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ABOUT COVER

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META-ANALYSIS

Fatigue prevalence in men treated for prostate cancer: A systematic review and meta-analysis

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Abstract

BACKGROUND

The side effects of prostate cancer (PCa) treatment are very prominent, with cancer-related fatigue (CRF) being the most common. Fatigue is a distressing symptom that interferes with daily functioning and seriously affects patient quality of life during, and for many years after, treatment. However, compared with other types of cancer, such as breast cancer, little is known about the prevalence of PCa-related fatigue.

AIM

To determine the prevalence of CRF in patients with PCa.

METHODS

A systematic search of EMBASE, PubMed, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, WANFANG DATA, Technology Journal Database and the Chinese Biological Medical Database was conducted up to July 28, 2020. Included studies measured the incidence of PCa-related fatigue and differentiated fatigue outcomes (incidence) between treatment modalities and fatigue assessment times. In our meta-analysis, both fixed and random-effects models were used to estimate the pooled prevalence of PCa-related fatigue.

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Subgroup analyses were performed using treatment modalities and fatigue assessment times. Publication and sensitivity bias analyses were performed to test the robustness of the associations.

RESULTS

Fourteen studies, involving 4736 patients, were eligible for the review. The pooled CRF prevalence was 40% in a total sample of 4736 PCa patients [95% confidence interval (CI): 29-52; $P < 0.01$; $I^2 = 98\%$]. The results of the subgroup analyses showed the prevalence of CRF after androgen deprivation therapy treatment, radical prostatectomy and radiotherapy to be 42% (95%CI: 20-67, $P < 0.01$, $I^2 = 91\%$), 21% (95%CI: 16-26, $P = 0.87$, $I^2 = 0\%$) and 40% (95%CI: 22-58, $P < 0.01$, $I^2 = 90\%$), respectively. The prevalence of acute and persistent fatigue was 44% (95%CI: 25-64; $P < 0.01$; $I^2 = 93\%$) and 29% (95%CI: 25-32; $P = 0.30$; $I^2 = 17\%$), respectively.

CONCLUSION

Our meta-analysis showed that fatigue is a common symptom in men with PCa, especially those using hormone therapy.

Key Words: Prostate cancer; Fatigue; Prevalence; Meta-analysis; Systematic review

Core Tip: This study was a systematic review conducted to determine the prevalence of cancer-related fatigue in patients with prostate cancer. Compared with other types of cancer, little is known about the prevalence of prostate cancer treatment-related fatigue. In this study, we reviewed the data in 14 papers (4736 patients) and found that the pooled prevalence of cancer treatment-related fatigue was 40%. Interestingly, the prevalence of cancer-related fatigue was associated with the type of treatment that the patients received; those undergoing radical prostatectomy had the lowest prevalence of fatigue.

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men after lung cancer, with an estimated 1.28 million newly diagnosed cases worldwide in 2018[1]. Treatment advances have improved PCa-specific survival, with 5-10-year disease-free survival rates in Western countries reported to be 75%-94%[2-5]. Androgen deprivation therapy (ADT), radiotherapy (RT), chemotherapy and surgery [radical prostatectomy (RP)] are the current mainstream treatment options due to their efficacy in reducing prostate-specific disease progression[6]. However, the side effects of PCa treatment are very prominent, and the clinical focus has shifted to controlling or reducing treatment-related side effects[7-10]. Fatigue is the most common treatment-related side effect of PCa, which seriously affects patient quality of life during treatment and for many years later[11-13].

Cancer-related fatigue (CRF) is defined as a sense of tiredness that persists over time, interferes with activities of daily living and is not relieved by adequate rest[14]. The prevalence of CRF is as high as 59%-100%[15]. Cancer patients who have partially completed treatment still feel tired for one or more years after treatment, and this symptom is listed by patients as the one with the longest duration and the most impact on daily life[16,17]. However, the exact statistics on the prevalence of CRF in patients with prostate cancer remain unknown.

Recently, there has been an increased interest in investigating the impacts of fatigue in men with PCa. Although these studies provide useful information, they are characterized by a number of methodologic limitations, such as small sample sizes and limited follow-up periods. Hence, they do not adequately reflect the current prevalence of fatigue in PCa patients. Therefore, we performed a meta-analysis with two main aims. The first aim was to compute a robust estimate of the prevalence of PCa-related fatigue based on high-quality studies with sufficiently large sample sizes. The second aim was to evaluate the effects of different treatment methods and the fatigue assessment times on the prevalence of CRF in patients.

MATERIALS AND METHODS

Literature search

The PRISMA statement guidelines were followed for the calculation and reporting of meta-analysis data[18]. Literature searches were conducted using EMBASE, PubMed, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, WANFANG DATA, Technology Journal Database and the Chinese Biological Medical Database; the search period was from database inception through July 2020. The following search terms were used: "prostatic neoplasms," "prostat* neoplasms," "prostate cancer," "prostat* cancer," "prostat* tumor*," "prostat* tumour*," "prostat* carcino*," "fatigue," "tired*," "cancer-related fatigue" and "CRF". The references identified in the relevant publications were also reviewed to identify additional studies.

Inclusion and exclusion criteria

Studies that met the following criteria were included: investigated fatigue in men with prostate cancer, measured the prevalence of prostate CRF using structured questionnaires with established psychometric properties, differentiated fatigue outcomes (incidence) between treatment options or fatigue assessment time; there were no limitations on the language of publication, year of publication or publication status. Reviews, lectures, case reports and articles in which the data were obviously abnormal or missing (and the author could not be contacted) were excluded from the analysis.

Study selection and data extraction

The identified studies were stored in reference management software (EndNote, Clarivate, Philadelphia, PA, United States). Literature screening and data extraction were independently performed by two reviewers. Any disagreements between the reviewers were resolved by discussion with a third reviewer. We extracted the first author's name, year of publication, study name, country in which the study was conducted, sample size, follow-up period, fatigue assessment scale, study design, fatigue assessment time (clinical fatigue diagnosed during treatment was defined as acute fatigue; fatigue continuing for ≥ 1 year after treatment was defined as persistent fatigue), treatment method and primary outcomes.

Quality assessment and publication bias

Papers that had small sample sizes, did not appropriately justify the questionnaires used, failed to properly control for confounding variables and did not fully explain the statistical methods of analysis were considered to be of low quality; fair- to high-quality papers met some or all of these criteria[19,20]. Publication bias was tested using Egger's Funnel plots.

Statistical analysis

We used R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses. The combined prevalence and 95% confidence interval (95%CI) of CRF in patients with PCa was calculated. Heterogeneity among the studies was assessed using Q and I^2 statistic indices. A significant Q value ($P < 0.1$) indicated a lack of finding homogeneity among the studies; $I^2 = 0$ indicated that an inconsistency among the results makes no statistical difference ($I^2 < 50\%$ indicated low inconsistency, $I^2 \geq 50\%$ indicated high inconsistency). If the heterogeneity test results are $P > 0.1$ and $I^2 < 50\%$, the homogeneity of the study was considered to be good, and a fixed-effects model was adopted; otherwise, the random-effects model was adopted. Subgroup analyses were performed based on the treatment modalities used and the fatigue assessment times.

RESULTS

Characteristics of the included studies

A flow chart of the study selection process and exclusion criteria is shown in Figure 1. According to the search criteria, a total of 2594 studies were identified; the total number of patients was 4736. We filtered the results by title, abstract and full text. In the end, 14 studies met the inclusion and exclusion criteria. Among them, three studies were about the incidence of CRF after ADT treatment for prostate cancer, six reported the incidence of CRF after RT treatment, and three reported the incidence of CRF after RP. Six studies reported the incidence of acute fatigue, and five reported the incidence of persistent fatigue. The characteristics of the included studies are shown in Table 1.

Study quality evaluation

Most studies were of fair[8,10,21-26] or high[7,11-13,27,28] quality. Only three of these studies had an adequate sample size[13,27,28].

Fatigue prevalence

Fourteen studies reported the incidence of fatigue in patients with PCa, with mean ages ranging from 60.0 to 75.3. The pooled CRF prevalence was 40% (95%CI: 29-52), in a total sample of 4736 patients, with a high level of heterogeneity ($P < 0.01$, $I^2 = 98\%$). Therefore, we used a random-effects model (Figure 2).

Fatigue prevalence by treatment

Three of the included studies reported on CRF after ADT treatment, with mean ages ranging from 67.3 to 73.3. The pooled CRF prevalence was 42% (95%CI: 20-67), in a total sample of 254 patients, with a high level of heterogeneity ($P < 0.01$, $I^2 = 91\%$). Therefore, we used a random-effects model (Figure 3).

Another three included studies reported on CRF after RP treatment, with mean ages ranging from 63.8 to 67.9. The pooled CRF prevalence was 21% (95%CI: 16–26), in a total sample of 260 patients, with a low level of heterogeneity ($P = 0.87$, $I^2 = 0\%$). Therefore, we used a fixed-effects model (Figure 4).

Six studies reported on CRF after RT therapy, with mean ages ranging from 64.1 to 66.0. The pooled CRF prevalence was 40% (95%CI: 22-58) in a total sample of 411 patients, with a high level of heterogeneity ($P < 0.01$, $I^2 = 90\%$). Therefore, we used a random-effects model (Figure 5).

Fatigue prevalence by fatigue assessment time

A total of six included studies reported on acute fatigue. The pooled CRF prevalence was 44% (95%CI: 25-64) in a total sample of 402 patients, with a high level of heterogeneity ($P < 0.01$, $I^2 = 93\%$). Therefore, we used a random-effects model (Figure 6).

Five included studies reported on persistent fatigue. The pooled CRF prevalence was 29% (95%CI: 25-32), in a total sample of 667 patients, with a high level of heterogeneity ($P = 0.30$, $I^2 = 17\%$). Therefore, a fixed-effects model was used (Figure 7).

Publication bias

A funnel plot was created to represent the total prevalence of CRF; the plot showed an asymmetric distribution of the study points. Egger's test result ($P = 0.02617$) also suggested the possibility of publication bias. A nonparametric shear complement method was used to estimate the number of missing studies and evaluate the influence of publication bias on the results. The results showed significant differences in the results before and after splicing. The prevalence of CRF, calculated before and after trimming, was 40% (95%CI: 29-52) and 20% (95%CI: 11-31), respectively, suggesting that publication bias had a great influence on the stability of the results (Figure 8).

Sensitivity analysis

To assess the stability of the results, we performed a sensitivity analysis on the 14 included studies by sequentially excluding individual studies. After arbitrarily excluding one study, the combined conversion rate based on the random-effects model was 40% (95%CI: 29-52), indicating that it had little influence on the combined effect size. Therefore, the results of our meta-analysis are stable and reliable (Figure 9).

Table 1 Characteristics of included studies

Ref.	Country	Time of case inclusion	Study design	Sample size	Number of CRF cases	The incidence of CRF, %	Scale	Assessment time	Treatment
Yu and Chen[21]	China	2015.4-2017.9	Cross-sectional	174	109	62.64	BFI	NA	ADT
Wang *et al* [22], 2017	China	2006.12-2016.12	Longitudinal	147	89	60.54	BFI	NA	NA
Ashton *et al* [11], 2019	United Kingdom	2016.10-2017.3	Cross-sectional	62	15	24.19	BFI	T1	RARP/ADT
Baden *et al* [28], 2020	Ireland	1995.1-2011.3	Cross-sectional	2879	556	19.31	EORTC QLQ-C30	NA	NA
Feng *et al* [23], 2017	United States	2009.9-2013.11	Longitudinal	34	14	41.17	FACT-F	T2	EBRT
Feng *et al* [8], 2019	United States	2009.9-2015.2	Longitudinal	47	16	34.04	FACT-F	T2	EBRT
Gonzalez *et al*[10], 2018	Spain	2014.7-2014.9	Longitudinal	26	5	19.23	FACT-F	T1	EBRT
Feng *et al* [7], 2020	United States	2009.9-2015.11	Longitudinal	64	36	56.25	FACT-F	T1/T2	ADT + RT/EBRT
Maliski *et al* [24], 2005	United States	NA	Longitudinal	147	28	19.04	SF-36	NA	NA
Nelson *et al* [12], 2016	United States	2008.9-2013.10	Case control study	145	35	24.13	BFI	T1/T2	ADT/RP
Saligan *et al* [25], 2016	United States	2009.4-2013.12	Longitudinal	47	39	82.97	FACT-F	T1	EBRT
Storey *et al* [13], 2012	United Kingdom	2005.8-2005.11	Cross-sectional	377	216	57.29	BFI	T2	RT/ RP
Jones *et al* [27], 2016	Canada	NA	Longitudinal	529	90	17.01	FACT-F	NA	NA
Ozdemir *et al*[26], 2019	Turkey	2014.3-2018.9	Cross-sectional	58	31	53.44	FACT-F	T1	NA

ADT: Androgen deprivation therapy; BFI: Brief Fatigue Inventory; CRF: Cancer-related fatigue; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Version 3.0; EBRT: External beam radiation therapy; FACT-F: 13-Item Functional Assessment of Cancer Therapy- Fatigue; NA: Not reported; RARP: Robotic-assisted radical prostatectomy; RP: Radical prostatectomy; RT: Radiation therapy; SF-36: 36-Item health survey; T1: During the period of treatment; T2: ≥ 1 year after treatment.

DISCUSSION

CRF is a common side effect of PCa treatment that can negatively affect a patient's daily life, physiology and psychology[29,30]. Previous studies on the fatigue status of PCa patients have shown that the prevalence of CRF is between 17% and 82%, varying broadly due to various associated factors[25,27]. The present meta-analysis estimated the CRF prevalence to be 40% in a sample of 4736 patients, indicating that a sizeable proportion of men with PCa experience severe fatigue.

This review found that fatigue is associated with all common PCa treatment types. Specifically, our results showed that the prevalence of CRF in patients receiving RP (21%) was lower than that in those receiving ADT (42%) or RT (40%), similar to other published results[11,12], suggesting that RP has little impact on fatigue prevalence. This finding is likely due to the fact that patients receiving ADT and RT are older, have more underlying diseases and are in advanced stages of disease. Conversely, RP is mainly suited to patients with localized, significant disease and having > 10 years of life expectancy and those with the ability to perform activities of daily living. The rate of clinical fatigue associated with ADT treatment was similar to that with RT treatment, as both primarily cause fatigue *via* their hematologic toxicity.

Only one study[7] included in this meta-analysis reported the incidence of CRF in patients treated with a combination of RT and ADT; thus, only a descriptive analysis was performed. The highest incidence of fatigue (68%) occurred in patients receiving a

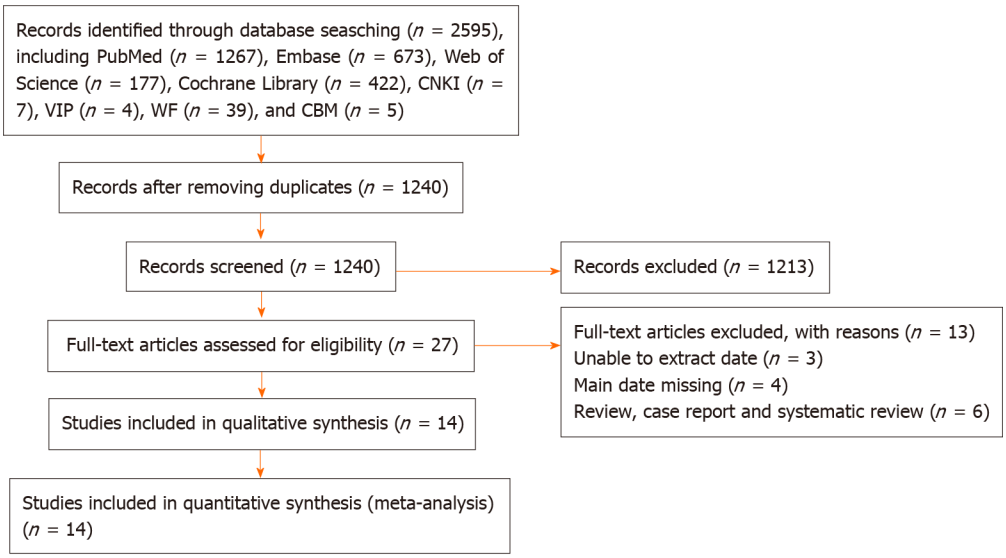

Figure 1 Study selection flow diagram (up to July 2020). CBM: Chinese Biological Medical database; CNKI: China National Knowledge Infrastructure; VIP: China Science and Technology Journal database; WF: WANFANG DATA database.

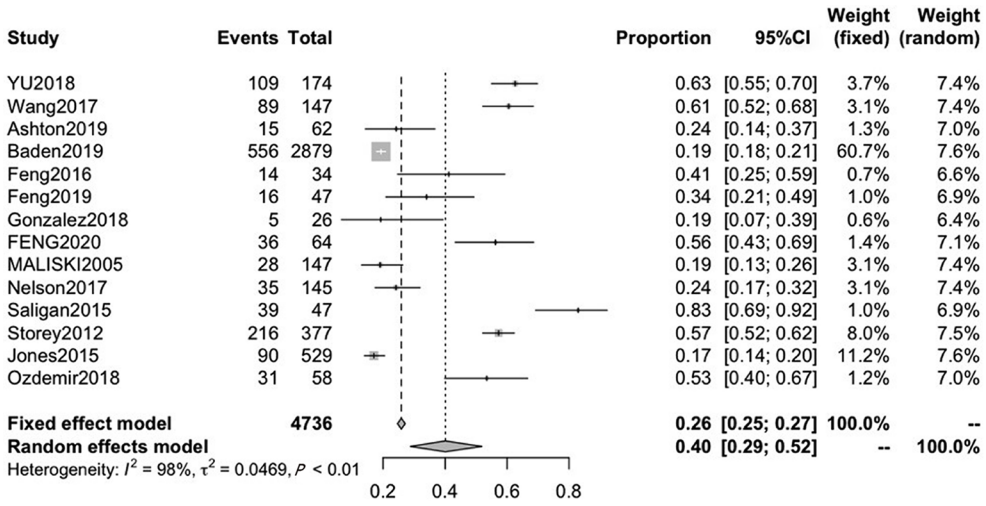

Figure 2 Forest plot of cancer-related fatigue prevalence in prostate cancer patients. CI: Confidence interval.

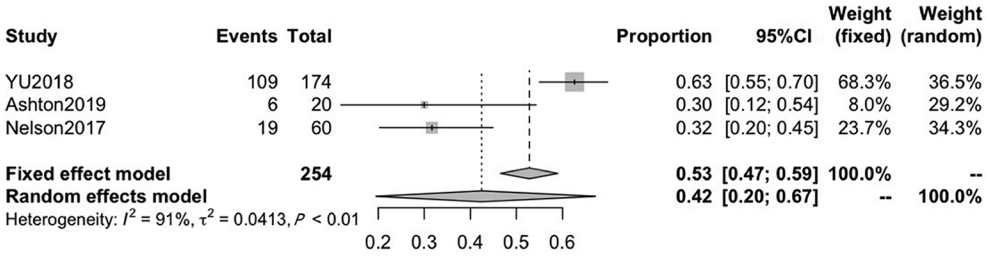

Figure 3 Forest plot of the prevalence of cancer-related fatigue in prostate cancer patients treated with androgen deprivation therapy. CI: Confidence interval.

combination of RT and ADT, which may be associated with the combination treatment aggravating the resultant hemotoxicity and peripheral and central nervous system mitochondrial dysfunction caused by either treatment alone.

Men with PCa are more likely than other cancer patients to report persistent fatigue for more than 6 mo after treatment, with a high incidence of functional impairment due to the fatigue[31]. The subgroup analysis results of this study showed that the

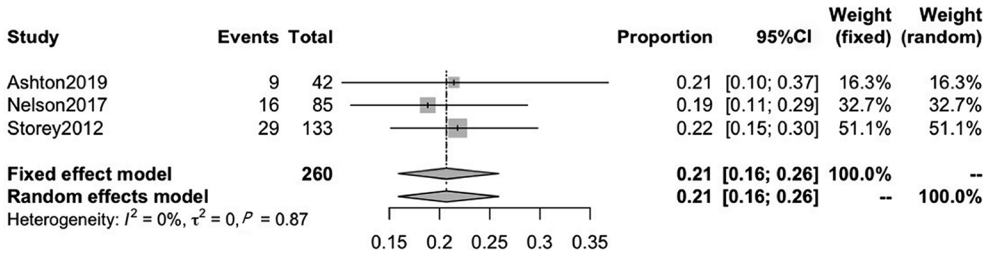

Figure 4 Forest plot of the prevalence of cancer-related fatigue in prostate cancer patients treated with radical prostatectomy. CI: Confidence interval.

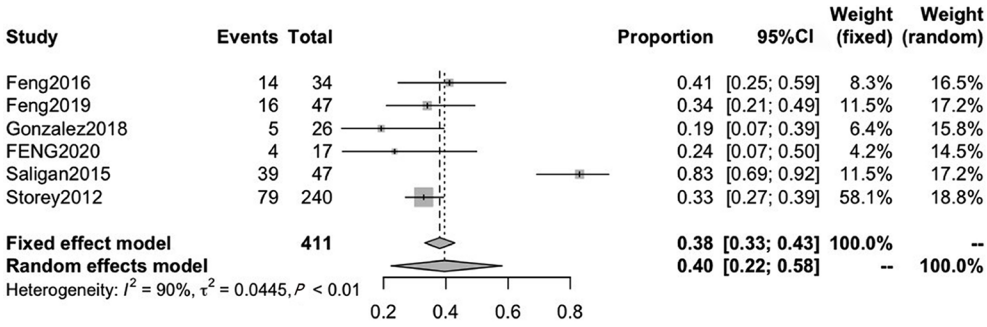

Figure 5 Forest plot of the prevalence of cancer-related fatigue in prostate cancer patients treated with radiation therapy. CI: Confidence interval.

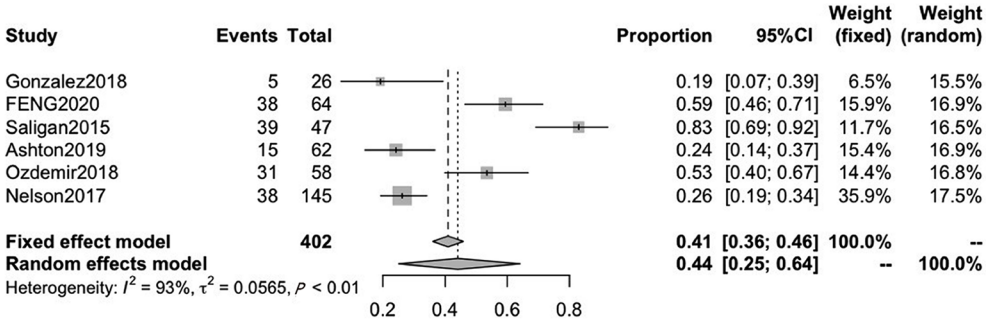

Figure 6 Forest plot of acute fatigue prevalence in prostate cancer patients. CI: Confidence interval.

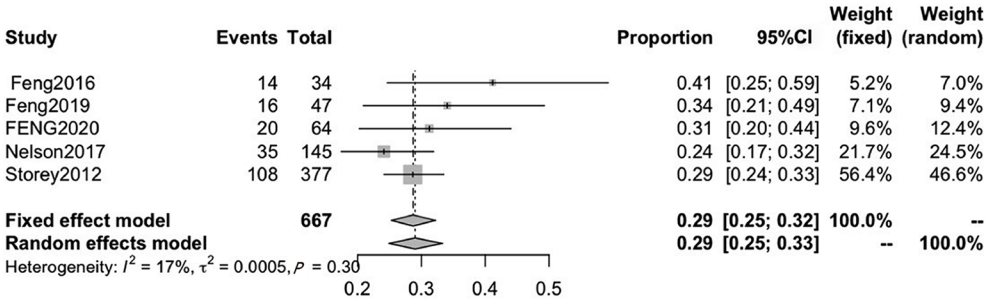

Figure 7 Forest plot of persistent fatigue prevalence in prostate cancer patients. CI: Confidence interval.

prevalence of acute and persistent fatigue was 44% and 29%, respectively. After the initiation of RT or ADT, the fatigue severity increases and continues to increase over time[20]. Although there is evidence that fatigue severity returns to baseline levels 6–8 wk after completing treatment[32,33], this was not the case in the study by Feng *et al* [34]. Rather, they found a subset of patients in their cohort who continued to experience fatigue for a year after RT, long after the treatment-associated hematologic

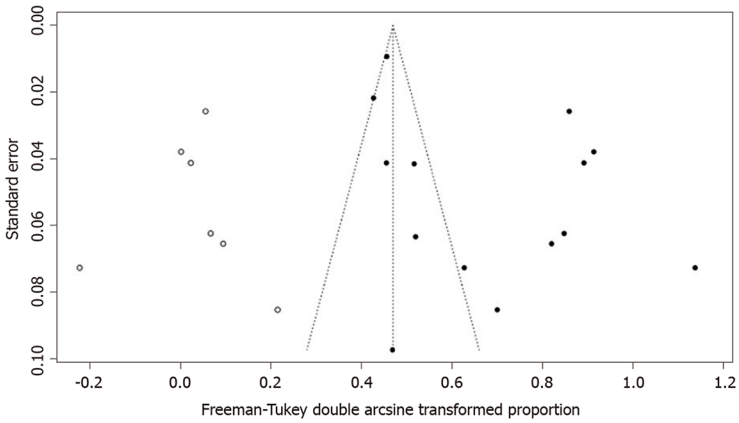

Figure 8 Egger's funnel plots for testing publication bias.

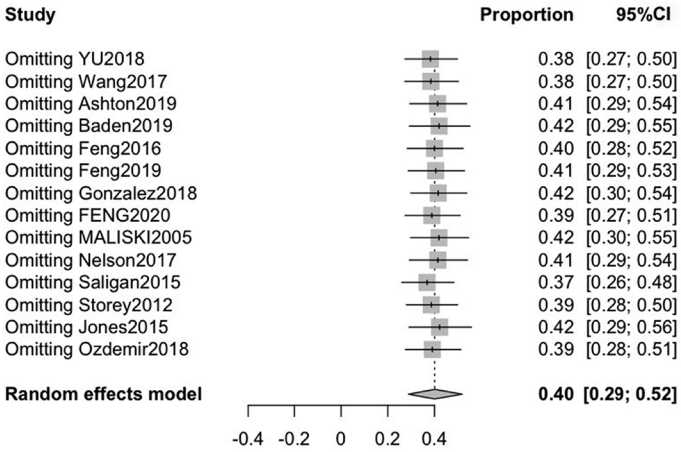

Figure 9 Sensitivity analysis of cancer-related fatigue prevalence in prostate cancer patients in all studies. CI: Confidence interval.

toxicities had resolved. These findings suggest that acute and persistent fatigue may be independent phenomena that are mechanistically different; each may be driven by distinct underlying pathogenic processes[8]. Storey *et al*[13] suggested that the presence of post-treatment CRF may be more influenced by the patient's current medical and psychological comorbidities than by the initial type of treatment received. Most evidence suggests that persistent fatigue is associated with depression, anxiety, urinary symptoms, pain and insomnia[8,23]. Furthermore, while effective treatments for persistent fatigue do not currently exist, targeting each of the fatigue-related symptoms may provide relief for patients suffering from this debilitating condition.

The present meta-analysis is characterized by some limitations. First, there was considerable heterogeneity among the primary studies. This might be attributable to differences in the cultures of the patients, the study settings and the variety of tools used to measure the prevalence of fatigue. Second, only one article analyzed the incidence of CRF associated with a combination therapy, precluding a meaningful analysis of the impacts of combination therapy. Third, the distribution of the funnel plot results was asymmetric, indicating possible publication bias, which might affect the accuracy of the results.

In conclusion, our meta-analysis revealed that patients with PCa have a high prevalence of CRF and that significant treatment-related differences in CRF incidence exist; further, there is a high prevalence of persistent fatigue. Similarly, high levels of symptoms have been reported in patients with breast cancer, and many interventions have been developed and tested to treat these symptoms[35,36]. Unfortunately, limited fatigue management research has been conducted in patients with PCa. Reported PCa research indicates that physical activity interventions, such as aerobic exercise and resistance exercise, are beneficial for reducing fatigue[37,38]. Additional behavioral interventions that have been shown to mitigate fatigue in cancer patients, including energy conservation[39], cognitive-behavioral therapy[40] and nutritional therapy[41], deserve further study to determine effective fatigue management strategies for

patients with PCa.

CONCLUSION

Fatigue is a common symptom in men with prostate cancer, especially those using hormone therapy.

ARTICLE HIGHLIGHTS

Research background

The side effects of prostate cancer (PCa) treatment are very prominent, with cancer-related fatigue (CRF) being the most common. Fatigue is a distressing symptom that interferes with daily functioning and seriously affects patient quality of life during, and for many years after, treatment. However, the exact statistics on the prevalence of CRF in patients with PCa remain unknown.

Research motivation

Recently, there has been an increased interest in investigating the impacts of fatigue in men with PCa. However, they do not adequately reflect the current prevalence of fatigue in PCa patients.

Research objectives

We performed a meta-analysis with two main aims. The first aim was to compute a robust estimate of the prevalence of PCa-related fatigue based on high-quality studies with sufficiently large sample sizes. The second aim was to evaluate the effects of different treatment methods and the fatigue assessment times on the prevalence of CRF in patients.

Research methods

A systematic search of EMBASE, PubMed, OVID, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, WANFANG DATA, Technology Journal Database and the Chinese Biological Medical Database was conducted up to July 28, 2020. Included studies measured the incidence of prostate CRF and differentiated fatigue outcomes (incidence) between treatment modalities and fatigue assessment times. In our meta-analysis, both fixed and random-effects models were used to estimate the pooled prevalence of prostate CRF. Publication and sensitivity bias analyses were performed to test the robustness of the associations.

Research results

Fourteen studies, involving 4736 patients, were eligible for the review. The results showed that the pooled prevalence of cancer treatment-related fatigue was 40%. Interestingly, the prevalence of CRF was associated with the type of treatment that the patients received; those undergoing radical prostatectomy had the lowest prevalence of fatigue. Further, there is a high prevalence of persistent fatigue.

Research conclusions

Fatigue is a common symptom in men with prostate cancer, especially those using hormone therapy.

Research perspectives

Our meta-analysis revealed that patients with PCa have a high prevalence of CRF. Unfortunately, limited fatigue management research has been conducted in patients with PCa. Many interventions deserve further study to determine effective fatigue management strategies for patients with PCa.

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