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doi:10.1017/S000711451800363X

Nutrition therapy for the management of cancer-related fatigue and quality of life: a systematic review and meta-analysis

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(Submitted 29 June 2018 – Final revision received 26 October 2018 – Accepted 27 November 2018)

Abstract

Cancer-related fatigue (CRF) is one of the most commonly reported disease- and treatment-related side effects that impede quality of life. This systematic review and meta-analysis describes the effects of nutrition therapy on CRF and quality of life in people with cancer and cancer survivors. Studies were identified from four electronic databases until September 2017. Eligibility criteria included randomised trials in cancer patients and survivors; any structured dietary intervention describing quantities, proportions, varieties and frequencies of food groups or energy and macronutrient consumption targets; and measures of CRF and quality of life. Standardised mean differences (SMD) were pooled using random-effects models. The American Dietetic Association's Evidence Analysis Library Quality Checklist for Primary Research was used to evaluate the methodological quality and risk of bias. A total of sixteen papers, of fifteen interventions, were included, comprising 1290 participants. Nutrition therapy offered no definitive effect on CRF (SMD 0·18 (95 % CI –0·02, 0·39)) or quality of life (SMD 0·07 (95 % CI –0·10, 0·24)). Preliminary evidence indicates plant-based dietary pattern nutrition therapy may benefit CRF (SMD 0·62 (95 % CI 0·10, 1·15)). Interventions using the patient-generated subjective global assessment tool and prescribing hypermetabolic energy and protein requirements may improve quality of life. However, the heterogeneity seen in study design, nutrition therapies, quality-of-life measures and cancer types impede definitive dietary recommendations to improve quality of life for cancer patients. There is insufficient evidence to determine the optimal nutrition care plan to improve CRF and/or quality of life in cancer patients and survivors.

Key words: Nutrition: Cancer: Cancer-related fatigue: Quality of life: Neoplasms

The prevalence of cancer survivorship is increasing due to innovations in cancer screening (early detection) and treatment, increasing life expectancy and population growth[1]. In Westernised countries, the 5-year survival rate of all cancers is approximately 68 %[1,2], with the expected number of cancer survivors projected to increase to 26·1 million by 2040 in the USA[1]. Across the cancer continuum from diagnosis to end-of-life care, both short- and long-term quality of life is often reduced due to disease- and treatment-related side effects, with cancer-related fatigue (CRF), pain and psychological distress reported most commonly[3]. Recent investigations have suggested CRF is one of the most prominently reported side effects of cancer treatments[4–7], with up to 80 % of cancer patients experiencing CRF during treatment[8–10] and for many years after treatment cessation[4,11–13]. Severe and persistent CRF have shown to inhibit quality of life by considerably reducing functional capacity to fully participate in daily living tasks[14]. The distressing impact of CRF not only affects quality of life but has also been shown to be a predictor of cancer recurrence and reduced overall survival[15]. The National Cancer Institute[16] has declared CRF to be a high research priority for future clinical trials to improve the quality of life of cancer survivors and, in turn, be prepared for the increasing demand of supportive care, given the projected cancer survivorship statistics.

The pathophysiology of CRF is relatively unknown and the treatment of CRF is largely symptomatic[17]. The cause of CRF is thought to be multi-dimensional, including pro-inflammatory responses to cancer treatment (i.e. IL-6, IL-8 and TNF-α) and lean muscle mass degradation[18–20]. Clinical practice recommendations suggest pharmaceutical interventions and lifestyle interventions (i.e. exercise, counselling and diet) to be effective treatments of CRF[17]. Whilst there is substantial evidence for exercise and psychological intervention to reduce CRF[21–23], to date pharmaceutical interventions have revealed inconsistent

Abbreviations: CRF, cancer-related fatigue; EORTC, European Organisation of Research and Treatment of Cancer; ESPEN, European Society of Clinical Nutrition and Metabolism; FACT, Functional Assessment of Cancer Therapy; PGSGA, Patient-Generated Subjective Global Assessment; RCT, randomised controlled trial; SMD, standardised mean difference;

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effects on CRF[22], and no systematic investigations have been conducted to inform targeted nutrition care for CRF. The dietary quality in cancer survivors is considerably poor, with only 15·1 % of cancer survivors meeting the diet recommendations for fruit (2 serves/d) and vegetables (5 serves/d)[24], which may in turn suggest there is significant scope to use nutrition therapy interventions to potentially improve cancer treatment side effects, such as CRF. In breast cancer survivors, a dietary intake high in fibre (>25 g/d)[25] and fruits and vegetables[26,27] has been positively associated with low levels of CRF. Anthropometric measures such as high BMI >30 kg/m^2[28], high adipose tissue (>34 %)[29] and low skeletal mass index (validated measure of muscle index through tomography scan of L3 or T4 muscle mass)[30] are also predictors of CRF in breast cancer. To support the National Cancer Institute research priority, it is imperative that the optimal nutrition care plan (including consult length, frequency, duration and delivery mode) and dietary recommendations (dietary energy, macronutrients and dietary patterns) to improve the outcomes of CRF are investigated to inform dietetic practice.

Existing evidence suggests nutrition therapy is inconsistently associated with improved quality of life for people with cancer[31]. However, the inclusion of adjunctive lifestyle interventions (i.e. exercise, meditation, mindfulness) alongside nutritional interventions in the studies comprised within this systematic review confounds the association of nutrition therapy with quality of life. Dietary recommendations aiming to improve quality of life and health outcomes in cancer patients may vary substantially based on the specific cancer population, treatment modality and disease- and treatment-related side effects (e.g. metabolic alterations, deteriorations in body composition, early satiety, nausea)[32,33]. Nutrition interventions that improve quality of life can be achieved by targeting and enhancing specific health outcomes (i.e. body mass) which are often compromised by cancer treatment. However, it is unknown whether targeting a health gain through nutrition therapy will also lead to improvements in CRF. Thus, systematically reviewing and meta-analysing the effects of different nutrition therapies aiming to improve CRF or quality of life through target health outcomes warrants exploration to inform future research and clinical practice. The aim of this study was to systematically review and meta-analyse randomised controlled trials (RCT) that investigated the isolated effects of nutrition therapy (i.e. without any adjunct lifestyle intervention such as exercise or psychology), on CRF and quality of life in people living with and beyond cancer.

Methods

Literature search

The systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement[34]. Electronic databases searched in September 2017 included PubMed, Scopus, CINAHL and CENTRAL (Cochrane Central Register of Controlled Trials). A full list of the search terms are provided in online Supplementary data (File 1).

Inclusion criteria

The inclusion criteria as specified by the Population, Intervention, Control Outcomes, Study design framework were as follows: (1) population: any histologically confirmed diagnosis of cancer (including all stages and treatments of cancer), (2) intervention: any structured dietary change or modification of dietary patterns (describing quantities, proportions, variety and frequency of food groups), (3) control: comparison group not receiving the intervention at any time point during the trial, comparison to a group receiving a different diet or a wait list control care, (4) outcomes: a measure of CRF and/or quality of life and (5) study design: RCT, randomised comparative trials, controlled trials or single-group cohort studies. Only full-text English articles of human trials, published in peer-reviewed journals, were included in the search process.

Titles and abstracts of articles identified through the search process were first reviewed by B. J. B. to exclude articles out of our study scope. Subsequently, B. J. B., O. R. L. W. and T. L. S. independently screened the full texts to identify eligible articles. Disagreements were discussed and resolved, with all parties agreeing on the exclusion or inclusion of articles. Articles that met the inclusion criteria were examined to ensure the same participants were not reported in more than one article. The data extraction procedure followed the PRISMA statement[34]. Reference lists of eligible articles were manually checked for additional references.

Data extraction

Details of (1) participant and study characteristics, (2) the nutrition intervention and (3) study results were independently extracted by one author (B. J. B.). Nutrition interventions were defined as any change in nutritional intake to increase/decrease foods or change in ratio of macronutrients, with the exception of any supplement use[35]. Studies involving oral feeding tubes were excluded from this review to enable accurate assessment of the efficacy of dietary pattern manipulation on CRF and quality of life. Any intervention incorporating strategies that may have influenced quality of life or CRF, for example, meditation, relaxation, exercise and psychological support were excluded. Measures of CRF included the Functional Assessment of Cancer Therapy (FACT)-fatigue, FACT-general, multidimensional fatigue inventory-short form, Schwartz Cancer Fatigue Scale, Piper Fatigue Scale, Brief Fatigue Inventory (BFI), and measures of quality of life included the Medical Outcomes Study: 36-Item Short-Form Survey (SF-36), European Organisation of Research and Treatment of Cancer (EORTC) quality of life questionnaire, any cancer-specific FACT or EORTC quality-of-life questionnaires or any other measure of CRF or quality of life. Data documented in tables included the raw questionnaire values (including standard deviation or measurements of error) and significance with the associated *P* value.

Data synthesis

The pooled effect size was calculated for CRF and quality of life for each study including details on sample size, mean, standard

deviation, standard error of the mean and/or 95% CI. The random effect standardised mean difference (SMD), 95% CI, z value, α value for z and Q statistic for heterogeneity were calculated using Review Manager Software[36]. For studies only reporting CI or standard error of the mean, the standard deviation was obtained following the Cochrane Handbook recommendations[37]. A two-tailed α value ≤0·05 for z and non-overlapping 95% CI were considered to represent statistically significant SMD changes in CRF or quality of life when nutrition therapy was compared with a usual care or control group. I^2 statistics for consistency and τ^2 were extracted from Review Manager Software, and a P-value for Cochrane Q $P \leq 0{\cdot}10$ or an I^2 statistic ≥50% indicated substantial heterogeneity[37]. Subgroup analyses were performed for the nutrition therapy, delivery of nutrition therapy and duration of the intervention.

Quality assessment

Methodological quality of the included articles was independently reviewed by two authors (B. J. B. and O. R. L. W.) using the American Dietetic Association (ADA)'s evidence analysis library quality criteria checklist for primary research[38]. The criteria are written as 'yes/no' questions to examine the validity of the study design and its execution of two categories: relevance and validity of questions. A final rating of positive, neutral or negative was assigned to each study, based on the number of questions answered as yes, neutral or no.

Results

Study design and research quality

The systematic search found 6988 articles identified through the databases (Fig. 1). After duplicate removal through the selected databases, a total of 6699 abstracts were screened for inclusion.

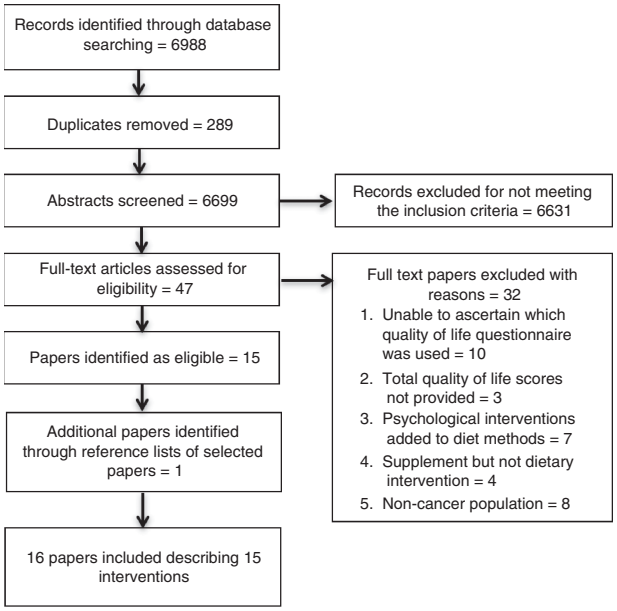

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta Analyses diagram.

Abstracts of the full-text records were assessed for eligibility; forty-eight articles were subsequently included for full-text revision, with one article additionally included through reference lists screening of the included articles. A total of sixteen articles met the inclusion criteria and were included in the review[39–54], with one intervention described in two separate studies[43,44].

Quality assessment

Results of the methodological quality assessment are presented in online Supplementary material (File 2). Methodological quality scores ranged from 76%[47] to 89%[44,54], with a mean score of 82%. All fifteen interventions scored a positive score[39–43,45–54] for methodological quality on the ADA quality assessment of study relevance and validity[55]. All studies scored high in the relevance of methodological design; however, only one intervention blinded data collectors from the treatment[48]. An intention to treat statistical approach was used in eight studies (53%)[39,43,45,49–51,53,54], and clinical significance along with statistical significance was provided in ten studies (67%)[39–43,45,46,48,52–54].

Study populations

A total of 1290 participants were included across the fifteen interventions. The sample sizes ranged from 18[40] to 358[39]. The average age of participants ranged from 51·5[42] to 72·0 years[52]. Studies included participants diagnosed with gastrointestinal (n 3)[39,49,52], breast (n 3)[41,46,54], undefined (n 3)[40,42,53], head and neck (n 2)[43,44,50], lung (n 2)[45,46], colorectal (n 2)[49,51] and ovarian (n 2)[46,48] cancer. Participants received various cancer treatments, including radiotherapy (n 4)[43–45,50,51], chemotherapy (n 3)[39,40,46], surgery (n 1)[47] and surgery with chemotherapy (n 1)[52]; the remaining six studies did not disclose the treatment modality[41,42,48,49,53,54].

Measures of cancer-related fatigue

A total of eight studies reported the effects of nutrition therapy on CRF[41,42,48–52,54]. In all, four studies used the EORTC-C30[42,49–52], whilst one study each used the SF-36[48], BFI[54] and FACT-F[41]. The efficacy of nutrition therapy on CRF was a primary outcome in only one of eight (13%) studies[54].

Measures of quality of life

A total of fourteen studies reported the effects of nutrition therapy on quality of life[39–53]. In all, nine studies used the EORTC-C30[39,40,42–44,49–53], two studies used the FACT-G[39,41], FACT-L[45], FACT-G, SF-36[48], Quality-of-Life Index[46] and Polyp Prevention Trial Quality of Life Factors[47]. The efficacy of nutrition therapy on quality of life was a primary outcome in eight of fifteen (53%) studies[39,46,49–53].

Table 1. Study characteristics

						Methodology of nutrition care plan				Nutrition therapy			
Author (Country)	Trial length and design	Cancer type	Group (*n*)	Nut/diet	PG-SGA	Consults (*n*)	Consults (min)	Consult frequency	Mode	Theme	Food groups	Energy	Protein
Baldwin *et al.*[39] UK	6-week RCT	GI	INT (96)	Y	NR	6	NR	Weekly	Telephone, written	Increase total energy intake for weight gain	NR	+2510 kJ	NR
			INT 2 (90)	Y	NR	6	NR	Weekly	Telephone, written	Nutrition supplement	NR	+2460 kJ	NR
			INT 3 (86)	Y	NR	6	NR	Weekly	Telephone, written	Nutrition supplement	NR	+250 kJ	NR
			CON (86)						No intervention				
Brown *et al.*[40] Australia	8-week RCT	Mixed cancer	INT (8)	Y	Y	8	15–30	Weekly-fortnightly	Face-to-face, telephone, written, video	NR	NR	NR	NR
			CON (10)	Y	Y	2	45–60	Monthly	Face-to-face	NR	NR	NR	NR
Darga *et al.*[41] USA	1-year RCT	Breast cancer	INT (13)	Y	NR	24	NR	Weekly, fortnightly and monthly	Telephone	Individual weight loss	Decrease total energy (about 2090–4180 kJ/d), 20–25 % energy from fat, 20 % energy from protein, 5 serves/day fruit and vegetable	NR	NR
			INT (11)	Y	NR	24	NR	Weekly, fortnightly and monthly	Telephone	Individual weight loss and Weight Watchers©	Decrease total energy (about 2090–4180 kJ/d), 20–25 % energy from fat, 20 % energy from protein, 5 serves/day fruit and vegetable	NR	NR
			INT (10)	NR	NR	NR	NR	NR	NR	Weight Watchers©	Decrease total energy	NR	NR
			CON (13)						Written material of dietary guidelines				
Gnagnarella *et al.*[42] Italy	24-week RCT	Mixed cancer	INT (64)	NR	NR	NR	NR	Weekly	Online peer support	Weight loss, healthy eating	NR	NR	NR
			CON (61)						Written material of intervention				
Isenring *et al.* 2007[43] & 2004[44] Australia	12-week RCT*	Head and neck, abdominal and rectal	INT (29)	Y	Y	9	NR	Weekly, fortnight	Face-to-face, written, Telephone	HPHE, Individualised to meet nutrition recommendations of EPR	NR	H-B equation (1·2–1·5 activity and stress factor)	1·2–1·5 g/kg body weight
			CON (31)	N	Y	NR	NR	NR	Written	HPHE, supplements	NR	NR	NR
Kiss *et al.*[45] Australia	Approx. 12-week prospective RCT	Lung	INT (12)	Y	Y	NR	NR	Weekly during treatment, fortnightly 6-weeks after treatment	Face-to-face, Telephone	Individualised to meet nutrition recommendations, treatment side effects	NR	NR	NR
			CON (12)	Y	Y	NR	NR	Fortnightly during treatment and follow-up 4-weeks	Face-to-face, Telephone	Individualised to meet nutrition recommendations, treatment side effects	NR	NR	NR
Ovesen *et al.*[46] Denmark	20-week RCT*	Lung, breast and ovarian	INT (57)	Y	NR	10	NR	Fortnightly	Face-to-face	Individualised to meet EER & EPR	NR	1·5–1·7 × basal energy	1·0–1·2 g/kg body weight
			CON (48)						No intervention				
Pakiz *et al.*[47] USA	48-week RCT*	Colon	INT (37)	Y	NR	NR	30–60	Daily 1–3 weeks, weekly 3–7 weeks, monthly 7–48 weeks	Telephone	Increase fruits and vegetables	Vegetables (serves/day 7–9), fruit (serves/day 2) diary (serves/day 3), 30–35 g fibre, 20–25 % energy from fat	NR	NR

Table 1. *Continued*

Author (Country)	Trial length and design	Cancer type	Group (*n*)	Nut/diet	PG-SGA	Methodology of nutrition care plan: Consults (*n*)	Consults (min)	Consult frequency	Mode	Nutrition therapy: Theme	Food groups	Energy	Protein
			CON (40)						Dietary guidelines provided				
Paxton *et al.*[48] USA	16-week RCT*	Ovarian	INT (24)	Y	NR	12	20–30	Weekly/fortnightly	Telephone	Healthy eating	Fruit (serves/day 2), vegetable (serves/day 5), 1/day vegetable juice 30 g fibre, <20 % energy from fat	NR	NR
			INT (27)	Y	NR	12	20–30	Weekly/fortnightly	Telephone	Healthy eating	5 serves/day of fruit and vegetables, >25 g fibre, <20 % energy from fat, 33 g soy supplement, 4 capsules of fruit and vegetable powder	NR	NR
Persson *et al.*[49] Sweden	2-year RCT	Colorectal and gastric	INT (67)	Y	NR	4–8	20	NR	Face-to-face, telephone, and group-based	Nordic nutrition guidelines and treatment side effects	NR	NR	NR
			CON (44)						No intervention				
Ravasco *et al.*[50] Portugal	12-week RCT	Head and neck	INT (25)	Y	Y	12	NR	Weekly	Face-to-face	Individualised food groups to meet EER & EPR	NR	EER (BMR × 1·5)	EPR (0·8–1·0 g/kg/d)
			INT (25)	Y	Y	12	NR	Weekly	Face-to-face	HPHE supplement (20 g protein, about 835 kJ)	NR	EER (BMR × 1·5)	EPR (0·8–1·0 g/kg/d)
			CON (25)						No intervention				
Ravasco *et al.*[51] Portugal	12-week RCT	Colorectal	INT (37)	Y	Y	12	NR	Weekly	Face-to-face	Individualised food groups to meet EER & EPR	NR	EER (BMR × 1·5)	EPR (0·8–1·0 g/kg/d)
			INT (37)	Y	Y	12	NR	Weekly	Face-to-face	HPHE supplement (20 g protein, about 835 kJ)	NR	EER (BMR × 1·5)	EPR (0·8–1·0 g/kg/d)
			CON (37)						No intervention				
Silvers *et al.*[52] Australia	18-week RCT	Upper GI	INT (10)	Y	Y	18	15–30	Weekly	Face-to-face, telephone	Weight management	NR	NR	NR
			CON (11)						No intervention				
Uster *et al.*[53] Switzerland	12-week RCT	Mixed cancers	INT (33)	Y	NR	3	NR	Every 6 weeks	NR	To meet EER & EPR	NR	Ireton-Jones formula	1·0 g/kg/d
			CON (34)						No intervention				
Zick *et al.*[54] USA	12-week RCT	Breast	INT (15)	Y	NR	9	15	Weekly/fortnightly	Face-to-face, telephone, written material	Anti-inflammatory diet	Fruit (serves/day 2), vegetable (serves/day 5), fish (serves/day 1), nuts seeds (serves/day 2)	NR	NR
			CON (15)						No intervention				

CON, control or comparison group; EER, estimated energy requirements; EPR, estimated protein requirements; GI, gastrointestinal; H-B, Harris–Benedict; HPHE, high protein high energy; INT, intervention; NR, not reported; nut/diet, intervention delivered by a nutritionist or dietitian; PG-SGA, Patient-Generated Subjective Global Assessment; RCT, randomised controlled trial; Y, yes.
* Randomised comparative trial.

Study characteristics

Intervention characteristics are displayed in Table 1. A total of nine RCT included a control or waitlist control group[46–54], six RCT used an alternative diet as a comparison group[40,42,45], one study used supplements as a comparison group[43,44], one three-arm study compared nutrition therapy, an oral supplement and a control group[39], and one four-arm study compared nutrition therapy, Weight Watchers©, combined nutrition therapy and Weight Watchers and a control group[41]. A pseudo-RCT (alternate method of group allocation) was seen in only one study where the nutrition therapy intervention group was compared with a group of hospital patients provided standard dietetic practice[40]. Of the fifteen, fourteen (94 %) studies reported that a dietitian or nutritionist delivered the intervention[39–41,43–54]; whilst one study did not indicate the health professional delivering the intervention[47].

Length

All fifteen studies reported the length of the intervention, ranging from 6 weeks[39] to 24 months[49]. Eight studies were of intervention length of <12 weeks[39,40,43,45,50,51,53,54]. One study each were of 16 weeks[48], 18 weeks[52] and 24 weeks[47]. One study was of 1 year[41] and two studies was of 2 years[48,49].

Duration of dietetic consults

Of the fifteen, five studies reported the duration of the prescribed nutrition consults[40,47,48,52,54]. The nutrition consults ranged from 15 to 60 min across the five studies[40,47,48,52,54]. Two studies prescribed 15–30 min consults[52,54], one study prescribed 20–30 min consults[48] and one study prescribed 30–60 min consults[47]. One study compared 15–30 min consults *v.* 45–60 min nutrition consults[40].

Frequency

All fifteen studies reported the frequency of nutrition consultations; six reported weekly consultations[39,40,42,50,51,53], one reported weekly or fortnightly[40], one reported fortnightly consultations[46]. One study reported daily (1–3 weeks), weekly (3–7 weeks) and monthly consults (7–48 weeks)[47]. Three studies reported the weekly consults were moved to fortnightly after 4 weeks[54], 6 weeks[44] and 8 weeks[48]. One study reported weekly consults were moved to fortnightly (at 12 weeks) and monthly (at 24 weeks)[41]. One intervention reported a nutrition consult occurred before treatment and then fortnightly during treatment[45]. One reported a range of three to seven consults over 24 months[49].

Mode

Of the fifteen studies, fourteen reported the mode of delivery of the nutrition consult[39–43,45–54]. Four studies utilised combined face-to-face and telephone consults[43–45,49,52], whilst three studies each examined face-to-face consults[46,50,51] or telephone consults[41,48,49]. The remaining studies used face-to-face, telephone and videoconferencing[40], face-to-face, telephone and written material[54], written and telephone consultations[39] and nutrition information delivered through online material, blogs and peer support[42].

Nutrition therapy

The prescribed nutrition therapy of the intervention and/or control groups was reported in fourteen of the fifteen studies[39,41–54]. Nutrition therapy to meet or exceed the estimated energy and protein requirements was prescribed in six of fifteen studies[39,46,50,51,53]. One study prescribed an additional 2500 kJ compared with the usual care[39], while four studies used formulas to estimate the total energy requirements: 1·5 times the BMR[50,51], 1·7 times the basal metabolic energy expenditure[46] and the Ireton–Jones formula (energy expenditure including age, weight, sex, trauma and burns)[53]. Estimated protein requirements were used in six of fifteen studies[43–46,50,51,53], ranging from 0·8[50,51] to 1·5[43] g/kg per d of body weight. According to one study, prescribed protein comprised 20 % of total energy intake[41], whilst another study prescribed weight management and nutrition advice for the management of treatment-related side effects[52]. Of the fourteen studies, two prescribed weight loss interventions, with one prescribing a 2090–4180 kJ/d deficit[42] whilst the other provided no defined deficit[41]. Dietary pattern interventions was seen in four studies and focused on recommendations for fruit and vegetable intake and obtaining 20–25 % energy from fat[41,47,48,54]. Two interventions recommending the same two fruits and five vegetables serves/d[48,54], whilst Zick *et al.*[54] further detailed one fish and one nuts/seeds serves per d to encompass an anti-inflammatory dietary pattern. The Nordic nutritional guidelines[56] were compared with the usual care in one RCT[49].

Nutrition outcome measurements

Total energy intake was reported in eight of fifteen studies[43,44,46,48–51,53,54] and total protein intake was reported in six of fifteen studies[43,46,49–51,53]. The Patient-Generated Subjective Global Assessment[57] (PGSGA; a nutrition assessment tool incorporating diet intake, physical parameters, treatment side effects and physical functioning for oncology patients) was measured in six of fifteen studies[40,43,45,50–52]. Of the fifteen studies, twelve reported the effect of nutrition interventions on anthropometrical outcomes of body mass[39,41,43,45–49,52,53], BMI[50,51,54] or fat-free mass[43,45,46].

Dropout, attendance and adverse effects

All studies reported dropout rates ranging from 0 %[50,51] to 43 %[53]. Only one of the fifteen (7 %) studies reported on the adverse effects of the nutrition intervention, with this study reporting zero adverse events[48]. Four studies (27 %) reported adherence to the nutrition intervention[39,45,48,54]. Three studies used checklists of food groups to measure adherence to the dietary strategies, with adherence reported as 11–47 %[48], 75 %[45] and 73–95 %[54]. One study used a food diary to report

adherence[39], however as only 25 % of these records were completed, the analysis was not documented[39]. Four studies reported nutrition consult attendance (face-to-face and/or telephone), with attendance rates of 75 %[48], 93 %[54] and 100 %[45,52].

Effects on cancer-related fatigue

The effects of the interventions on CRF are displayed in Table 2. The pooled effects (SMD 0·18 (95 % CI −0·02, 0·39)) of nutrition therapy compared with usual care showed no apparent improvements in CRF (Fig. 2). There was no heterogeneity $I^2 = 28\,\%$, $P = 0{\cdot}23$. One (13 %) of eight nutrition interventions showed between-group improvements in CRF compared with the usual care[54]. Three (38 %) of eight nutrition interventions showed within-group improvements in CRF from the nutrition intervention[50–52], whilst no significant within-group changes were seen in the comparative or control groups (Fig. 3).

Subgroup analysis for cancer-related fatigue

Six of eight interventions were eligible for CRF meta-analysis[41,42,48,49,52,54]. Both Ravasco *et al.*[50,51] studies did not report a measurement of error to the mean and was excluded in the meta-analysis. Subgroup analysis for CRF are found in online Supplementary data (File 3).

Length

There appeared to be no definitive improvement in CRF when ≤6 month (SMD 0·31 (95 % CI −0·06, 0·68) consults were

Table 2. Cancer-related fatigue outcomes

			Cancer-related fatigue (mean ± SD)			Cancer-related fatigue post-intervention (mean ± SD (95 % CI))	
Author (Country)	Measure of cancer-related fatigue	Group	Baseline	Post-intervention	Follow-up	Between-group	Within-group
Darga *et al.*[41] USA	FACT-F	INT 1	9·2 ± 6·1	9·3 ± 6·5		NR	$P = 0{\cdot}964$
		INT 2	9·9 ± 6·6	10·1 ± 7·1			$P = 0{\cdot}942$
		INT 3	9·2 ± 8·3	9·2 ± 8·3			$P > 0{\cdot}999$
		CON	12·1 ± 9·9	12·1 ± 9·9			$P > 0{\cdot}999$
Gnagnarella *et al.*[42] Italy	EORTC-30 (F)	INT	50·5 ± 23·7	41·6 ± 25·2		$P = 0{\cdot}17$	INT: −8·1 ± 2·8
		CON	45·6 ± 23·7	43·6 ± 21·5			−2·7 ± 2·7
Paxton *et al.*[48] USA	SF-36 (F)	INT	58·8 ± 20·3	57·6 ± 23·4		$P = 0{\cdot}842$	−1·20 ($P = 0{\cdot}933$)
		CON	65·8 ± 22·1	66·6 ± 19·7			0·80 ($P = 0{\cdot}584$)
Persson *et al.*[49] Sweden	EORTC-30 (F)	INT	46 ± 28	21 ± 24		$P > 0{\cdot}05$	$P > 0{\cdot}05$
		CON	43 ± 30	25 ± 24			$P > 0{\cdot}05$
Ravasco *et al.*[50] Portugal	EORTC-30 (F)	INT 1	30	55*	26*	NR	Baseline *v.* T1; $P < 0{\cdot}05$ Baseline *v.* T2; $P < 0{\cdot}05$
		INT 2	31	75*	78*		Baseline *v.* T1; $P < 0{\cdot}05$ Baseline *v.* T2; $P < 0{\cdot}05$
		CON	29	78	79		Baseline *v.* T1; $P < 0{\cdot}05$ Baseline *v.* T2; $P < 0{\cdot}05$
Ravasco *et al.*[51] Portugal	EORTC-30 (F)	INT 1	30	55*	26*	NR	Baseline *v.* T1; $P < 0{\cdot}05$ Baseline *v.* T2; $P < 0{\cdot}05$
		INT 2	31	75*	78*		Baseline *v.* T1; $P < 0{\cdot}05$ Baseline *v.* T2; $P < 0{\cdot}05$
		CON	29	78*	79*		Baseline *v.* T1; $P < 0{\cdot}05$ Baseline *v.* T2; $P < 0{\cdot}05$
Silvers *et al.*[52] Australia	EORTC-30 (F)	INT	50 ± 37	40 ± 22	8 ± 15	−12·8 (−29·8, 4·2), $P = 0{\cdot}13$	−19·4 (−29·1, −9·7) $P < 0{\cdot}001$
		CON	32 ± 17	40 ± 18	31 ± 16		NR
Zick *et al.*[54] USA	BFI	INT	5·4 ± 1·1	3·0 ± 2·2		$P < 0{\cdot}01$	2·4 ± 2·0
		CON	5·6 ± 1·3	4·9 ± 1·6			0·77 ± 1·8

BFI, Brief Fatigue Inventory; CON, control; EORTC-30, European Organisation for Research and Treatment of Cancer-30 (questions); F, fatigue; FACT, Functional Assessment of Cancer Therapy; INT, intervention; NR, not reported; SF-36, Medical Outcome Study 36-Item Short-Form Health Survey; T, time point.
* Significance <0·05.

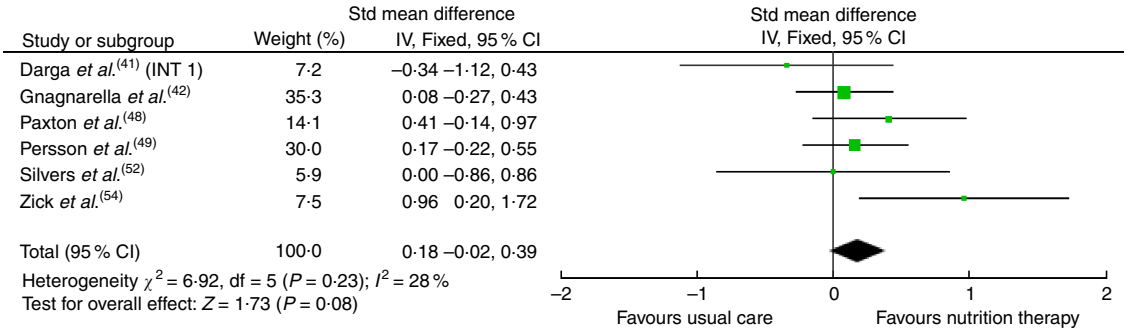

Fig. 2. Forest plot for standardised mean difference effect size in cancer-related fatigue when nutrition therapy is compared with usual care. The squares represent the pooled standardised mean difference effect size for each study, with the total pooled effect shown in the black diamond. All analyses are based on a random effects model. INT1, intervention group 1.

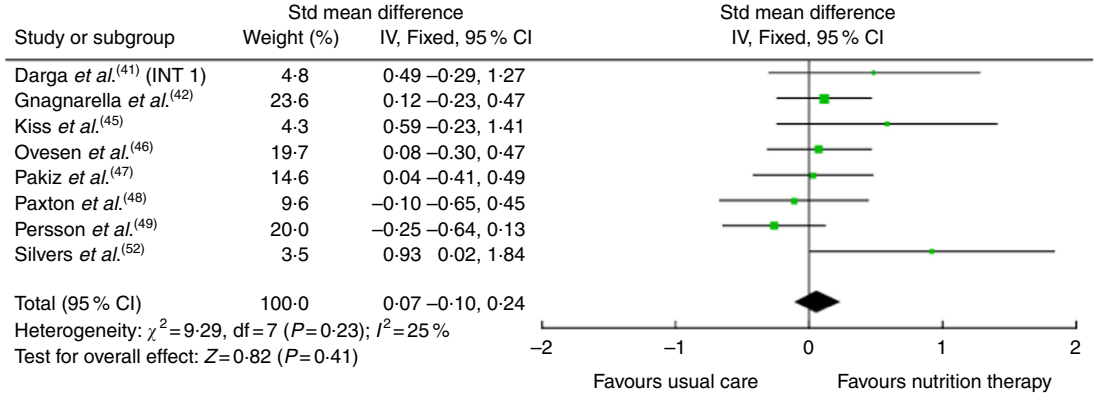

Fig. 3. Forest plot for standardised mean difference effect size in quality of life when nutrition therapy is compared with usual care. The squares represent the pooled standardised mean difference effect size for each study, with the total pooled effect shown in the black diamond. All analyses are based on a random effects model. INT1, intervention group 1.

compared with >6 month (SMD 0·03 (95 % CI –0·41, 0·47)). One of the three interventions showed between-group improvements in CRF compared with a control group after 12 weeks[54], whilst two intervention showed within-group improvements in CRF from the interventions[50,51]. The one intervention of 18 weeks only showed within-group improvements from the intervention[52].

Duration of dietetic consults

Four of eight interventions exploring CRF reported the duration of nutrition consults in the nutrition care plan[48,49,52,54], and as such pooled effects could not be performed. The only intervention with 15 min consults showed between-group improvements in CRF[54]. The only intervention prescribing 15–30 min consults showed within-group improvements in CRF[52].

Frequency

Weekly and fortnightly consults showed improvements in CRF (SMD 0·62 (95 % CI 0·10, 1·15)), whilst weekly (SMD 0·12 (95 % CI –0·14, 0·38)) and progressive weekly and month (SMD –0·34 (95 % CI –1·12, 0·43)) interventions showed no apparent improvements on CRF.

Mode

The mode of intervention delivery showed no apparent effect on CRF. Interventions using face-to-face with telephone consults (SMD 0·34 (95 % CI –0·17, 0·86)), or intervention that were telephone or online only (SMD 0·11 (95 % CI –0·22, 0·43)) showed no effect on CRF.

Nutrition therapy

Nutrition therapy detailing dietary patterns showed improvements in CRF (SMD 0·62 (95 % CI 0·10, 1·15)), whilst weight loss (SMD 0·01 (95 % CI –0·31, 0·33)) and interventions following dietary healthy eating guidelines (SMD 0·14 (95 % CI –0·21, 0·49)) showed no apparent effects on CRF. Of the two interventions that prescribed dietary pattern recommendations[48,54], one intervention reported between-group improvements in CRF when the intervention (anti-inflammatory-based diet) was compared with the control group[54]. Two of five interventions demonstrating between-group improvements in energy and protein intake also showed within-group improvements in CRF[50,51]. All three interventions showing between-group improvements in PGSGA also demonstrated within-group improvements in CRF[50–52].

Table 3. Quality of life outcome scores

			Outcome measure ± SD			Quality of life post-intervention (mean ± SD (95 % CI))	
Author (Country)	Measure of quality of life	Group	Baseline	Post-intervention	Follow-up	Between-group	Within-group
Baldwin *et al.*[39] UK	EORTC-C30	NR	NR	NR		$P > 0{\cdot}05$	$P > 0{\cdot}05$
	FACT	NR	NR	NR		$P > 0{\cdot}05$	$P > 0{\cdot}05$
Brown *et al.*[40] Australia *α*	EORTC-C30	INT	71 (17–92)	71 (17–92)		$P > 0{\cdot}05$	NR
		CON	83 (33–92)	67 (33–83)			NR
Darga *et al.*[41] USA	FACT-G	INT 1	91·1 ± 11·1	98·4 ± 6·8		NR	$P = 0{\cdot}094$
		INT 2	86·7 ± 10·5	92·8 ± 7·3		NR	$P = 0{\cdot}094$
		INT 3	85·9 ± 11·0	94·7 ± 8·5		NR	$P = 0{\cdot}113$
		CON	93·2 ± 12·2	94·2 ± 9·5		NR	$P = 0{\cdot}836$
Gnagnarella *et al.*[42] Italy	EORTC-C30 (General health status)	INT	62·1 ± 20·4	63·3 ± 21·4		$P = 0{\cdot}87$	2·8 ± 2·9
		CON	56·0 ± 20·7	60·9 ± 18·8			3·5 ± 2·8
Isenring *et al.* 2007[43] & 2004[44] Australia	EORTC-C30 (General health status)	INT	67·7 ± 18·8	72·7 (NR)		$P = 0{\cdot}009$*	NR
		CON	75·3 ± 19·2	62·6 (NR)			NR
Kiss *et al.*[45] Australia *β*	FACT-G	INT	82·3 (4·7)	82·4 (4·9)	86·5 (4·3)	6·78 (–4·78, 18·33)	0·09 (–8·33, 8·50)ψ 4·19 (–3·76, 12·14)ɵ
		CON	79·0 (4·7)	72·3 (4·7)	85·0 (4·2)	–1·77 at FU (–12·78, 9·23)	–6·69 (–14·61, 1·23)ψ 5·96 (–1·65, 13·57)ɵ
Ovesen *et al.*[46] Denmark	Quality of Life Index	INT	7·0 ± 2·2	8·1 ± 2·1*		$P > 0{\cdot}05$	$P < 0{\cdot}05$
		CON	6·6 ± 2·2	7·9 ± 2·6*			$P < 0{\cdot}05$
Pakiz *et al.*[47] USA	Polyp Prevention Trial QF	INT	153·9 ± 21·2	157·6 ± 18·9		$P > 0{\cdot}05$	$P = 0{\cdot}058$
		CON	154·5 ± 15·6	156·9 ± 15·7			$P > 0{\cdot}05$
Paxton *et al.*[48] USA	SF-36 (General Health)	INT	71·3 ± 17·9	70·0 ± 19·4		$P = 0{\cdot}804$	–1·30 ($P = 0{\cdot}644$)
		CON	71·3 ± 21·9	72·1 ± 20·5			0·80 ($P = 0{\cdot}746$)
Persson *et al.*[49] Sweden	EORTC-C30	INT	57 ± 12	70 ± 20		$P > 0{\cdot}05$	$P > 0{\cdot}05$
		CON	57 ± 12	75 ± 19			$P > 0{\cdot}05$
Ravasco *et al.*[50] Portugal	EORTC-C30	INT 1	48	75*	82*	NR	Baseline *v.* T1; $P = 0{\cdot}003$ Baseline *v.* T2; $P = 0{\cdot}008$
		INT 2	46	70*	62*		Baseline *v.* T1; $P = 0{\cdot}009$ Baseline *v.* T2; $P = 0{\cdot}03$
		CON	47	30*	30*		Baseline *v.* T1; $P < 0{\cdot}001$ Baseline *v.* T2; $P = 0{\cdot}004$
Ravasco *et al.*[51] Portugal	EORTC-C30	INT 1	48	75*	82*	NR	Baseline *v.* T1; $P = 0{\cdot}003$ Baseline *v.* T2; $P = 0{\cdot}008$
		INT 2	46	70*	62*		Baseline *v.* T1; $P = 0{\cdot}009$ Baseline *v.* T2; $P = 0{\cdot}03$
		CON	47	35*	30*		Baseline *v.* T1; $P < 0{\cdot}001$ Baseline *v.* T2; $P = 0{\cdot}004$
Silvers *et al.*[52] Australia	EORTC-C30	INT	45 ± 20	53 ± 15	71 ± 8	28·4 (19·8, 37·1)*	NR
		CON	46 ± 16	38 ± 16	40 ± 16	$P < 0{\cdot}001$	NR
Uster *et al.*[53] Switzerland	EORTC-C30	INT	52·4	56·3	53·7	NR	NR
		CON	54·4	67·3	67·3		NR

CON, control; EORTC, European Organisation for Research and Treatment of Cancer; FACT, Functional Assessment of Cancer Therapy; FU, follow-up; INT, intervention, NR, not reported; QF, quality of life factors; SF-36, Medical Outcome Study 36-Item Short-Form Health Survey; T, time point; *α*, data presented as median and range; *β*, data presented as estimated mean and standard error; ψ, measured directly after radiotherapy; ɵ, measured 4–6 weeks after radiotherapy.

* Significance <0·05.

Effects on quality of life

The effects of the interventions on quality of life are shown in Table 3. The pooled effects (SMD 0·07 (95 % CI –0·10, 0·24)) of nutrition therapy compared with usual care showed no apparent effects on quality of life. There was no heterogeneity $I^2 = 25\%$, $P = 0{\cdot}23$. Of the fourteen, two (14 %) interventions showed between-group improvements in quality of life compared with the usual care[52] or compared with written healthy eating information with supplements[43,44]. Of the fourteen, three (21 %) interventions reported within-group improvements from the nutrition intervention[46,50,51].

Subgroup analysis for quality of life

Of the fourteen interventions, eight were eligible for quality-of-life meta-analysis[41,42,45–49,52]. Studies by Baldwin *et al.*[39], Brown *et al.*[40], Isenring *et al.*[44], Ravasco *et al.*[50,51] and Uster *et al.*[53] did not report a measurement of error and were excluded in the meta-analysis. Subgroup analysis for CRF are found in online Supplementary data (File 4).

Length

There appeared to be no definitive improvement in quality of life when ≤6 month (SMD 0·17 (95 % CI –0·09, 0·42)) consults were compared with >6 month (SMD –0·02 (95 % CI –0·37, 0·34)). One of four 12-week intervention showed between-group improvements in quality of life when compared with a control group[43,53], whilst two of four interventions showed within-group improvements in quality of life from the intervention[50,51].

Duration of dietetic consults

Of the fourteen interventions, six reported the duration of the nutrition consults[40,47–49,52], and as such pooled effects could not be performed. One of two 15–30 min interventions showed between-group improvements in quality of life from the intervention[52].

Frequency

Weekly (SMD 0·41 (95 % CI –0·35, 1·17)), weekly and fortnightly (SMD 0·10 (95 % CI –0·20, 0·39)) or progressive daily and weekly and monthly interventions (SMD 0·15 (95 % CI –0·24, 0·54)) did not show improvements in quality of life.

Mode

Telephone or online (SMD 0·09 (95 % CI –0·15, 0·33)), face-to-face with telephone (SMD 0·26 (95 % CI –0·86, 1·41)) or face-to-face interventions (SMD 0·20 (95 % CI –0·22, 0·62)) did not show improvements in quality of life. Zero of the three interventions using face-to-face nutrition therapy showed between-group improvements, however all three interventions showed within-group improvements from the intervention[46,50,51].

Nutrition therapy

Weight loss (SMD 0·18 (95 % CI –0·14, 0·50)), nutrition therapy to meet individual requirements (SMD 0·20, (95 % CI –0·22, 0·62)), guidelines and health eating (SMD 0·10 (95 % CI –0·42, 0·61)) and dietary patterns (SMD –0·10 (95 % CI –0·42, 0·61)) did not show improvements in quality of life. Five of seven interventions showed between-group improvements in energy and protein intake[43,46,50,51,53]; one study showed between-group improvements in quality of life[43], whilst three studies showed within-group improvements in quality of life from the intervention[46,50,51]. Five of six studies showed between-group improvements in the PGSGA[40,43,50–52]; two interventions also showed between-group improvements in quality of life[43,52] and two intervention also showed within-group improvements in quality of life[50,51].

Discussion

This is the first systematic review and meta-analysis to analyse the key characteristics of the nutrition care plan, apart from adjunctive lifestyle interventions (i.e. with psychology, exercise or meditation), on CRF and quality of life in cancer. Results from this systematic review and meta-analysis demonstrate no definitive effect of nutrition therapy on CRF (SMD 0·18 (95 % CI –0·02, 0·39)) or quality of life (SMD 0·07 (95 % CI –0·10, 0·24)) in people with cancer and cancer survivors. Preliminary evidence indicates dietary pattern interventions aiming to improve fruits (2 serves/d) and vegetables (serves/d)[48], an anti-inflammatory dietary pattern high in fruits (2 serves/d), vegetables (5 serves/d), nuts and seeds (2 serves/d), and fish (1 serve/d)[54] may improve CRF (SMD 0·62 (95 % CI 0·10, 1·15)). Interventions improving nutritional status through the PGSGA showed improvements in quality of life and should be a future research priority. Differences in methodological design, nutrition therapies and reporting of data in the dietetic literature impede conclusive findings regarding the efficacy of nutrition therapy on CRF and quality of life. There was a low number of participants in studies assessing CRF and only one intervention was designed with CRF as the primary outcome measure. In addition, the limited reporting of adherence or dietary outcomes in the literature limits practical recommendations specific to cancer types. In turn there is insufficient evidence to determine the optimal nutrition care plan (consult frequency, duration, mode and length) or nutrition therapy (energy, protein or dietary pattern) for outcomes of CRF or quality of life.

Cancer-related fatigue and key nutrition care parameters

There is a clear lack of dietetic interventions that effectively improve CRF, with only one of eight interventions (13 %) reporting a between-group improvement compared with usual care[54]. The lack of specificity of nutrition therapy studies targeting improvements in CRF is highlighted by the fact that only one of eight interventions that explored the efficacy of nutrition therapy included CRF as the primary outcome[54], and there was a small sample size among the included interventions (range 30[54]–125[42]). The one intervention by Zick *et al.*[54] with CRF

as a primary outcome demonstrated between-group improvements compared with the usual care monitoring group, and combined with other interventions that aimed to increase dietary patterns of fruits and vegetables[48], collectively offer promising results for future interventions focusing on CRF in cancer survivors (SMD 0·62 (95 % CI 0·10, 1·15). Whilst the number of studies investigating dietary pattern nutrition therapies are limited, these results suggest future research is needed in larger RCT, to elucidate these findings and improve the nutrition literature in CRF.

CRF outcomes from Zick *et al.*[54] intervention indicated changes in dietary pattern composition (high in fruits, vegetables, fish and nuts and seeds) may be more important than focusing on total energy and/or protein prescriptions[50,51] for generating benefits in CRF. This is demonstrated by Zick *et al.*[54] intervention group showing between-group improvements ($P<0·05$) in dietary patterns of fruits, vegetables, fish and nuts and seeds compared with the control group after 12 weeks, whilst energy intake was similar across both groups. High adherence to the prescribed dietary patterns in the intervention by Zick *et al.*[54] may also explain why similar improvements in CRF were not seen in the study by Paxton *et al.*[48], where there was no between-group changes in fruit ($P=0·889$) or vegetable ($P=0·271$) intake. Whilst these two dietary pattern interventions had similar fruit (2 serves/d) and vegetable (5 serves/d) prescriptions for people with cancers of the breast[54] and ovaries[48], Zick *et al.*[54] also prescribed foods with high anti-inflammatory properties such as fish (1 serve/d) and nuts and seeds (1 serve/d). The difference seen between study inclusion criteria may also, at least in part, explain the differences seen in CRF between breast[54] and ovaries cancer[48]. Further, Zick *et al.*[54] only included CRF symptomatic breast cancer survivors, whilst Paxton *et al.*[48] reported CRF as a tertiary measure with no CRF-specific study inclusion criteria.

Insights from Bower *et al.*[18,20] suggest the associated CRF-physiological pathways appear to be alterations in inflammatory biomarker and anthropometrical parameters (body mass and composition) from the cancer stage, type or treatment. Whilst Zick *et al.*[54] demonstrated significant between-group improvements ($P<0·001$) in CRF, the absence of measurements of inflammatory biomarkers or anthropometrical parameters limits exploration of the physiological effects of dietetic intervention on CRF. Furthermore, zero studies included in this systematic review measured CRF-associated inflammatory markers (e.g. IL-6 or -8 or TNF-α), highlighting a clear need for further research in this area. Zero interventions measured change in body composition, which also limits our understanding of the effectiveness of nutrition therapy for counteracting the physical deconditioning associated with CRF. Conversely, the results from Zick *et al.*[54] may only be applicable to overweight breast cancer survivors, and in turn further investigations are needed to determine whether a similar dietary pattern is effective in reducing CRF in well-nourished cancer survivors or in patients undergoing treatment. Elucidating the efficacy of dietetic interventions on these CRF pathways offers novel and clinically relevant outcomes for dietetic healthcare management of CRF.

Nutrition therapy and quality of life

The current European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines for cancer survivors recommend nutrition therapy to be included in the clinical management of oncology patients, with the aim to improve nutritional intake (i.e. energy, protein), maintain skeletal muscle mass, reduce treatment-related side effects, and in turn improve quality of life[32]. The current research in dietetic oncology predominantly focuses on improving the nutrition-related response to treatment (i.e. reducing malnutrition, nausea and early satiety); whilst this is of high clinical importance, this systematic review suggests the majority (86 %) of dietetic interventions measuring quality of life failed to find improvements relative to usual care or a comparison/usual care group, and collectively the pooled effects of nutrition therapy interventions showed no apparent effects on quality of life (SMD 0·07 (95 % CI –0·10, 0·24)). Body mass loss during cancer treatment is associated with decrements in quality of life[58], and in a clinical context, maintaining body mass is identified in the ESPEN guidelines as one of many clear nutrition-related goals for preventing malnutrition[32]. The majority (60 %) of interventions from this systematic review failed to improve body mass compared with a comparison or usual care, which may in part explain the minimal changes also seen in quality of life from the published literature. Total energy and protein intake is central to mitigating body mass and composition wasting in cancer patient; however, nutrition interventions showing between-group improvements in energy and protein compared with a usual care or comparison group[43,46,50,51,53], did not necessarily improve body mass from the intervention[43]. Furthermore, nutrition therapy appears to maintain body mass during cancer treatment consistent with the ESPEN guidelines; however, maintenance of body mass may not be a surrogate marker for improving quality of life.

Cancer patients have elevated energy and protein requirements from the metabolic derangements from both the tumour and cancer treatment[59,60]; thus, it is of high clinical importance to increase both energy and protein to address these metabolic demands and avoid potential treatment-related side effects associated with reductions in quality of life. Results from this systematic review suggest nutrition therapy is successful in improving energy and protein intake in cancer patients, with four out of the five interventions showing between-group improvements in protein and energy intake and also showing between-[43] or within-[46,50,51] group improvements in quality of life. Protein intake is of high clinical importance during cancer treatment to avoid protein catabolism from muscle mass and cancer-related malnutrition[32]; both of which are associated with reduced quality of life[61]. Whilst energy prescription was similar between all four interventions, protein prescription in the study by Isenring *et al.*[43] (1·2–1·5 g/kg per d) was higher compared with the other interventions of 0·8–1·0 g/kg per d[50,51], and 1·0–1·2 g/kg per d[46], and in part may explain the between-group improvements seen in quality of life from this intervention. Furthermore, clinically significant improvements in fat-free mass were observed in the intervention by Isenring *et al.*[43]; this may warrant future inclusion of physical functioning parameters into nutrition therapy investigations

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with cancer patients. Further exploration is necessary to determine the optimal protein requirements for mitigating muscle deconditioning during cancer treatment and the associated impact on quality of life.

Validated nutrition assessments, such as the PGSGA[57] or the recommendations to assess nutrition status by Kubrak & Jensen[62], determine changes in nutrition status by assessing anthropometrical parameters (body mass, subcutaneous fat and muscle wasting), symptoms impacting eating, functional status and the metabolic stress of the disease. Such tools may, in turn, be useful for isolating nutritional factors associated with improvements in the quality of life of cancer patients. When using a nutrition assessment tool, clinicians should start with a valid/reliable tool, then ensure the tool addresses cancer-specific nutritional concerns. The PGSGA is recommended in the ESPEN guidelines to be utilised by all dietitians in oncology to inform the nutrition care plan[32]. However, to date, systematic exploration of the PGSGA and quality of life in cancer patients has yet to be investigated. Successful interventions showing between-group improvements in the PGSGA (66 %) also showed between-[44,52] and within-group[50,51] improvements in quality of life, further highlighting the importance of the PGSGA to inform the nutrition care plan. Minimising patient eating difficulties from cancer treatment is thought to be one strategy to improve quality of life during cancer treatment[63], and in turn, all interventions reducing nutrition-related difficulties (i.e. nausea, vomiting, swallowing) were associated with improvements in quality of life[50–52]. In a clinical context, nutrition assessment tools can offer flexibility for different cancer patients, treatments and side effects to direct a patient-centred nutrition care process to improve quality of life. However, considering the majority (60 %) of studies in this systematic review failed to use a nutrition assessment tool, it is imperative future interventions consider the ESPEN guidelines and utilise the PGSGA, or another nutrition assessment tool, to identify patients at nutritional risk and inform the nutrition intervention.

Key parameters of the nutrition care plan were well reported in the studies included in this systematic review. Three of four 12-week interventions showed between-[43] or within-group[50,51] improvements in quality of life, whilst only two of seven interventions longer than 12 weeks showed between-group[52] or within-group[46] improvements. All three interventions utilising face-to-face consults showed within-group improvements in quality of life[46,49,50], whilst no between- or within-group differences were found with telephone or Internet interventions. There appeared to be minimal influence of the frequency of nutrition therapy delivery, with three of six interventions using weekly consults reporting between-[52] or within-group[50,51] improvements in quality of life. In contrast, the duration of nutrition consults was scarcely reported and impeded comparative analysis.

Limitations

Several methodological issues were identified among the included studies which confound the ability to explore relationships between various study variables and CRF or quality of life. The heterogeneity seen among the interventions in length of time, the duration of nutrition therapy consults, frequency and mode of consults (i.e. group-based, face-to-face), nutrition therapies (i.e. dietary requirements of energy, protein, dietary pattern interventions, weight loss interventions), compounded by the low number of articles included in this review, limits recommendations for clinical practice from this systematic review and meta-analysis. CRF was the primary outcome in only one intervention, and the low number of participants in each study suggests further investigations are needed to describe the potential effect of nutrition therapy on CRF. Furthermore, eight different cancers were included across fifteen interventions, which further limits any cancer-specific nutrition therapy recommendations for CRF and quality of life.

Nutrition guidelines for cancer survivors recommend dietary induced weight loss to achieve a healthy BMI for improved quality of life[33], however the literature to date offers minimal recommendations for clinical practice to achieve this per cancer type. Whilst some cancer (i.e. breast and prostate) treatments may induce weight gain, only two interventions[41,42] explored weight loss nutrition therapy on CRF and quality of life across breast and mixed cancer types. Interventions aiming to improve total energy and protein intake to avoid body mass loss were well described, however the reporting of dietary pattern and food group analysis was scarce across the literature, limiting the identification of relationships between dietary outcome characteristics with CRF and quality of life. The lack of reporting of dietary adherence was also a caveat in the literature, with only four of fifteen interventions reported adherence to the nutrition intervention[39,45,48,54]. Future nutrition investigations should include nutrition adherence measures (i.e. 24 h diet recalls or dietary pattern (serves/d)) to evaluate the feasibility and efficacy of prescriptive nutrition therapy on outcomes of CRF and quality of life. Approximately half (53 %) of the included studies did not blind data collectors, which may have confounded the accuracy of diet histories.

Limitations were also seen in the reporting of data for meta-analysis. The number of articles included for CRF and quality-of-life analysis was also fewer than ten studies, and as such this study could not perform funnel plots asymmetry of publication bias[64]. Both Ravasco *et al.*[50,51] studies showed within-group improvements in CRF and within-group improvements in CRF; however, neither study reported measures of error in CRF and thus could not be included in the meta-analysis. Similarly for quality of life, Isenring *et al.*[44] and Ravasco *et al.*[50,51] showed between- and within-group improvements in quality of life but were not eligible for inclusion in the meta-analysis because neither study reported measures of error.

Future recommendations

Interventions specifically targeting oncology patients experiencing high levels of CRF will further strengthen the body of literature in dietetic oncology by limiting the ceiling effect of the CRF questionnaires. To establish comparative literature, future investigations require the inclusion of consistent and valid measures of CRF and quality of life. Results from this systematic review and meta-analysis revealed a large variety of CRF and

quality-of-life measures are being used, and as such harmony is needed in these assessment measures. Future interventions should consider only using reliable and validated measures of CRF and quality of life; and from these questionnaires it is essential to select the tool that is best suited for the cancer population and the specific research question. The FACT-fatigue[65] offers high internal consistency[66] and should be considered for future investigations in nutrition therapy on CRF. The FACT and EORTC quality-of-life tools are cancer specific, which should be utilised over generic quality-of-life measures.

Future interventions should investigate the potential CRF benefits of a high anti-inflammatory dietary pattern in different cancer types and treatments to determine the application of the dietary pattern across multiple oncological populations. Measuring diet changes through the Dietary Inflammatory Index[67] may provide further insight to the efficacy of dietary therapy in CRF. Isolating and identifying the effects of nutrition therapy on biomarkers (i.e. inflammatory markers, body composition change) potentially associated with CRF will inform targeted dietetic literature and applied practice. Considering CRF as a treatment-related side effect, future interventions should also consider using the nutrition assessment tools, such as the PGSGA, and nutrition screening recommendations by Kubrak & Jensen[62] to assess nutritional risk in CRF symptomatic patients.

Future investigation of all key parameters of the intervention is necessary (consult frequency, length, duration and mode) to inform the structure of the nutrition therapy. Future interventions should consider the importance of the timing of nutrition therapy (i.e. pre-, during- or post-treatment) to counteract treatment-related side effects and potentially improve quality of life. Quality (biologically available) and timing of protein, similar to that recommended in the dietetic and cancer cachexia literature[68,69], may offer novel insight to maintaining lean muscle, considering the anabolic demand from cancer-induced muscle wasting and potentially improving quality of life. In turn, future investigations are necessary to determine the optimal hypermetabolic energy and protein requirements on body composition and quality of life in cancer patients.

Conclusion

Systematic exploration of the available literature revealed dietetic intervention has no definitive benefit on CRF or quality of life in people with cancer and cancer survivors. Preliminary evidence indicates dietary pattern interventions high in fruit, vegetables, fish, nuts and seeds may improve CRF. This systematic review suggests assessing nutrition status through the PGSGA, to inform the nutrition therapy positively influences quality of life in cancer patients. Methodological caveats in the dietetic literature reveal heterogeneous reporting of nutrition therapy (i.e. dietary pattern, energy and protein requirements), length of interventions, duration, frequency and mode of consults, which limit the ability to ascertain whether dietetic interventions can improve CRF and/or quality of life. Furthermore, the low number of participants seen in the CRF literature, along with only one intervention with CRF as a primary outcome, suggests there is currently limited evidence exploring the potential effect of nutrition therapy on CRF. Harmony in CRF and quality-of-life tools are needed, with consistent and clear detail in the nutrition interventions, and adherence to dietary recommendations, to identify the optimal nutrition therapy for improving CRF and quality of life in cancer patients and survivors.

Acknowledgements

No external funding was received to support this work.

B. J. B., T. L. S. and O. R. L. W. were each responsible for the conception and design of the study. B. J. B. was responsible for the literature search, and B. J. B. together with O. R. L. W. screened for final inclusion of the articles. B. J. B. was responsible for data synthesis. B. J. B. wrote and edited the manuscript, with both T. L. S. and O. R. L. W. revising and editing the manuscript.

The authors have no relevant interests to declare.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711451800363X

References

1. Bluethmann SM, Mariotto AB & Rowland JH (2016) Anticipating the "Silver Tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev* **25**, 1029–1036.
2. Australian Institute of Health and Welfare (2017) *Australian Cancer Incidence and Mortality*. Canberra: AIHW.
3. American Cancer Society (2014) *Cancer Treatment and Survivorship Facts and Figures 2014-2015*. Atlanta: American Cancer Society.
4. Wang XS, Zhao F, Fisch MJ, *et al.* (2014) Prevalence and characteristics of moderate-to-severe fatigue: a multicenter study in cancer patients and survivors. *Cancer* **120**, 425–432.
5. Servaes P, Verhagen S & Bleijenberg G (2002) Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol* **13**, 589–598.
6. Weis J (2011) Cancer-related fatigue: prevalence, assessment and treatment strategies. *Expert Rev Pharmacoecon Outcomes Res* **11**, 441–446.
7. Cella D, Peterman A, Passik S, *et al.* (1998) Progress toward guidelines for the management of fatigue. *Oncology (Williston Park)* **12**, 369–377.
8. Hofman M, Ryan JL, Figueroa-Moseley CD, *et al.* (2007) Cancer-related fatigue: the scale of the problem. *Oncologist* **12**, Suppl. 1, 4–10.
9. Henry DH, Viswanathan HN, Elkin EP, *et al.* (2008) Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. *Support Care Cancer* **16**, 791–801.
10. Nelson AM, Gonzalez BD, Jim HS, *et al.* (2016) Characteristics and predictors of fatigue among men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. *Support Care Cancer* **24**, 4159–4166.
11. Servaes P, Verhagen S, Schreuder HW, *et al.* (2003) Fatigue after treatment for malignant and benign bone and soft tissue tumors. *J Pain Symptom Manage* **26**, 1113–1122.

British Journal of Nutrition

12. Storey DJ, McLaren DB, Atkinson MA, *et al.* (2012) Clinically relevant fatigue in men with hormone-sensitive prostate cancer on long-term androgen deprivation therapy. *Ann Oncol* **23**, 1542–1549.
13. Langston B, Armes J, Levy A, *et al.* (2013) The prevalence and severity of fatigue in men with prostate cancer: a systematic review of the literature. *Support Care Cancer* **21**, 1761–1771.
14. Olson K, Krawchuk A & Quddusi T (2007) Fatigue in individuals with advanced cancer in active treatment and palliative settings. *Cancer Nurs* **30**, E1–E10.
15. Groenvold M, Petersen MA, Idler E, *et al.* (2007) Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. *Breast Cancer Res Treat* **105**, 209–219.
16. National Cancer Institute (2015) *Strategic Priorities: Symptom Management and Quality of Life Steering Committee*. Bethesda, MD: National Institutes of Health.
17. Berger AM, Mooney K, Alvarez-Perez A, *et al.* (2015) Cancer-related fatigue, version 2.2015. *J Natl Compr Canc Netw* **13**, 1012–1039.
18. Bower JE, Ganz PA, Tao ML, *et al.* (2009) Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin Cancer Res* **15**, 5534–5540.
19. Berger AM, Abernethy AP, Atkinson A, *et al.* (2010) Cancer-related fatigue. *J Natl Compr Canc Netw* **8**, 904–931.
20. Bower JE & Lamkin DM (2013) Inflammation and cancer-related fatigue: mechanisms, contributing factors, and treatment implications. *Brain Behav Immun* **30**, S48–S57.
21. Baguley BJ, Bolam KA, Wright ORL, *et al.* (2017) The effect of nutrition therapy and exercise on cancer-related fatigue and quality of life in men with prostate cancer: a systematic review. *Nutrients* **9**, 1003–1033.
22. Mustian KM, Alfano CM, Heckler C, *et al.* (2017) Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncol* **3**, 961–968.
23. Mustian KM, Sprod LK, Janelsins M, *et al.* (2012) Exercise recommendations for cancer-related fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction: a review. *Oncol Hematol Rev* **8**, 81–88.
24. Blanchard CM, Courneya KS & Stein K (2008) Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. *J Clin Oncol* **26**, 2198–2204.
25. Guest DD, Evans EM & Rogers LQ (2013) Diet components associated with perceived fatigue in breast cancer survivors. *Eur J Cancer Care (Engl)* **22**, 51–59.
26. Alfano CM, Day JM, Katz ML, *et al.* (2009) Exercise and dietary change after diagnosis and cancer-related symptoms in long-term survivors of breast cancer: CALGB 79804. *Psychooncology* **18**, 128–133.
27. Alfano CM, Imayama I, Neuhouser ML, *et al.* (2012) Fatigue, inflammation, and omega-3 and omega-6 fatty acid intake among breast cancer survivors. *J Clin Oncol* **30**, 1280–1287.
28. Reinertsen KV, Cvancarova M, Loge JH, *et al.* (2010) Predictors and course of chronic fatigue in long-term breast cancer survivors. *J Cancer Surviv* **4**, 405–414.
29. Winters-Stone KM, Bennett JA, Nail L, *et al.* (2008) Strength, physical activity, and age predict fatigue in older breast cancer survivors. *Oncol Nurs Forum* **35**, 815–821.
30. Neefjes ECW, van den Hurk RM, Blauwhoff-Buskermolen S, *et al.* (2017) Muscle mass as a target to reduce fatigue in patients with advanced cancer. *J Cachexia Sarcopenia Muscle* **8**, 623–629.
31. Kassianos AP, Raats MM, Gage H, *et al.* (2015) Quality of life and dietary changes among cancer patients: a systematic review. *Qual Life Res* **24**, 705–719.
32. Arends J, Bachmann P, Baracos V, *et al.* (2017) ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* **36**, 11–48.
33. Rock CL, Doyle C, Demark-Wahnefried W, *et al.* (2012) Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin* **62**, 242–274.
34. Moher D, Liberati A, Tetzlaff J, *et al.* (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* **8**, 336–341.
35. Mahan LK & Raymond JL (2017) *Krause's Food & the Nutrition Care Process*. Maryland Heights, MO: Elsevier Saunders.
36. The Cochrane Collaboration (2014) *Review Manager (RevMan) [Computer program]. Version 5.3*. Copenhagen: The Nordic Cochrane Centre.
37. Higgins J & Green S (editors) (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). http://handbook.cochrane.org (accessed October 2018).
38. Academy of Nutrition and Dietetics (2016) *Evidence Analysis Libaray: Steps in the Academy Evidence Analysis Process*. Chicago, IL: Academy of Nutrition and Dietetics.
39. Baldwin C, Spiro A, McGough C, *et al.* (2011) Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. *J Hum Nutr Diet* **24**, 431–440.
40. Brown L, Capra S & Williams L (2008) A best practice dietetic service for rural patients with cancer undergoing chemotherapy: a pilot of a pseudo-randomised controlled trial. *Nutr Diet* **65**, 175–180.
41. Darga LL, Magnan M, Mood D, *et al.* (2007) Quality of life as a predictor of weight loss in obese, early-stage breast cancer survivors. *Oncol Nurs Forum* **34**, 86–92.
42. Gnagnarella P, Misotti AM, Santoro L, *et al.* (2016) Nutritional online information for cancer patients: a randomized trial of an internet communication plus social media intervention. *J Cancer Educ* **31**, 472–480.
43. Isenring EA, Bauer JD & Capra S (2007) Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients improves dietary intake compared with standard practice. *J Am Diet Assoc* **107**, 404–412.
44. Isenring EA, Capra S & Bauer JD (2004) Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* **91**, 447–452.
45. Kiss N, Isenring E, Gough K, *et al.* (2016) Early and intensive dietary counseling in lung cancer patients receiving (chemo) radiotherapy – a pilot randomized controlled trial. *Nutr Cancer* **68**, 958–967.
46. Ovesen L, Allingstrup L, Hannibal J, *et al.* (1993) Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *J Clin Oncol* **11**, 2043–2049.
47. Pakiz B, Flatt SW, Mills KC, *et al.* (2005) Quality of life and diet intervention in individuals at risk for recurrence of colorectal adenomas. *Psychooncology* **14**, 85–93.
48. Paxton RJ, Garcia-Prieto C, Berglund M, *et al.* (2012) A randomized parallel-group dietary study for stages II–IV ovarian cancer survivors. *Gynecol Oncol* **124**, 410–416.
49. Persson CR, Johansson BB, Sjöden PO, *et al.* (2002) A randomized study of nutritional support in patients with colorectal and gastric cancer. *Nutr Cancer* **42**, 48–58.
50. Ravasco P, Monteiro-Grillo I, Marques Vidal P, *et al.* (2005) Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck* **27**, 659–668.

British Journal of Nutrition

51. Ravasco P, Monteiro-Grillo I, Vidal PM, *et al.* (2005) Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol* **23**, 1431–1438.
52. Silvers M, Savva J, Huggins C, *et al.* (2015) Exploring potential benefit of earlier nutritional interventions in adults with upper gastrointestinal cancer: a randomised trial. *Support Care Cancer* **23**, S172–S173.
53. Uster A, Ruefenacht U, Ruehlin M, *et al.* (2013) Influence of a nutritional intervention on dietary intake and quality of life in cancer patients: a randomized controlled trial. *Nutrition* **29**, 1342–1349.
54. Zick SM, Colacino J, Cornellier M, *et al.* (2017) Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial. *Breast Cancer Res Treat* **161**, 299–310.
55. American Dietetic Association (2008) *ADA Evidence Analysis Manual, Steps in the ADA Evidence Analysis Process*. Chicago, IL: Academy of Nutrition and Dietetics.
56. Nordic Nutrition Recommendations (2004) *Integrating Nutrition and Physical Activity*. Copenhagen: Nordic Council of Ministers.
57. Ottery FD (1996) Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* **12**, Suppl. 1, S15–S19.
58. Dewys WD, Begg C, Lavin PT, *et al.* (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* **69**, 491–497.
59. Fearon K, Strasser F, Anker SD, *et al.* (2011) Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* **12**, 489–495.
60. Muscaritoli M, Anker SD, Argilés J, *et al.* (2010) Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* **29**, 154–159.
61. Lis CG, Gupta D, Lammersfeld CA, *et al.* (2012) Role of nutritional status in predicting quality of life outcomes in cancer – a systematic review of the epidemiological literature. *Nutr J* **11**, 27–27.
62. Kubrak C & Jensen L (2007) Critical evaluation of nutrition screening tools recommended for oncology patients. *Cancer Nurs* **30**, E1–E6.
63. Capra S, Bauer J, Davidson W, *et al.* (2002) Nutritional therapy for cancer-induced weight loss. *Nutr Clin Pract* **17**, 210–213.
64. Sterne JAC, Sutton AJ, Ioannidis JP, *et al.* (2011) Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* **343**, d4002.
65. Yellen SB, Cella DF, Webster K, *et al.* (1997) Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage* **13**, 63–74.
66. Cella D, Eton DT, Lai JS, *et al.* (2002) Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* **24**, 547–561.
67. Shivappa N, Steck SE, Hurley TG, *et al.* (2013) Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* **17**, 1689–1696.
68. Gullett NP, Mazurak VC, Hebbar G, *et al.* (2011) Nutritional interventions for cancer-induced cachexia. *Curr Probl Cancer* **35**, 58–90.
69. Aoyagi T, Terracina KP, Raza A, *et al.* (2015) Cancer cachexia, mechanism and treatment. *World J Gastrointest Oncol* **7**, 17–29.

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