. (2017)	Serum	NR	NR	ELISA	No	No

3.2 Paper Characteristics

Symptoms which were most frequently examined were depression, fatigue, pain, and loss of appetite. Ten studies recruited patients from oncology settings. Nine studies examined people with a single specified tumour type (i.e. pancreatic cancer, mesothelioma, astrocytoma, non-small cell lung cancer (NSCLC) while the remainder included people who had a mix of tumour types. In total, 31 different cytokines were evaluated with IL-6, TNF-α, IL-1β, IL-8 and 1L-10 the most commonly assessed (20, 12, 8, 6 and 6 studies respectively). A total of 31 different symptom evaluation methods were employed; only six methods appeared in more than one study, including the Structured Clinical Interview using Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition Criteria (SCID-IV) (five studies), Hospital Anxiety and Depression Scale (HADS) (five studies) Brief Fatigue Inventory (four studies), European Organisation for the Research and Treatment of Cancer – Quality of Life Questionnaire – C30 (EORTC-QLQ-C30) (four studies) and the Brief Pain Inventory (three studies). Key primary findings for each eligible study can be found in **Table 3.**

Table 3. Eligible Studies Key Primary Findings

Reference	Cytokines Studied	Main Symptom Studied	Symptom Measure	Key Primary Finding(s)	P=	Key Secondary Finding(s)	P=
Breitbart et al. (2014)	IL-1ß, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12p70, TNF-α, TGF-ß, IFN-γ	Depression	SCID-DSM-IV HAM-D BHS BAI HARS PSQ BPI BFI	Severity of depressive symptoms was associated with IL-6	0.03	Poor sleep was associated with IL-4 Pain severity was associated with IL-12p70 Fatigue intensity was associated with TGF-ß	<0.05 <0.05 <0.05
de Raaf et al. (2012)	IL-6, IL-1ra, IL-8	Fatigue	MFI – physical and mental subscales	IL-6, IL-1ra levels significantly associated with physical fatigue	0.003 0.03	No inflammatory markers related to mental fatigue	NR
Heitzer et al. (2012)	IL-1ß, IL-1α, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-18, TNF-α, TNF-ß, IFN-γ, MCP-1, MIP-1ß, MIP-1α, OPG	Pain	NRS BPI MPQ	Decrease in levels of IL-7, IL-18, MCP-1, MIP-1ß, OPG associated with pain relief	0.045 0.016 <0.001 <0.001 <0.001	OPG levels significantly elevated in nociceptive pain compared to visceral or bone pain	0.028(visceral) 0.019(bone)
Inagaki et al. (2008)	IL-6	Fatigue	SCID-DSM-IV CFS	IL-6 levels significantly elevated in clinical fatigue	0.02	IL-6 levels associated with the physical subscale of the CFS	0.02
Inagaki et al. (2013)	IL-6, GM-CSF, IL-1ß, IL-2, IL-8, IL-10, IL-12p70, TNF-α, IFN-γ	Depression	SCID-DSM-IV HADS Cavanaugh Criteria	IL-6 levels associated with physical symptoms of depression (appetite loss/ insomnia/ fatigue)	0.04 <0.001 0.04	IL-6 not associated with affective symptoms of depression (i.e. depressed mood, loss of interest) No significant difference in IL-6 levels between those with or without a diagnosis of depression	0.91 0.34 0.14 0.67

Jacobs et al. (2017)	IL-1ß, IL-6, TNF-α, TGF-α	Depression	PHQ-9 M.I.N.I	TNF-α levels significantly elevated in depression	0.005	No significant difference in levels of TGF-α, IL-1ß, IL-6	0.35 0.17 0.19
Jacobson et al. (2008)	IL-6	Depression	HAM-D	There was no association between IL-6 and depression for the whole cohort	>0.05	For those participants where blood was taken 48 hours after the initial interview IL-6 was significantly associated with depression	<0.05
Jehn et al. (2010)	IL-6	Depression	HADS-D	IL-6 values significantly elevated in depression	<0.001	IL-6 levels were also associated with depression severity score	<0.001
Jehn et al. (2012)	IL-6	Anxiety and Depression	HADS SCID-DSM-IV	IL-6 values significantly elevated in depression, but not in anxiety	<0.001 0.41	IL-6 strongly associated with severity of symptoms of depression IL-6 associated with severity of symptoms of anxiety	<0.001 0.001
Jehn et al. (2015)	IL-6	Depression, Cognitive Function	HADS-D SCID-DSM-IV VLMT	IL-6 levels significantly elevated in depression	<0.001	IL-6 levels associated with severity of depressive symptoms Short term memory was negatively associated with IL-6	0.02 0.02
Kao et al. (2013)	IL-6, IL-6 Soluble Receptor, VEGF	Health Related Quality of Life	LCSS	Anorexia, Fatigue, overall symptomatic distress, interference with normal activity and global QOL all associated with VEGF	<0.05 (anorexia, fatigue, OSD) <0.001 (INA,GQL)	Fatigue, interference with normal activity, global QOL all associated with IL-6	<0.001(fatigue) <0.05 (INA, GQL)
Kwak et al. (2012)	IL-6, TNF-α	Fatigue	BFI-K Structured Interview	IL-6 and TNF-α levels were not significantly different between mild, moderate and severe fatigue	0.94 0.68	IL-6 and TNF-α levels not significantly correlated with BFI-K subscale scores	0.29
Kwekkeboom et al. (2018)	IL-1ß, IL-6, TNF-α	Pain, Fatigue, Sleep Disturbance	BPI BFI MDASI MSAS FACIT-PAL	TNF-α was associated with symptom cluster distress	0.00	Psychological stress was not related to any inflammatory biomarkers	

Liu et al. (2018)	IL-10, IL-6, IL-8,TNF-α	Depression	SDS	IL-6, IL-10, TNF-α levels were associated with degree of depression (mild, moderate)	<0.01	There was no association between degree of depression and IL-8	>0.136
Paulsen et al. (2017)	IL-1ß, IL-1rα, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL- 12p70, IL-13, IL-18, TNF-α, MCP-1, MIP-1α, OPG, IFN-γ, sTNF-r1, TGF-ß1, MIF	Pain, Appetite, Fatigue	EORTC-QLQ-C30	IL-6 was associated with loss of appetite Fatigue was associated with IL-1ra	<0.001 <0.01	Pain was not associated with any biomarkers	NR
Rich et al. (2005)	IL-6, TNF-α, TGF-α	Fatigue, Appetite Loss, Nausea	EORTC-QLQ-C30	IL-6, TGF-α levels were significantly elevated in appetite loss	0.012	IL-6 was associated with nausea and vomiting TGF-α levels were associated with fatigue	0.016 0.018
Rodrigues et al. (2016)	IL-1, IL-6, TNF-α	Fatigue	EORTC-QLQ-C30 HADS CFQ FACIT-F PSQI-BR	TNF- α levels were negatively associated with mental fatigue	0.007	IL-6 levels were negatively associated with physical wellbeing	0.017
Scheede-Bergdahl et al. (2012)	IL-1β, IL-6, IL-8, TNF-α	Weakness, loss of appetite, fatigue, quality of life	ESAS- Weakness scale ESAS- loss of appetite scale BFI MQL	IL-1β, IL-6, IL-8 were associated with weakness and lack of appetite TNF-α also associated with lack of appetite	<0.05 (weakness) <0.01 (appetite) <0.05	IL-6, IL-8 were associated with quality of life Nil cytokines were associated with fatigue	<0.05 <0.01

Starkweather et al. (2014)	IL-1ß, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-15, IL-17, VEGF, TNF-α	Depression	BDI-II	IL-8 levels in serum negatively associated with depressive symptoms	<0.0004		
Thomsen et al. (2017)	IL-6	Health related quality of life	EORTC-QLQ-C30	Higher levels of IL-6 were associated with poorer global QOL, fatigue, nausea, vomiting, pain dyspnoea, appetite loss and constipation	NR		

Glossary

BAI Beck Anxiety Inventory, *BDI-II* Beck Depression Inventory-II, *BFI* Brief Fatigue Inventory, *BHS* Beck Hopelessness Scale, *BPI* Brief Pain Inventory, *CFQ* Chalder Fatigue Questionnaire, *CFS* Cancer Fatigue Scale, *EORTC-QLQ-C30*- European Organisation for the Research and Treatment Of Cancer Quality of Life Questionnaire C30, *ESAS* Edmonton Symptom Assessment System, *FACIT-F* Functional Assessment for Chronic Illness Therapy-Fatigue, *GM-CSF* Granulocyte Macrophage Colony Stimulating Factor, *GQL* Global Quality of Life, *HADS-D/A* Hospital Anxiety and Depression Scale-Depression /Anxiety Subscale, *HAM-D*- Hamilton Depression Scale, *HARS* Hamilton Anxiety Rating Scale, *IFN-γ* Interferon-γ, *IL* Interleukin, *INA* Interference with Normal Activities, *LCSS* Lung Cancer Symptoms Scale, *M.I.N.I* Mini International Neuropsychiatric Interview, *MCP-1* Monocyte Chemoattractant Protein-1, *MFI* Multi-Dimensional Fatigue Inventory, *MIP* Macrophage Inflammatory Protein, *MPQ* McGill Pain Questionnaire, *MQL* McGill Quality of Life, *NR* Not Reported, *NRS* Numerical Rating Scale, *OPG* Osteoprotegerin, *OSD* Overall Symptomatic Distress, *PHQ-9* Patient Health Questionnaire-9, *PSQI-BR* Pittsburgh Sleep Quality Index- Brazilian Portuguese, *PSS* Perceived Stress Scale, *QOL* Quality of Life, *SCID-DSM-IV SDS* Self Rating Depression Scale, *TGF* Transforming Growth Factor, *TNF* Tumour Necrosis Factor, *VEGF* Vascular Endothelial Growth Factor, *VLMT* Verbal Learning and Memory Test

3.3 Depression

Clinical depression/depressive symptoms were examined in nine studies (n= 633, controls=72). Five studies included patients with specific tumour types (lung [25,33], breast [28], pancreas [20], and astrocytoma [38]) and four included patients with a mix of tumour types [24,29,27,36]. Clinical depression was most frequently diagnosed using the criteria set out in the Structured Clinical Interview using DSM-IV Criteria (SCID-IV). Depressive symptoms were assessed most commonly using HADS; however, many other scales were used to examine individual symptoms related to depression, such as hopelessness (Beck Hopelessness Scale), poor sleep (Pittsburgh Sleep Quality Index) and poor short-term memory (Verbal Learning and Memory Test).

The relationship between clinical depression/depressive symptoms and IL-6 was the most consistently studied. Jehn et al. (n=243) found that IL-6 levels were significantly higher in patients with a diagnosis of clinical depression [29,28,27]. Jehn, Liu and Breitbart (n=378) also found that the severity of depressive symptoms was associated with IL-6 level [20,29,28,27,33]. When symptoms of depression were divided into physical (appetite loss/insomnia/fatigue) or affective (depressed mood, anhedonia) symptoms, Inagaki found that IL-6 was only associated with physical symptoms in 112 patients [24].

As expected, sampling window had an important role in interpretation of results- Jacobson found no association between IL-6 and depression in 73 patients with a mix of tumour types. However, in a sub-analysis where results were separated according to blood sampling time there was a significant association between IL-6 and depression in the nine patients who had had blood taken 48 hours after the initial interview; they also found that as time increased between the initial interview and blood draw, the magnitude of the correlation decreased [26].

In contrast to the results linking IL-6 and depression, both Jacobs and Starkweather (n=72) found no association between diagnosis/ symptoms of depression and IL-6 [25,38]. In fact, Starkweather found that in 22 patients with astrocytoma depressive symptoms were negatively associated with IL-8 in serum [38].

Breitbart and Jehn studied anxiety alongside depression. Breitbart found no association between anxiety symptoms and cytokines in 43 patients with pancreatic cancer [20]. While Jehn observed that whilst IL-6 levels were not associated with a diagnosis of anxiety, they were correlated with severity of anxiety symptoms in 59 patients with breast cancer [29].

Sleep disturbance was examined in the context of depression by Breitbart and Inagaki. Breitbart et al. found an association between overall sleep quality and IL-4 in patients with pancreatic cancer [20]. They also found that insomnia was associated with IL-6 in patients with depression and a variety of tumour types [24]. Short term memory dysfunction was also studied as a symptom of depression by Jehn et.al they found that memory was negatively associated with IL-6 [29].

There was significant methodological heterogeneity in these studies. Five studies excluded participants who were taking anti-depressant medication [20,29,28,27,38], while three studies included them [24-26]. One study made no mention of medication [33]. Time of blood sampling ranged from 08:00 to 17:30 and two studies did not record when samples were taken [25,38]. Although HADS was the most common method of measuring symptoms of depression, other measures were also used. These included the Hamilton Depression Rating Scale, Patient Health Questionnaire-9, Beck Depression Inventory and the Self Rating Depression Scale.

3.4 Fatigue

Fatigue was examined in 12 studies (n=1288; controls=79) with four using this as their primary focus [21,23,31,36]. The remainder examined fatigue alongside a variety of other symptoms [20,24,30,32,34,35,37,39]. The most frequently studied cytokine in relation to fatigue was IL-6. IL-6 levels were significantly correlated with fatigue in patients with mesothelioma (n=63) [30] and in patients with mixed tumour types (n=112) [24]. Elevated levels of IL-6 were found in patients with fatigue and colorectal cancer (n=447) [39], and various tumour types (n=46) [23]. De Raff and Inagaki (n=101) found that when fatigue was divided into physical and mental fatigue, there was an association between IL-6 and physical fatigue [21,23]. Rodrigues and Kwekkeboom also found that TNF-α was linked to different aspects of fatigue. Rodrigues found that TNF-α had an association with mental

fatigue in 51 patients while Kwekkeboom found an association with distress from a pain/fatigue/sleep disturbance symptom cluster in 155 patients [32,36].

In contrast to these findings, Kwak, Paulsen, Rich and Scheede-Bergdahl (n=326) all found no association between fatigue and IL-6 or TNF-α. These studies were performed in patients with a mix of tumour types, colorectal cancer and gastrointestinal (GI) cancer/ non-small cell lung cancer (NSCLC) [31,34,35,37]. Paulsen and De Raff (n=104) found that IL1-ra levels correlated with physical fatigue and overall fatigue respectively [21,34]. Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor Alpha (TGF-α), and Transforming Growth Factor Beta (TGF-β) were associated with fatigue in one study each; including patients with mesothelioma (n=63) [30], colorectal cancer (n=80) [35], and pancreatic cancer (n=43) [20], respectively.

In this set of studies fatigue was evaluated using eight different measurement scales with some studies using multiple scales to capture different aspects of fatigue – the fatigue subscale of the EORTC QLQ-C30 and the Brief Fatigue Inventory were the most commonly used (four studies each). Blood sampling times ranged from 08:00 to 17:00, with five studies giving no indication of when samples were taken [30,32,34,37,39].

3.5 Pain

Pain was examined in seven studies in total (n=803; controls=20). One study was focused on pain alone [22] while the remaining six studies examined pain alongside other symptoms[30,32,34,36,39]. Rodrigues, Kao and Paulsen (n=163) each found no association found between any measured cytokine and pain [30,34,36].

Heitzer measured pain via a numerical rating scale in 38 patients with mixed tumour types. This was assessed in the context of a trial of opioid analgesia. Pain was categorised within five separate entities - nociceptive, visceral, bone, neuropathic, and mixed pain. Osteoprotegerin (OPG) was found to be significantly elevated in nociceptive pain as compared with others. The study observed that a decrease in serum levels of IL-7, IL-18, Monocyte Chemoattractant Protein-1 (MCP-1), Macrophage

Inflammatory Protein-1β (MIP-1ß) and OPG were all associated with targeted pain relief from opiate analgesia [22].

Thomsen found that higher levels of IL-6 were associated with pain in 447 patients with colorectal cancer, as measured by the pain subscale of the EORTC-QLQ-C30 [39]. Breitbart found associations between average pain intensity, and IL1-β, IL-4 and IL-12p70 in 43 patients with pancreatic cancer, as measured by the Brief Pain Inventory [20].

3.6 Appetite Loss

Appetite loss was measured in five studies (n=771) including patients with a mix of tumour types [24,34], patients with colorectal cancer [35,39] and patients with either gastrointestinal cancer or NSCLC [37]. In all five studies, there was either a higher level of IL-6 or a significant correlation between IL-6 and appetite loss scores. In addition to IL-6 Scheede-Bergdahl also found an association between appetite loss and IL-8, IL-1β and TNF-α in 83 patients with either gastrointestinal cancer or NSCLC [37].

3.7 Other Symptoms

Several other symptoms were analysed in a small number of studies. These included nausea and vomiting (three studies, n=576) [34,35,39], dyspnoea (three studies, n=559) [30,34,39], constipation (two studies n=496) [34,39], diarrhoea (two studies, n=496) [34,39], and weakness (one study, n=83) [37]. Paulsen examined all the above symptoms (aside from weakness) in 49 patients with a mix of tumour type and found no associations with any measured cytokine [34]. Thomsen found that the nausea and vomiting, constipation, and dyspnoea subscales of the EORTC-QLQ-C30 were all associated with IL-6 in 447 patients with colorectal cancer [39]. Rich also found an association between IL-6 and nausea and vomiting in 80 patients with colorectal cancer [35]. Kao found no association between any measured cytokines and dyspnoea/ cough in 63 patients with pleural mesothelioma [30]. Scheede-Bergdahl found that weakness assessed using the Edmonton Symptom Assessment System was associated with IL-1β, IL-6 and IL-8 in 83 patients with GI/NSCLC [37].

4. DISCUSSION

The aim of the present systematic review was to examine the association between cytokines and symptoms in people with incurable cancer. We identified clear associations between certain symptoms and various cytokines in the eligible studies.

To illustrate, IL-6 was linked to depression [20,24,29,28,27,33], fatigue [21,24,23,30,39], appetite loss [23,34,35,37,39] and pain [39]. This link between IL-6 and symptoms is unsurprising, given its key role in the acute phase immune response and as a key mediator in the evolution of chronic inflammatory states [41]. Our observations are in keeping with the role of IL-6 in cancer per se including promotion of metastasis, angiogenesis, apoptosis, and invasiveness [42-44]. TNF-α was linked to fatigue [32,36] and appetite loss [37] which is consistent with its role in the NF-κB pathway and maintenance of local and systemic inflammation [45,46,11]. IL-1 was associated with pain, weakness, appetite loss and fatigue, again consistent with its general cancer role [47].

Despite the observations reported herein, disentangling the associations between the magnitude of cytokine levels and symptoms is challenging. Paradigms with sickness behaviour are useful in understanding this and have demonstrated that communication between the periphery and the brain is key in symptom generation; and that circulating cytokines are crucial mediators of this communication. There are several proposed mechanisms for this communication including direct access to the brain via blood brain barrier deficient areas such as the circumventricular organs and ascending communication via cytokine receptors on vagal afferents [9]. Indeed it is widely known that pain, appetite and fatigue are centrally controlled and it seems rational that symptom genesis in cancer is at least part mediated through cerebral mechanisms [48].

Further supporting evidence of the role of cytokines in symptom generation in cancer can be gleaned by comparisons with non-malignant inflammatory illness. Kappelmann, in a meta-analysis of anti-cytokine medications in trials for chronic inflammatory conditions, found that depression symptoms improved independently of improvement in physical manifestations of disease [49]. These observations

are now being seen in trials of anti-cytokine drugs, including mono-clonal antibodies, in patients with cancer. Clazakizumab, a mono-clonal antibody against IL-6, demonstrated significant improvements in lung cancer symptom score and fatigue scores in a phase II trial in a population with advanced NSCLC [50]. Additionally a phase III trial of MABp1, an antibody that targets IL-1α, in patients with advanced colorectal cancer, showed improvements in quality of life [51]. These studies provide grounds for optimism that cancer symptoms such as pain and fatigue may be targeted via pro-inflammatory cytokine pathways.

The present review has however raised several areas where further elucidation of the role of pro-inflammatory cytokines in both symptom genesis and treatment, will present challenges. Inflammatory signalling patterns are dynamic and are likely to change as cancer progresses [2] whilst studies did not control for factors known to affect cytokine levels; such as concomitant medications, diurnal variation, and co-morbid illness. There was also little consensus on the methods of measuring symptom severity. For example, eight different scales were used to assess fatigue.

Integration of the findings of these studies is also affected by variation in methods for measuring cytokine levels. Researchers used a variety of methods, including ELISA, bead-based assays, and electro-chemiluminescent assays and there was little consistency in the way in which cytokines were selected for measurement. In earlier studies, single-plex measurement of one cytokine was more common while more recent studies more often employed multiplex technology to measure a wide range of pro- and anti-inflammatory cytokines. Sensitivity of assays and lower limits of quantification were poorly reported. Data regarding selected assay types is recorded in **Table 2**.

4.1 Future Perspectives

Cytokine profiles, in combination with subjective patient reported outcome measures, have the potential to act as objective measures of symptom severity, and indicators of improvement with treatment. Through this, the precise biological and clinical profiles of symptoms could be identified and form the basis of personalised symptomatic management strategies. Cytokine profiles could be used alongside current oncological strategies to identify groups of people who are more susceptible to increased

symptom severity and allow the initiation of symptom management programs at the beginning of treatment which may help to avoid long term complications. This potential may be realised with strict adherence to consensus measurement tools and consistency in longitudinal measurement of cytokines in well-defined populations.

4.2 Limitations

This review has several limitations. Relevant articles may have been excluded due to close adherence to exclusion criteria. Articles which examined other markers of the SIR including acute phase proteins were excluded as this review focussed solely on cytokines. A common reason for studies to be excluded from this review was that people with early and advanced stages of disease had been included together in analysis and the results which pertained only to people with incurable cancer were impossible to separate. There was also a risk of bias in the selection of patients which was acknowledged by several of the authors. For example, patients included in these studies were all well enough to attend for blood testing and to complete multiple symptom measure questionnaires. Patients who were confined to their home or unable to efficiently access medical care due to poorly controlled symptoms were by nature, excluded. The majority of studies had a cross-sectional design and in order to build a true characterisation of contributing factors studies must be longitudinal with cytokines and symptom severity measured at multiple time points. It is also important to acknowledge that in many studies in this review there were patients who, despite not having increased levels of one cytokine, still suffered from symptoms. This observation contributes to our understanding that cytokines are likely to act as part of a multifactorial process and are not solely implicated in the onset of specific symptoms. It is clear that further work is required to disentangle the relationships between the complex networks which link cytokines and symptoms in incurable cancer. Future work in this area should build on research to date and where possible address limitations.

5. CONCLUSIONS

Cancer symptoms such as pain, fatigue and appetite loss are associated with levels of several circulating cytokine proteins, notably IL-6, IL-1 and TNF-α. The observations provide a sound rationale

for further work to characterise these relationships more fully. Through identifying key cytokine pathways in symptom development, this may represent targets for therapies. Such studies are already in progress (NCT04406662) and findings are awaited with interest.

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7. APPENDIX A – SEARCH STRATEGY

Database	Search Strategy
MEDLINE	1. exp cancer/ 2. neoplasm.ab,ti. 3. metastasis$.ab,ti. 4. 1 or 2 or 3 5. exp cytokines/ 6. exp Inflammation/ 7. exp interferon/ 8. tumo$r necrosis factor.ab,ti. 9. tnf.ab,ti. 10. exp interleukin/ 11. 5 or 6 or 7 or 8 or 9 or 10 12. symoptom*.ab,ti.kw. 13. depress*.ab,ti.kw. 14. nausea.ab,ti.kw. 15. fatigue.ab,ti.kw. 16. sleep.ab,ti.kw. 17. quality of life.ab,ti.kw. 18. anxiety.ab,ti.kw. 19. pain.ab,ti.kw. 20. cachexia.ab,ti.kw. 21. weight loss.ab,ti.kw. 22. anorexia.ab,ti.kw. 23. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 18 or 20 or 21 or 22 24. 4 and 11 and 23 25. limit 24 to (humans and yr=”2004-Current”)
EMBASE	1. exp cancer/ 2. neoplasm.ab,ti. 3. metastasis$.ab,ti. 4. 1 or 2 or 3 5. exp cytokines/ 6. exp Inflammation/

	7. exp interferon/ 8. tumo$r necrosis factor.ab,ti. 9. tnf.ab,ti. 10. exp interleukin/ 11. 5 or 6 or 7 or 8 or 9 or 10 12. symoptom*.ab,ti.kw. 13. depress*.ab,ti.kw. 14. nausea.ab,ti.kw. 15. fatigue.ab,ti.kw. 16. sleep.ab,ti.kw. 17. quality of life.ab,ti.kw. 18. anxiety.ab,ti.kw. 19. pain.ab,ti.kw. 20. cachexia.ab,ti.kw. 21. weight loss.ab,ti.kw. 22. anorexia.ab,ti.kw. 23. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 18 or 20 or 21 or 22 24. 4 and 11 and 23 25. limit 24 to (humans and yr=”2004-Current”)
COCHRANE	*Central – Cochrane Library* 1. MeSH descriptor: [Cytokines] explode all trees 2. MeSH descriptor: [Inflammation] this term only 3. MeSH descriptor: [Interferons] explode all trees 4. MeSH descriptor: [Interleukins] explode all trees 5. MeSH descriptor: [Tumor Necrosis Factors] in all MeSH products 6. MeSH descriptor: [Acute-Phase Proteins] explode all trees 7. (cytokine*):ti,ab,kw 8. (interleukin*):ti,ab,kw 9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 10. MeSH descriptor: [Neoplasms] explode all trees 11. (“Cancer”):ti,ab,kw

	12. MeSH descriptor: [Neoplasm Metastasis] explode all trees 13. #10 or #11 or #12 14. symptom:ti,ab,kw 15. depression:ti,ab,kw 16. nausea:ti,ab,kw 17. fatigue:ti,ab,kw 18. sleep:ti,ab,kw 19. quality of life:ti,ab,kw 20. anxiety:ti,ab,kw 21. pain:ti,ab,kw 22. cachexia:ti,ab,kw 23. weight loss:ti,ab,kw 24. anorexia:ti,ab,kw 25. #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 26. #9 and #13 and #25 with Publication Year from 2004 to 2019, in Trials
CINAHL	S1 MJ cancer S2 TI neoplasm OR AB neoplasm S3 TI metastasis OR AB metastasis S4 S1 OR S2 OR S3 S5 MH cytokines S6 MJ interleukin S7 MH inflammation S8 MJ interferon S9 TI tumor necrosis factor OR AB tumor necrosis factor S10 TI tnf OR AB tnf S11 S5 OR S6 OR S7 OR S8 OR S9 OR S10 S12 TI symptom OR AB symptom OR SU symptom S13 TI depression OR AB depression OR SU depression S14 TI fatigue OR AB fatigue OR SU fatigue S15 TI sleep OR AB sleep OR SU sleep

	S16 TI quality of life OR AB quality of life OR SU quality of life S17 TI anxiety OR AB anxiety OR SU anxiety S18 TI pain OR AB pain OR SU pain S19 TI cachexia OR AB cachexia OR SU cachexia S20 TI weight loss OR AB weight loss OR SU weight loss S21 TI anorexia OR AB anorexia OR SU anorexia S22 TI nausea OR AB nausea OR SU nausea S23 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 S24 S4 AND S11 AND S23
WEB OF SCIENCE	1. TS=(cancer) 2. TS=(neoplasm) 3. TS=(metastasis) 4. #1 or #2 or #3 5. TS=(cytokine*) 6. TS=(inflammation) 7. TS=(interferon) 8. TS=(tumor necrosis factor) 9. TS=(tnf) 10. TS=(interleukin) 11. #5 or #6 or #7 or #8 or #9 or #10 12. TI=(symptom) 13. TI=(depression) 14. TI=(nausea) 15. TI=(fatigue) 16. TI=(sleep) 17. TI=(quality of life) 18. TI=(anxiety) 19. TI=(pain) 20. TI=(cachexia) 21. TI=(weight loss) 22. TI=(anorexia)

	23. #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 24. #4 and #11 and #23
PSYCHINFO	S1 MJ cancer S2 TI neoplasm OR AB neoplasm S3 TI metastasis OR AB metastasis S4 S1 OR S2 OR S3 S5 MJ cytokines S6 MJ interleukin S7 MJ inflammation S8 MJ interferon S9 TI tumor necrosis factor OR AB tumor necrosis factor S10 TI tnf OR AB tnf S11 S5 OR S6 OR S7 OR S8 OR S9 OR S10 S12 TI symptom OR AB symptom OR SU symptom S13 TI depression OR AB depression OR SU depression S14 TI fatigue OR AB fatigue OR SU fatigue S15 TI sleep OR AB sleep OR SU sleep S16 TI quality of life OR AB quality of life OR SU quality of life S17 TI anxiety OR AB anxiety OR SU anxiety S18 TI pain OR AB pain OR SU pain S19 TI cachexia OR AB cachexia OR SU cachexia S20 TI weight loss OR AB weight loss OR SU weight loss S21 TI anorexia OR AB anorexia OR SU anorexia S22 TI nausea OR AB nausea OR SU nausea S23 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 S24 S4 AND S11 AND S23

CONFLICT OF INTEREST STATEMENT

Declarations of Interest: None

Disclaimers: The authors are presently working on the REVOLUTION Trial (NCT04406662)