A SYSTEMATIC REVIEW OF THE ASSOCIATION BETWEEN THE INFLAMMATORY CYTOKINES POLYMORPHISMS AND CANCER-RELATED FATIGUE

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ABSTRACT

Background: Fatigue, which is one of the most common symptoms of cancer, can seriously affect the quality of life and subsequent treatment of patients with cancer. After reviewing the existing literature systematically, we discussed the association between inflammatory cytokine polymorphisms and cancer-related fatigue (CRF).

Methods: We conducted a search on the association of inflammatory cytokine polymorphisms and cancer-related fatigue in PubMed, ISI Web of Science, the Cochrane Central Register of Controlled Trials, Embase, the Chinese Biomedical Literature Database (CBM), the Chinese Journal Full-text Database (CJFD) and the Wanfang Database. Studies were selected using specific inclusion and exclusion criteria. We finished the manuscript followed the checklist of PRISMA statement.

Results: We identified 15 studies in the published literature that specifically assessed the association between fatigue and inflammatory cytokine polymorphisms in cancer patients. There were 13 studies exploring positive associations between inflammatory cytokine polymorphisms and CRF. Because of the heterogeneity of these studies in terms of cancer type, cancer-related fatigue measures, diagnosis of CRF, and selection of controls, it was difficult to merge correlation estimates between inflammatory cytokine polymorphisms and cancer-related fatigue for a quantitative review and clear results. Nevertheless, the present review evaluated the gaps of knowledge in this topic to advance CRF research.

Conclusion: Future efforts should define CRF and select appropriate questionnaires for CRF measures and controls. Publications in this field have focused on single race (e.g. the white) and a few cancer type (e.g. breast and lung cancer). Therefore, additional studies should be performed in other races and cancer types to obtain more convincing evidence. Meanwhile, the development of clear definition and unified questionnaires of CRF is an important avenue for future research.

Keywords: cancer-related fatigue, inflammatory cytokines, polymorphisms.

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Introduction

Fatigue is one of the most common symptoms of cancer and cancer treatment, with a prevalence rate range from 59% to nearly 100% (1, 2). Cancer-related fatigue (CRF) is defined as “a distressing, persistent subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning” (3).

CRF is a highly distressing condition that has a serious impact on quality of life and desire to continue treatment by imposing physical limitations and psychological impairments (4). The current understanding of the biological mechanisms of CRF is based on limited evidence. Some of the proposed mechanisms include anemia, cytokine dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, 5-hydroxytryptophan neurotransmitter dysregulation, and alterations...
in ATP and muscle metabolism\(^5,6\). Nonetheless, the specific mechanisms of cancer-related fatigue remain unclear.

During the last decade, links between CRF and inflammatory cytokines have received increasing attention in cancer research. Bower and colleagues determined that changes in serum levels of inflammatory markers C-reactive protein and IL-1 receptor antagonist were positively associated with increases in fatigue symptoms during radiation therapy for breast and prostate cancer\(^7\). Other studies including two reviews\(^8,9\) have likewise demonstrated the influences of inflammatory cytokines levels on the severity of the cancer-related fatigue\(^10-12\).

Single nucleotide polymorphisms (SNPs) in genes involved in inflammation have been shown to alter these genes’ expressions or functions\(^13,14\). Thus, SNPs may be associated with altering the risk for cancer-related fatigue. Of note, cytokine polymorphisms have been associated with fatigue in non-cancer patient populations\(^15,16\) and with other cancer-related symptoms, such as pain\(^17-19\). By reviewing the existing literature on this topic systematically, we discussed the association between inflammatory cytokine polymorphisms and cancer-related fatigue, in order to offer directions for future research.

### Methods

#### Search and selection strategy

We performed a publication search in PubMed, the Cochrane Central Register of Controlled Trials, Embase, the Chinese Biomedical Literature Database (CBM), the Chinese Journal Full-text Database (CSJD) and the Wanfang Database with the following MESH headings, keywords and text words: (“chronic related fatigue” OR CRF) AND [(Neoplasm OR cancer OR tumor OR carcinoma) AND (Fatigue OR “Fatigue Syndrome, Chronic” OR “Mental Fatigue”) ] AND (polymorphism OR SNP OR variation OR “Single Nucleotide Polymorphism”) AND (“inflammatory cytokines”). The search was performed by two independent investigators (A and C, last search update: November 25\(^\text{th}\), 2016. The reference lists of retrieved studies and recent reviews were also manually searched for further relevant studies.

#### Inclusion and exclusion criteria

Both authors separately screened titles, abstracts and full texts based on two eligibility criteria. The first criterion was that each study must have been conducted in humans. The second criterion was that a study evaluated the associations between inflammatory cytokine polymorphisms and fatigue in cancer patients. Exclusion criteria: comment, review or editorial. Any dispute was resolved by a discussion.

#### Information extraction procedures

Data from the eligible studies were independently extracted in duplicate by two investigators (Li and Wen). The extracted information included the name of the first author, year of publication, country of origin, ethnicity, cancer types, genotyping methods, fatigue measures, polymorphism site, number of cases and controls, and the Hardy-Weinberg equilibrium. Both authors checked the extracted data and reached a consensus on all the data. If there was a dissent, the authors would recheck the original data of the included studies and have a discussion to reach a consensus. If a dissent still existed, a third investigator (Mi) would adjudicate the disagreement.

We followed the checklist of PRISMA statement, we could not be able to provide the summary measures (e.g., P, I\(^2\)) and forest plot because this is a descriptive research.

### Results

#### Search outcome

A flow chart of the study selection process is shown in Figure 1. A total of 15 relevant studies that met the eligibility criteria were reviewed\(^20-34\). Table 1 shows several details of the 15 retrieved articles.

![Figure 1: Flow chart of the study selection process.](image-url)
All of the studies included in our review were from America, except a study by Reinertsen. The earliest article appeared in 2008, and 87% (n = 13) of the articles were published from 2010 to the present. Two (13%) of the studies used longitudinal designs, and 13 (87%) were cross-sectional. Five (33%) studies enrolled only women subjects with breast cancer. One study recruited only men with prostate cancer treated with ADT (androgen deprivation therapy). One study enrolled pediatric patients receiving treatment for acute lymphoblastic leukemia.

Cancer types included breast cancer (33.33%), lung cancer (20%), prostate cancer (6.67%), acute lymphoblastic leukemia (6.67%) and multiple myeloma (6.67%). In addition, four articles included more than one type of cancer patient, including 185 oncology patients with breast, prostate, lung, or brain cancer (26.67%). Two studies investigating lung cancer were written by one research team who recruited participants from the same subject data pool. A similar situation also occurred with the studies by Aouizerat, Miaskowski, Dhruva, Aouizerat, Kober KM and Doong SH.

Several genotyping methods were used, including TaqMan, PCR–RFLP, DNA Print Genomics, and Illumina Golden Gate Genotyping Assay. As might be expected, fatigue measures...
widely varied and included the LFS, MFSI-SF, FSI, SF-12, LCSS, FQ, MDASI-MM and Fatigue Scale. All of the scales are multidimensional scale which contains different facets or domains of fatigue such as physical, affective, and cognitive subscales.

Discussion

Inflammatory cytokines are known to act on brain structures and alter behavior. Variations in the cytokine concentrations, especially IL-6, IL-1b, and TNF-a, can lead to sickness behavior, including symptoms of fatigue\(^{(31)}\). Because there is a high rate of polymorphisms in cytokine genes, most inflammation-related SNPs have been hypothesized to play a role in the development of CRF during and after treatment. However, results assessing this role are inconsistent. Despite increasing interest in this area, to the best of our knowledge, there are no methodical reviews in the literature.

We identified 15 studies in the published literature that specifically assessed the association between fatigue and inflammatory cytokine polymorphisms in cancer patients. There were 13 studies exploring positive associations between inflammatory cytokine polymorphisms and CRF.

Aouizerat et al.\(^{(30)}\) found that patients with homozygous (GG) alleles of the TNF-a gene reported higher morning LFS scores (p=0.02) than minor allele carriers (GA + AA), but there were no differences in evening fatigue scores. In the same population of cancer patients and family caregivers, homozygous (AA) alleles of IL-6-6101A>T (rs4719714) were associated with higher levels of evening and morning fatigue symptoms\(^{(25)}\). Bower et al.\(^{(31)}\) determined that TNF -308 and IL6-174 were independently associated with fatigue (P=0.032). Fatigue levels were approximately twice as high in patients with a TNF 308 GG genotype as GA and twelve times higher in patients with GG than AA (P=0.034). Fatigue was also elevated in an IL6-174-GG genotype relative to GC or CC (P=0.037). Fatigue was more pronounced in patients with an IL1B-511-CC genotype relative to GC or CC (P=0.037).

A study by Vallance et al.\(^{(36)}\) was the first to explore associations between genomic markers and fatigue in a pediatric cancer population. However, these researchers observed that polymorphisms in the IL6 gene were significantly associated with sleep measures but not fatigue.

10 studies with recruited cancer cases ignored racial factors. These cases included a mixture of whites, Africans and Asians. According to a previous study\(^{(36)}\), cytokine genes differ by race. Therefore, a study design in which a majority of cases are white may influence the results because of the genetic variance between Caucasians and African Americans. In a study by Collado-Hidalgo, patients were subdivided into two ethnic groups (whites and non-whites) to control for ethnicity. However, there were still limitations because there were no Asian subjects in the non-fatigued group, despite Asian subjects accounting for 40% of the non-white subjects who were fatigued.

We found that nine studies were cross-sectional studies without control group, which could reduce the strength of evidence to a certain extent. Furthermore, we have no limit with the study language and the region, but all the studies included were from the USA, except Reinertsen’s study from Norway, indicating that further research are needed in this field with a precise sample and control selection in other regions and races, especially in Asian populations.

There were four articles\(^{(20, 24, 33, 34)}\) used the same population of cancer patients and family caregivers in their studies. Such a design may influence the results because there were different types of fatigue being analyzed: cancer-related fatigue and fatigue not related to cancer. Moreover, choosing family
Caregivers as a control group in a study on genetic polymorphisms may also impair the results. In addition, the studies by Collado-Hidalgo et al. (22) and Jim et al. (23) must be considered with caution because of their small samples.

In the next section of the review, we discussed in relation to: (a) the definition for CRF, (b) standard CRF measures (c) other candidate genes, and (d) recommendations for future research.

The first limitation in this field is the lack of a consistent operational definition for CRF. None of the included studies referred to a definition for CRF, except the study by Collado-Hidalgo (22), which used the vitality subscale of the SF-36 to determine fatigue status. In his study, breast cancer patients were classified as fatigued if their vitality score was ≤ 55. Though most studies used questionnaires to evaluate fatigue level, there was no clear definition of diagnosis criteria for CRF. A review performed by Kristine et al. (37) found that diagnostic criteria have received relatively limited attention in this clinical research community due to the complexity of the diagnosis. They suggested it is necessary to refine criteria and promote a more consistent application of the criteria. The lack of a standard definition has resulted in imprecise case diagnoses and inconsistent use of instruments and criteria for significant fatigue (38, 39). Therefore, the adoption of a consistent definition of cancer-related fatigue is highly needed. It is important to integrate global perspectives of this phenomenon and promote cross-study analyses and meta-analyses (40).

Another limitation we identified is the lack of standard CRF measures. There were 43 questionnaires (with 55 different names) that have been used for measuring CRF and are available in English (41). Generally, unidimensional scale is frequently used as a screening tool, and multidimensional scales could explore broader fatigue issues and help create a global score. Furthermore, multidimensional scales have produced subscale scores for a range of different facets or domains of fatigue (42).

In the present review, all the articles used the multidimensional scales. However, none of the questionnaires was simultaneously used by two studies from different subject data pools. There were 6 articles chose together the LFS as CRF measures, because of coming from the same team. According to different aspects of emphasis, cultural background and difficulty level of finishing the CRF measure, the investigators always choose different fatigue scales in their studies. However, the differences about the fatigue scales could make a horizontal comparison or merge correlation estimates with meta-analysis. Therefore, standardizing CRF measurement will contribute to better management of cancer-related fatigue and reduce phenotypic heterogeneity in the first evaluation (43, 36).

SNPs that affect a function of the gene product, including those in the coding region, promoter, 3′ untranslated region (UTR), and 5′ UTR of a gene are typically investigated in genetic association studies (38, 43, 44). SNPs with minor allele frequency of more than 5% are good candidates for genetic association studies of complex diseases because of their universality in the population. Therefore, they have more power to detect associations with a complex disease (45, 46, 47).

In the present review, we discussed the correlation between CRF and inflammatory cytokine polymorphisms, including IL-6, IL1B, and TNF. Because cancer-related fatigue is a multifactor disease, it is possible that other mechanisms are involved in the development of fatigue. Therefore, it is important to assess the role of other candidate genes in CRF in addition to inflammatory cytokine genes. Fernandez-de-las-Penas et al. (48) examined the influence of a COMT (catechol-O-methyltransferase) genotype on cancer-related fatigue in breast cancer survivors and demonstrated that breast cancer survivors with a Met/Met genotype exhibit higher fatigue.

Currently, publications in this field have focused on white patients and breast and lung cancer. Therefore, additional studies should be performed in other races and cancer types to obtain more convincing evidence. Additionally, future research needs to be performed with a precise sample and control selection and properly designed to utilize valid and reliable CRF measures. Identifying an association between inflammatory cytokine polymorphisms and CRF will contribute not only to an improved understanding of the etiologic mechanisms and clinical outcomes of CRF but also to better symptom management for cancer patients.

Conclusions

The studies that we evaluated were heterogeneous by cancer type, cancer-related fatigue measures, diagnosis of CRF, and selection of controls, which led to the result that we could hardly to
merge correlation estimates between inflammatory cytokine polymorphisms and cancer-related fatigue to complete a quantitative review and obtain clear results. Nevertheless, the present review evaluated the gaps in the research that may be addressed to advance CRF research. Standardization the CRF measurement may be an efficiency method to deal with the heterogeneity.

Future efforts should focus on defining CRF and selecting appropriate questionnaires of CRF measures and study controls. Well-designed studies with larger sample sizes and more gene polymorphisms are greatly needed in Asia, Africa and other regions, as well as for different races.

References

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