BMJ Oncology

Elucidating the mechanisms of lifestyle interventions in mitigating radiotherapy adverse effects: a scoping review

Oliver Chalmers,[1] Alex Waddell,[2,3] Ananya Choudhury,[4,5] Craig Sale,[1] Amy E Harwood [1]

To cite: Chalmers O, Waddell A, Choudhury A, *et al*. Elucidating the mechanisms of lifestyle interventions in mitigating radiotherapy adverse effects: a scoping review. *BMJ Oncology* 2025;**4**:e000615. doi:10.1136/bmjonc-2024-000615

Received 30 September 2024
Accepted 23 June 2025

[1]Department of Sport and Exercise Sciences, Institute of Sport, Manchester Metropolitan University, Manchester, UK
[2]Centre for Physical Activity, Sport and Exercise Sciences, Coventry University, Coventry, UK
[3]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK
[4]Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK
[5]Division of Cancer Sciences, The University of Manchester, Manchester, UK

Correspondence to
Dr Amy E Harwood;
A.Harwood@mmu.ac.uk

ABSTRACT

The aim of this work was to review the literature on the mechanisms by which lifestyle interventions attenuate radiation therapy-induced side effects. A scoping review based on the Joanna Briggs Institute methodological framework was undertaken. MEDLINE, CINAHL and CENTRAL were searched up until 13 March 2024. Studies assessing the potential mechanistic effects of lifestyle interventions on outcomes in adult (>18 years of age) cancer patients undergoing radiotherapy, including any cancer type or intervention timing (before, during, after radiotherapy), were included. Data were extracted regarding study design, intervention characteristics and included outcome measures. Nine studies were included in the review. Study populations included patients with a range of cancers, including head and neck, prostate, breast, lung, lower gastrointestinal, rectal, pelvic and leukaemia. Lifestyle interventions consisted primarily of nutritional supplements, diets or traditional Chinese medicinal ingredients. Exercise programmes were also included. Those that were available involved either resistance training alone or in combination with aerobic exercise. The most common side effects included site-specific toxicity, with some interventions noting improvements to symptoms, alongside alterations to inflammatory cytokine and lymphocyte concentrations. Radiation-induced weight loss and frailty were noted, which may be prevented with interventions that target skeletal muscle metabolism. With more research to fully elucidate the potential mechanisms and consistent evidence of efficacy, lifestyle interventions may present promising non-pharmacological therapeutic options to alleviate some of the side effects of radiotherapy.

INTRODUCTION

Radiotherapy (RT) stands as a cornerstone in the treatment against cancer, offering a means of tumour control and symptom relief.[1] Around 50% of individuals with cancer receive RT over the course of their illness,[2] with its utility both curative and palliative. In contrast to drug-based systemic chemotherapy or immunotherapy, which affects the whole body, RT is a localised treatment where the tumour-destroying effect is focused on a specific area, referred to as the radiation field. RT acts to destroy cancer cells through ionising or particle radiation, a mechanism that damages cell DNA causing the cells to stop dividing or die.

Despite its efficacy, RT is accompanied by a spectrum of adverse effects that can significantly impact patients' quality of life (QoL). Complications resulting from radiation toxicity can occur and predominantly impact the site of radiation.[3] Systematic effects, such as debilitating fatigue, nausea and weakness, are also common side effects of RT.[4] Both systemic and local adverse effects resultant from RT can induce weight loss, exhaustion and physical deconditioning. The term cancer-related fatigue (CRF) is also used, which encompasses the physical, emotional and cognitive fatigue associated with cancer and cancer treatment.[5] These adverse effects not only compromise patients' QoL but can also lead to treatment interruptions and dose reductions, potentially impacting treatment efficacy.

In light of this, there arises a need to explore complementary strategies that can attenuate these adverse effects. Lifestyle interventions, such as exercise and nutrition, have garnered increasing attention in this context, with a growing body of evidence suggesting their potential to mitigate the burdensome side effects associated with RT.[6–9] Studies have demonstrated that tailored exercise regimens can alleviate fatigue, improve functional capacity and mitigate muscle wasting in patients with cancer undergoing RT.[6 9] Similarly, dietary interventions focusing on optimising nutritional status or supplementation and minimising inflammation have shown promise in reducing the severity of gastrointestinal symptoms and enhancing tissue repair following radiation exposure.[8]

Despite this, the mechanisms underlying the beneficial effects of these interventions remain incompletely understood. Where

work has presented mechanistic understanding of the effect of lifestyle interventions, they have often not distinguished between treatment modality.[10 11] Given that RT is a localised treatment, with its own spectrum of local and systemic side effects, it may not be comparable to other cancer-related therapies.

The purpose of this scoping review is to identify the potential mechanisms through which lifestyle interventions may alleviate potential side effects in the context of RT, via a comprehensive evaluation of the available literature. By elucidating how interventions interact with the biological pathways affected by RT, we can gain insights into how they attenuate radiation-induced effects and optimise their implementation in clinical practice. The work seeks to address this gap by synthesising existing literature on the topic, with the aim of informing future research directions and enhancing patient care in the context of cancer treatment.

MATERIALS AND METHODS

Protocol and registration

We conducted a scoping review in line with the methodological framework of the Joanna Briggs Institute (JBI),[12] following five key stages: (1) identifying the research questions; (2) identifying the relevant studies; (3) selecting the studies; (4) charting the data and (5) collating, summarising and reporting the results. An a priori draft review protocol was developed and then revised on receiving feedback from the research team. The final version of the protocol was published on the Open Science Framework and is available at: https://doi.org/10.17605/OSF.IO/HRCTX. Findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA) checklist.[13]

Eligibility criteria

We sought to summarise studies that explored or evaluated local mechanistic processes of lifestyle interventions on the effects associated with radio-therapeutic treatments. We considered studies that explored mechanisms related to a range of RT toxicity associated outcomes such as CRF, physical function (strength, mobility), QoL, gastrointestinal issues and mucositis. Sources of evidence pertaining to any contextual setting, that is, health setting, country or health system were eligible for inclusion. In addition, mechanistic studies that applied interventions either prior (prehabilitation), during and/or post treatment were all considered.

Study participants were individuals with a diagnosis of cancer who had received RT of any type and were at least 18 years old. All types and stages of cancer were considered. We excluded studies that included individuals who had undergone chemotherapy, hormone therapy or immunotherapy only and did not have RT as the primary treatment. Surgical treatment was not an exclusion criterion.

Information sources

An initial limited search of CINAHL and PubMed was undertaken to identify articles on the topic. In addition, a limited search of the Cochrane Database for systematic reviews was also undertaken. The text words contained in the titles and abstracts of relevant articles, the index terms used to describe the articles, and adapting existing search strategies from systematic reviews within the field were used to develop a full search strategy for CINAHL (EBSCO) (see online supplemental appendix 1). The search strategy was reviewed by AH and OC and refined following the identification of syntax errors (online supplemental appendix 2). The revised search strategy was then adapted for MEDLINE (PubMed) and Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library). The final searches were conducted on 13 March 2024.

Published (peer-reviewed) articles in the English language from database conception to March 2024 were included. No limits were placed on study type. In addition to searching bibliographic databases, reference lists of relevant adjacent reviews were screened for relevant studies. Search results were imported for screening and further reviewing in Covidence systematic review software 2020 (Veritas Health Innovation, Melbourne, Australia) where duplicates were identified and removed.

Search

The search strategy has been included as online supplemental material.

Selection of sources of evidence

Three authors (OC, AH and AW) independently screened titles and abstracts of all retrieved citations against the inclusion and exclusion criteria. If disagreement occurred, consensus was achieved by the final vote of the author yet to screen the respective paper. The full texts of included studies were then further examined for eligibility via the same process.

Data charting process

A data extraction excel spreadsheet was jointly developed by two authors (OC and AH), created in line with the JBI data extraction methodology.[12] The tool was designed to capture relevant information, including key study characteristics and details used to elucidate the effects of the interventions on RT-induced side effects. One author (OC) then independently extracted all prespecified data from each included study, with member checking (AH).

Data items

The following data were extracted from each included study:

1. Author(s).
2. Year of publication.
3. Origin/country of origin (where the source was published or conducted).
4. Aims/purpose.

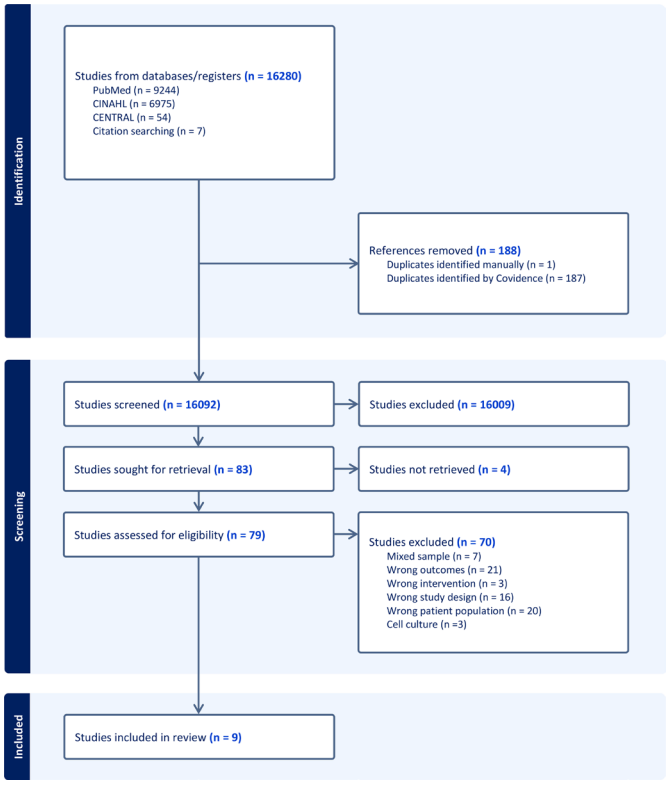

Figure 1 PRISMA diagram—scoping review of interventions for patients undergoing radical radiotherapy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5. Population (cancer type) and sample size within the source of evidence.
6. Methodology/methods.
7. Intervention type and further details (ie, duration, timing, etc).
8. Outcomes and details of these (if measured).
9. Key findings that relate to the scoping review question/s.

Synthesis of results

We grouped the studies by the type of lifestyle intervention they employed (nutritional or exercise). We narratively summarised the content and delivery of interventions for each group, along with the outcomes and main findings in the context of RT-induced side effects.

RESULTS

Selection of sources of evidence

The literature search identified a total of 16 280 papers. Following an additional search of relevant study reference lists, duplicate removal and screening, 78 studies had their full texts examined for eligibility, with 9 being included in the final review. For full details of the search, the PRISMA flow diagram is presented in figure 1.

Characteristics of sources of evidence

General characteristics of the included studies are displayed in table 1. Four of the included studies were randomised controlled trials (RCTs),[14–17] and two were pilots of RCTs.[18 19] The final three studies were a prospective pilot study,[20] a prospective case series[21] and a non-RCT.[22]

Results of sources of evidence

Intervention-specific information for each included study is presented in table 2. Studies included a wide range of cancers, with head and neck, prostate and breast cancers being the most common. Most studies included at least one participant who was receiving concomitant RT alongside either chemo or hormone therapy. Three studies included participants who had received prior surgery,[18 19 23] five did not[14–17 20] and the remaining study did not provide this information.[21] There were seven nutritional interventions,[14–18 21 22] consisting of Chinese/traditional medicine, a nutritional supplement or a diet over the course of treatment. The remaining two studies involved an exercise intervention,[19 20] consisting of either resistance training alone or in combination with aerobic exercise.

RESULTS

Nutritional interventions

A study in head and neck cancer delivered a solution of indigowood root powder and water to be rinsed in the mouth and swallowed three times daily over the course of treatment and showed the grade of site-specific inflammation, mucositis, was reduced compared with the control group.[14] The reduction in symptoms was correlated with lower serum concentrations of the cytokine IL-6. Another trial, in lung cancer, delivering daily rhubarb extract, observed reductions in lung toxicity, which was also correlated with concentrations of IL-6, along with the growth factor TGF-B1.[17] Wedlake *et al*[15] had participants with gastrointestinal cancer consume either a high fibre, low fibre or habitual diet for 5–7 weeks during RT. While gastrointestinal toxicity was reduced, no differences were shown in short-chain fatty acid production, which would have been indicative of an anti-inflammatory response.

Another study of head and neck cancer compared the use of a daily mouth solution of QYN to a placebo over the course of treatment. They noted lower grades of mucositis and elevations of salivary epithelial growth factor in the intervention group compared with the placebo group following treatment.[16] Furthermore, concentrations of CD4 and CD8 T-lymphocytes were elevated compared with the placebo group, indicating an enhanced immune response. Bounous *et al*[22] showed similar findings in those with pelvic malignancies, following the use of an elemental diet powder consisting of hydrolysed protein, triglycerides and carbohydrates. Compared with a control group following what the authors only describe as a 'normal diet', the intervention group demonstrated elevations in immunoglobulin concentrations, and a blunted decline in lymphocyte levels following RT. This was paired with reductions in the incidence of diarrhoea.

Table 1 Study characteristics of the included studies in the scoping review

Study	Country	Design	Cancer treatment	Sample size (n)	Intervention group		Control group	
					Age, years±SD	Sex, female n (%)	Age, years±SD	Sex, female n (%)
You *et al* 2009[14]	Taiwan	RCT	Concomitant chemotherapy	20 (11 intervention, 9 control)	56±11	2 (18)	58±13	0 (0)
Wedlake *et al* 2017[15]	UK	RCT	Concomitant chemotherapy	166 (55 intervention 1, 56 intervention 2, 55 control)	Group 1: 62 (26–91); Group 2: 64 (28–87);	29 (53)	63 (35–88)	32 (58)
Wu *et al* 2007[16]	China	RCT	Radiotherapy alone	60 (30 per group)	52±5.6	15 (50)	49±7.7	13 (43)
Yu *et al* 2008[17]	China	RCT	Concomitant chemotherapy	80 (40 per group)	64.10±6.85	13 (33)	63.03±6.91	9 (23)
Bounous *et al* 1975[22]	Canada	Non-RCT	Radiotherapy alone	18 (9 per group)	58.8±13.2	4 (44)	53.4±14.8	7 (78)
Klementnd and Sweeney[21]	Germany	Prospective case series	Concomitant chemotherapy or hormonotherapy	6	60.3±14.3	2 (33)	NA	NA
Lonkvist *et al* 2017[20]	Denmark	Prospective pilot study	Concomitant chemotherapy	12	56 (27–66)	5 (42)	NA	NA
Saadipoor *et al* 2019[18]	Iran	RCT pilot	Adjuvant hormone therapy	64 (31 placebo, 33 intervention)	69±8.6	NA	71.5±7.3	NA
Sprod *et al* 2010[19]	USA	RCT pilot	Adjuvant hormone therapy	38 (19 exercise, 19 control)	55.6±13.7	19 (100)	63.3±9.4	19 (100)

NA, not available; RCT, randomised controlled trial.

Table 2 Intervention characteristics for the included studies in the scoping review

Study	Intervention	Time and duration	Control	Key findings
You *et al* 2009[14]	Indigowood root powder solution	3 min 3 times per day before meals for 7 weeks over course of RT	Saline solution	Intervention group had less severe mucositis and this correlated with significantly reduced serum IL-6.
Wedlake *et al* 2017[15]	Low-fibre or high-fibre diet	5–7 weeks over the course of radiotherapy	Habitual diet	High-fibre diet reduced GI toxicity both acutely and at 1 year. However, this did not correlate with increased SCFA production.
Wu *et al* 2007[16]	QYD	28 days over course of RT	Dobell's solution	QRLYS increased EGF concentration in saliva and reduced mucocitis. In addition, QRLYS increased peripheral T-lymphocyte counts.
Yu *et al* 2008[17]	Rhubarb powder	6 weeks over the course of RT	Placebo containing starch	Rhubarb extract reduced RILT and improved pulmonary function. This correlated with significantly lower TGF-B1 and IL-6.
Bounous *et al* 1975[22]	Elemental diet powder dissolved in water	Over the course of RT—time frame not specified	Normal diet	Intervention group had lower incidence of diarrhoea, maintained serum protein and the drop in lymphocytes was significantly less compared with control.
Klement and Sweeney, 2016[21]	Self-administered ketogenic diet	Over the course of RT—ranging from 36 to 73 days	None	Although significant weight loss occurred in some patients, this occurred mainly due to fat mass loss. The diet had no significant impact on blood biomarkers.
Saadipoor *et al* 2019[18]	Nanocurcumin capsule	3 times per day during the course of RT until study endpoint of proctitis development.	Placebo capsule	No significant difference was found between groups for radiation-induced proctitis, cystitis or heamtologic nadirs.
Lonkvist *et al* 2017[20]	Resistance exercises of major muscle groups. 2–3 sets and 15–8 RM, moving from low load/high rep to high load/low rep over the 12 weeks.	12 weeks, 3 times per week (36 sessions)	NA	Functional performance maintained during treatment and increased during follow-up. Strength was regained after an initial dip during treatment and paralleled responses in lean body mass and sarcomere protein content. This correlated with the upregulation of the pentose phosphate pathway.
Sprod *et al* 2010[19]	Instructions to increase daily steps by 5%–20% while performing activity at a moderate intensity. Combined with low to moderate intensity resistance training.	4 week programme, with exercise prescribed daily	Encouragement to remain only as active as they were prior to study inclusion.	There was a greater improvement in sleep quality in the exercise group from preintervention to postintervention, although the difference was not significant. Additionally, there were associations between IL-6 and sleep efficiency/duration.

EGF, epidermal growth factor; GI, gastrointestinal; NA, not available; QRLYS, Qingre Liyan Decoction; QYD, Qingre Liyan Decoction; RILT, radiation induced lung toxicity; RM, repetition maximum; RT, radiotherapy; SCFA, short-chain fatty acid.

Serum total protein (albumin and globulin) was also maintained throughout the intervention in the intervention group, but not in the control condition. Conversely, a randomised, placebo-controlled trial in prostate cancer did not detect any differences in concentrations of lymphocytes, neutrophils, platelets or haemoglobin, nor reductions in the grade of proctitis following oral supplementation of nanocurcumin.[18] Finally, one study had participants consume a ketogenic diet over the course of RT.[21] While weight loss was apparent, this occurred mainly via reductions in fat mass (as measured via bioelectrical impedance), with participants largely maintaining

muscle mass. No differences were, however, shown in blood biomarkers, including markers of insulin signalling or concentrations of cholesterol or triglycerides.

Exercise interventions

Only two studies were included that involved an exercise intervention. The first investigated an exercise intervention among participants with breast or prostate cancer, and outcomes included sleep quality/efficiency/duration and mediators of sleep.[19] The intervention consisted of increasing daily step counts, alongside a 4-week progressive resistance training regime, exercising daily, while the control group maintained their regular lifestyle. Concentrations of IL-6 did not change between baseline and follow-up in either group. However, the exercise group had significantly lower concentrations than the control group postintervention, when adjusting for baseline values and age. Associations were noted between sleep quality and sTNF, and between sleep efficiency and IL-6, which the authors took to indicate that the sleep-mediating cytokines may be moderated by exercise.

The other study recruited participants with head and neck cancer.[20] The intervention involved progressive resistance training, three times per week over the course of 12 weeks. Functional performance was maintained and eventually improved during long-term follow-up. An initial decline in muscular strength and lean body mass during RT was shown, which then recovered following treatment. This was not the case for sarcomeric protein abundance, as differences were not significant. Metabolic pathways were examined with biopsies from the vastus lateralis, via the expression of enzymes involved in glycolysis and the pentose phosphate pathway. The authors report an upregulation of the pentose phosphate pathway at 6 weeks, while the glycolysis pathway was unchanged. However, it is not discernible which enzymes were differentially expressed.

DISCUSSION

This scoping review sought to elucidate the mechanisms by which lifestyle interventions may attenuate RT-induced side effects and to identify gaps in the existing literature. Most included studies comprised nutritional interventions, consisting of either supplementation, traditional Chinese medicine or prescription of specific diets. Exercise programmes were also used, consisting of either resistance training alone, or in combination with aerobic exercise.

Summary of evidence

Site-specific toxicity

Exposure to RT is known to induce a pro-inflammatory tumour microenvironment. It is thought that to drive an immune response, inflammatory cytokines modulate tumour neo-antigen expression, allowing for the targeting of cancerous cells.[23] High doses of ionising radiation can, however, also lead to myriad negative inflammatory-related side effects, such as mucositis, proctitis, pneumonitis and dermatitis.[24] There may also be systemic, non-targeted effects, resulting in chronic, low-grade inflammation, which may inadvertently lead to carcinogenesis.[25 26] There is, therefore, a trade-off between the immuno-stimulatory effects of RT, driving inflammation to promote cancer targeting by the immune system, and the negative side effects of chronic inflammation. Approaches to ameliorate these inflammatory cascades are warranted, with lifestyle interventions becoming a promising avenue for exploration. Nutritional supplements, diets and traditional Chinese medicinal ingredients have shown promise at alleviating inflammation.[27–29] While reductions in the concentration of singular cytokines do not necessarily indicate alleviations in inflammation, studies in the present review have demonstrated alterations in cytokine concentrations alongside reductions in symptoms associated with RT-induced inflammation. While exercise in acute bouts, as with RT, induces a pro-inflammatory environment,[30] long-term exposure to endurance exercise and/or physical activity is known to reduce chronic low-grade inflammation,[31] by stimulating the release of nitric oxide, a potent free radical scavenger, as well as promoting mitochondrial biogenesis to alleviate oxidative stress.[32 33] One study in the present review investigated cytokine concentration following an intervention of aerobic and resistance exercise. While the authors noted significantly lower concentrations of IL-6 in the exercise compared with control group postintervention, neither group significantly changed from baseline.[19] More work is therefore required to clarify whether exercise training can offset radiation-induced inflammation. Given that those who chronically exercise have reduced systemic inflammation, future work should also assess whether those who are active prior to the commencement of RT are protected from ionising radiation-induced inflammation, and thus RT-associated side effects.

The release of inflammatory cytokines because of RT is thought to drive an immune response, thereby reversing the immuno-suppressive tumour microenvironment to target cancer cells.[34] RT can also upregulate immuno-suppressive molecules such as CTLA-4 and PD-1 involved in the DNA damage repair pathway.[35] Increased expression of both CTLA-4 and PD-1 exerts an inhibitory effect on circulating lymphocytes and so are frequently the target of immune checkpoint inhibitors.[36] Lymphopenia, or a reduced number of circulating lymphocytes, can exacerbate cancer-related side effects, diminish survival rates and reduce the effectiveness of RT.[37–39] There is, therefore, a need[40] for interventions or treatment options that enhance lymphocyte production to both improve the effects of RT and elicit positive outcomes. Again, lifestyle interventions present a promising option. Studies in the present review that assessed lymphocyte numbers in response to nutritional interventions demonstrate conflicting findings. This could be explained as lymphocyte distribution throughout the human body is not uniform and varies by organ.[41] Furthermore, the degree of

immune response to RT appears to be dictated by the location of treatment. A meta-analysis of lymphocyte responses to RT showed that in response to radiation, a reduction in T-lymphocytes occurred in head and neck cancer, but not prostate or breast cancer.[42] Among studies included in the present review, lymphocyte numbers and site-specific toxicity improved following a nutritional intervention in a study of head and neck cancer,[16] whereas a study in prostate cancer saw no changes.[18] While this could be due to the difference in supplements used, if lymphocyte numbers do not reduce following RT in prostate cancer, a nutritional supplement is less likely to produce a positive change. One study noted maintenance of lymphocyte numbers when consuming an elemental diet powder,[22] whereas those following what was described as a 'normal diet' experienced declining numbers. The experimental group also experienced less incidence of gastrointestinal toxicity. Diets deficient in protein have previously demonstrated reductions in lymphocyte numbers, which can be overcome with protein supplementation.[43 44] However,[45] the authors stated the protein content of the diet powder in this study was only 8.8%. Despite this, serum protein levels were significantly greater in the intervention group, although the authors did not clarify the macronutrient breakdown in the control group to compare protein intake. Furthermore, both groups had their ideal calorie requirement calculated, with no difference between groups, so the difference shown in lymphocyte numbers is likely not due to discrepancies in calorie intake. Studies comparing varying doses of dietary protein on RT-induced side effects are therefore warranted to confirm whether there is a protective effect of protein intake, and whether this is mediated by lymphocyte concentrations.[3 46–49]

Loss of lean body mass and strength

A common adverse side effect of RT is the progressive loss of lean body mass, leading to muscular weakness, poor QoL and impaired survival.[50 51] Approaches to mitigate such detrimental effects are therefore vital for ensuring superior RT-related outcomes. Both dietary protein intake and resistance exercise are non-pharmacological approaches, known to stimulate muscle protein synthesis, playing a key role in the regulation of lean body mass.[52 53] The studies included herein utilising both nutritional and exercise interventions demonstrated beneficial effects on muscle mass and protein metabolism. A study using a ketogenic diet showed maintenance of lean body mass, while total weight declined.[21] While an emphasis was placed on certain ingredients, the diets were self-administered, with no macronutrient breakdown, and so total protein intake was not discernible. One study showed serum total protein concentrations were reduced over a course of RT while on 'normal diets' but were maintained in those consuming an elemental diet powder with hydrolysed protein, although there was no accompanying data on functional outcomes. Additionally, although there was no information on lean body mass, the control group saw a greater reduction in body weight, despite calorie intake being similar. Furthermore, one study deployed a resistance exercise programme and showed both strength and lean body mass to recover following resistance training.[20] This study also showed an upregulation of enzymes in the pentose phosphate pathway within skeletal muscle biopsies, which plays a key role in anabolism and protecting from oxidative stress.[54] Employing either exercise interventions or dietary changes alongside RT may, therefore, offset some of the detrimental effects of RT and have therapeutic potential in mitigating the occurrence of cancer-related frailty and the resultant impairments to QoL.

Limitations

This review is not without limitations. First, given the nature of the topic area, there was a wide range of cancer subtypes and side effects investigated. This, combined with the diversity of interventions, made direct comparisons between studies difficult. Additionally, the delivery of therapy varied across studies, with some delivering RT alone, while others involved concomitant chemotherapy or hormone therapy, further restricting the comparison of side effects. Only four of the included studies were RCTs,[14–17] meaning possible conclusions regarding the effects of each intervention in the remaining studies are limited. Only two studies[19 20] examined the effects of exercise programmes. As a result, comparisons across different types, durations and intensities of exercise, and whether this influences RT-induced side effects were not possible.

Research gaps

In vitro research into the mechanisms by which RT-induced side effects may be alleviated is well established, for example, with cell culture models identifying affected genetic pathways and associated effects of different lifestyle interventions.[55 56] However, the present review highlights that there is a lack of translational research in this area, with few studies examining potential mechanisms in response to lifestyle interventions in humans. Without statistically powered RCTs, the causality of these mechanisms is unable to be established. While the authors of one of the studies included in the present review[20] had planned to explore their findings further with an RCT, this was terminated prematurely due to poor recruitment.[57] This highlights the challenges of conducting such large-scale trials in these populations.

Furthermore, many of the studies classed as 'nutritional' consisted of supplements at a single dose. Research examining dose responses to these interventions may further our understanding of both potential mechanisms responsible, as well as optimal strategies to alleviate any side effects. Additionally, only three studies investigated specific diets. While supplements allow for a more controlled study (ie, being able to have placebo control), the broader impact of full dietary modifications remains underexplored. The studies in the present review provided no detail on the specific macro and/or micronutrient composition of the diets provided, greatly limiting

our ability to attribute any links to potential mechanisms. While diets rich in protein will inevitably aid in offsetting losses in lean body mass during RT, investigating whether different diets, with detailed macronutrient and micronutrient compositions, influence other RT-induced side effects through distinct biological pathways represents a promising research direction. Such studies could provide more clinically applicable dietary recommendations for patients undergoing RT.

Additionally, while the feasibility and clinical benefits of exercise programmes in patients undergoing cancer treatment are relatively well established, research into the mechanisms offsetting some of the RT-induced side effects is much less extensively reported. Only two studies in the present review explored exercise interventions, none of which had an aerobic-only training programme. To fully determine the mechanisms responsible for alleviating RT-induced side effects, a range of exercise modes and intensities, alongside in vitro/ex vivo data collection, is required. Future research should also explore whether those who are habitually active prior to RT are protected from associated side effects, and, if so, what mechanisms are responsible.

CONCLUSIONS

This scoping review assessed the existing literature regarding whether lifestyle interventions may mitigate RT-induced side effects. We identified some evidence that both nutritional and exercise interventions can attenuate a variety of side effects because of RT. The most common side effects studied included site-specific toxicity and losses in lean body mass and muscle strength. Potential mechanisms by which these were alleviated included alterations to inflammatory cytokine and lymphocyte concentrations, as well as skeletal muscle metabolism. However, to confidently assign causality to these potential mechanisms in these populations, robust RCTs are required. Additionally, future research should explore whether differing doses of supplements, as well as whole-diet changes with varying macronutrient and micronutrient breakdowns, have diverging effects on RT-induced side effects. A wider breadth of research investigating mechanisms by which exercise interventions may alleviate these side effects is also needed, across a range of modes and intensities. Elucidating whether those who are habitually active are protected from RT-induced side effects may also further our understanding of the mechanisms responsible. This could help refine both exercise prescription and nutritional guidance, ensuring that they are optimised to mitigate treatment-related toxicity and potentially enhance patient outcomes.

X Ananya Choudhury @achoud72 and Amy E Harwood @amyharwood91

Contributors Conceptualisation (AH, CS and AC) methodology (OC, AW and AH); data acquisition (OC, AW and AH); data analysis (OC and AW); draft manuscript (OC and AW); final manuscript revisions (all authors). Guarantor: AH.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was not required for this study as it was a scoping review of existing data from the literature.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. All relevant study data are included in the article or uploaded as supplementary information.

ORCID iD

Amy E Harwood http://orcid.org/0000-0002-5745-2564

REFERENCES

1 Thariat J, Hannoun-Levi J-M, Sun Myint A, *et al*. Past, present, and future of radiotherapy for the benefit of patients. *Nat Rev Clin Oncol* 2013;10:52–60.
2 Delaney G, Jacob S, Featherstone C, *et al*. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer* 2005;104:1129–37.
3 De Ruysscher D, Niedermann G, Burnet NG, *et al*. Radiotherapy toxicity. *Nat Rev Dis Primers* 2019;5:13.
4 Hsiao CP, Daly B, Saligan LN. The Etiology and management of radiotherapy-induced fatigue. *Expert Rev Qual Life Cancer Care* 2016;1:323–8.
5 Berger AM, Mooney K, Alvarez-Perez A, *et al*. Cancer-Related Fatigue, Version 2.2015. *J Natl Compr Canc Netw* 2015;13:1012–39.
6 Piraux E, Caty G, Aboubakar Nana F, *et al*. Effects of exercise therapy in cancer patients undergoing radiotherapy treatment: a narrative review. *SAGE Open Med* 2020;8:2050312120922657.
7 Peters MDJ, Marnie C, Tricco AC, *et al*. Updated methodological guidance for the conduct of scoping reviews. *JBI Evid Synth* 2020;18:2119–26.
8 Mercier BD, Tizpa E, Philip EJ, *et al*. Dietary Interventions in Cancer Treatment and Response: A Comprehensive Review. *Cancers (Basel)* 2022;14:5149.
9 Trommer M, Marnitz S, Skoetz N, *et al*. Exercise interventions for adults with cancer receiving radiation therapy alone. *Cochrane Database Syst Rev* 2023;3:CD013448.
10 Wang Q, Zhou W. Roles and molecular mechanisms of physical exercise in cancer prevention and treatment. *J Sport Health Sci* 2021;10:201–10.
11 Zhu C, Ma H, He A, *et al*. Exercise in cancer prevention and anticancer therapy: Efficacy, molecular mechanisms and clinical information. *Cancer Lett* 2022;544:215814.
12 Peters MDJ, Marnie C, Tricco AC, *et al*. Updated methodological guidance for the conduct of scoping reviews. *JBI Evidence Synthesis* 2020;18:2119–26.
13 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169:467–73.
14 You WC, Hsieh CC, Huang JT. Effect of extracts from indigowood root (Isatis indigotica Fort.) on immune responses in radiation-induced mucositis. *J Altern Complement Med* 2009;15:771–8.
15 Wedlake L, Shaw C, McNair H, *et al*. Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal toxicity during pelvic radiotherapy. *Am J Clin Nutr* 2017;106:849–57.

16 Wu M, Yuan B, Liu Q, *et al*. Study of qingre liyan decoction in treating and preventing acute radioactive oral mucositis. *Chin J Integr Med* 2007;13:280–4.
17 Yu HM, Liu YF, Cheng YF, *et al*. Effects of rhubarb extract on radiation induced lung toxicity via decreasing transforming growth factor-beta-1 and interleukin-6 in lung cancer patients treated with radiotherapy. *Lung Cancer* 2008;59:219–26.
18 Saadipoor A, Razzaghdoust A, Simforoosh N, *et al*. Randomized, double-blind, placebo-controlled phase II trial of nanocurcumin in prostate cancer patients undergoing radiotherapy. *Phytother Res* 2019;33:370–8.
19 Sprod LK, Palesh OG, Janelsins MC, *et al*. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. *Community Oncol* 2010;7:463–71.
20 Lonkvist CK, Vinther A, Zerahn B, *et al*. Progressive resistance training in head and neck cancer patients undergoing concomitant chemoradiotherapy. *Laryngoscope Investig Otolaryngol* 2017;2:295–306.
21 Klement RJ, Sweeney RA. Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. *BMC Res Notes* 2016;9:143.
22 Bounous G, Le Bel E, Shuster J, *et al*. Dietary protection during radiation therapy. *Strahlentherapie* 1975;149:476–83.
23 McLaughlin M, Patin EC, Pedersen M, *et al*. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. *Nat Rev Cancer* 2020;20:203–17.
24 Sourati A, Ameri A, Malekzadeh M. *Acute side effects of radiation therapy*. Cham: Springer, 2017.
25 Farhood B, Mortezaee K, Goradel NH, *et al*. Curcumin as an anti-inflammatory agent: Implications to radiotherapy and chemotherapy. *J Cell Physiol* 2019;234:5728–40.
26 Ma L, Gonzalez-Junca A, Zheng Y, *et al*. Inflammation Mediates the Development of Aggressive Breast Cancer Following Radiotherapy. *Clin Cancer Res* 2021;27:1778–91.
27 Ye J, Hu Y, Chen X, *et al*. Comparative Effects of Different Nutritional Supplements on Inflammation, Nutritional Status, and Clinical Outcomes in Colorectal Cancer Patients: A Systematic Review and Network Meta-Analysis. *Nutrients* 2023;15:2772.
28 Buonocore D, Negro M, Arcelli E, *et al*. Anti-inflammatory Dietary Interventions and Supplements to Improve Performance during Athletic Training. *J Am Coll Nutr* 2015;34 Suppl 1:62–7.
29 Pan MH, Chiou YS, Tsai ML, *et al*. Anti-inflammatory activity of traditional Chinese medicinal herbs. *J Tradit Complement Med* 2011;1:8–24.
30 Brown WMC, Davison GW, McClean CM, *et al*. A Systematic Review of the Acute Effects of Exercise on Immune and Inflammatory Indices in Untrained Adults. *Sports Med Open* 2015;1:35.
31 Monteiro-Junior RS, de Tarso Maciel-Pinheiro P, da Matta Mello Portugal E, *et al*. Effect of Exercise on Inflammatory Profile of Older Persons: Systematic Review and Meta-Analyses. *J Phys Act Health* 2018;15:64–71.
32 Higashi Y, Yoshizumi M. Exercise and endothelial function: Role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients. *Pharmacol Ther* 2004;102:87–96.
33 Hood DA, Uguccioni G, Vainshtein A, *et al*. Mechanisms of exercise-induced mitochondrial biogenesis in skeletal muscle: implications for health and disease. *Compr Physiol* 2011;1:1119–34.
34 Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol* 2009;10:718–26.
35 Balázs K, Kis E, Badie C, *et al*. Radiotherapy-Induced Changes in the Systemic Immune and Inflammation Parameters of Head and Neck Cancer Patients. *Cancers (Basel)* 2019;11:1324.
36 Rotte A. Combination of CTLA-4 and PD-1 blockers for treatment of cancer. *J Exp Clin Cancer Res* 2019;38:255.
37 Liu H, Wang H, Wu J, *et al*. Lymphocyte nadir predicts tumor response and survival in locally advanced rectal cancer after neoadjuvant chemoradiotherapy: Immunologic relevance. *Radiother Oncol* 2019;131:52–9.
38 Grossman SA, Ellsworth S, Campian J, *et al*. Survival in Patients With Severe Lymphopenia Following Treatment With Radiation and Chemotherapy for Newly Diagnosed Solid Tumors. *J Natl Compr Canc Netw* 2015;13:1225–31.
39 Fang P, Jiang W, Davuluri R, *et al*. High lymphocyte count during neoadjuvant chemoradiotherapy is associated with improved pathologic complete response in esophageal cancer. *Radiother Oncol* 2018;128:584–90.
40 van Gorkom GNY, Klein Wolterink RGJ, Van Elssen CHMJ, *et al*. Influence of Vitamin C on Lymphocytes: An Overview. *Antioxidants (Basel)* 2018;7:41.
41 Blum KS, Pabst R. Lymphocyte numbers and subsets in the human blood. Do they mirror the situation in all organs? *Immunol Lett* 2007;108:45–51.
42 Wang Q, Li S, Qiao S, *et al*. Changes in T Lymphocyte Subsets in Different Tumors Before and After Radiotherapy: A Meta-analysis. *Front Immunol* 2021;12:648652.
43 Carlomagno MA, Alito AE, Almiron DI, *et al*. T and B lymphocyte function in response to a protein-free diet. *Infect Immun* 1982;38:195–200.
44 Wang H, Zhou B, Niu R, *et al*. Analysis of the roles of dietary protein and calcium in fluoride-induced changes in T-lymphocyte subsets in rat. *Environ Toxicol* 2017;32:1587–95.
45 Balcer-Kubiczek EK. Apoptosis in radiation therapy: a double-edged sword. *Exp Oncol* 2012;34:277–85.
46 Barazzuol L, Coppes RP, van Luijk P. Prevention and treatment of radiotherapy-induced side effects. *Mol Oncol* 2020;14:1538–54.
47 Malorni W, Rivabene R, Santini MT, *et al*. N-acetylcysteine inhibits apoptosis and decreases viral particles in HIV-chronically infected U937 cells. *FEBS Lett* 1993;327:75–8.
48 Janssens S, Tschopp J. Signals from within: the DNA-damage-induced NF-κB response. *Cell Death Differ* 2006;13:773–84.
49 Di Maggio FM, Minafra L, Forte GI, *et al*. Portrait of inflammatory response to ionizing radiation treatment. *J Inflamm (Lond)* 2015;12:14:14:.
50 Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. *Support Care Cancer* 2013;21:1569–77.
51 Tsai S. Importance of lean body mass in the oncologic patient. *Nutr Clin Pract* 2012;27:593–8.
52 Pasiakos SM, Cao JJ, Margolis LM, *et al*. Effects of high-protein diets on fat-free mass and muscle protein synthesis following weight loss: a randomized controlled trial. *FASEB j* 2013;27:3837–47.
53 McGlory C, Devries MC, Phillips SM. Skeletal muscle and resistance exercise training; the role of protein synthesis in recovery and remodeling. *J Appl Physiol (1985)* 2017;122:541–8.
54 TeSlaa T, Ralser M, Fan J, *et al*. The pentose phosphate pathway in health and disease. *Nat Metab* 2023;5:1275–89.
55 Lambros MP, Kondapalli L, Parsa C, *et al*. Molecular signatures in the prevention of radiation damage by the synergistic effect of N-acetyl cysteine and qingre liyan decoction, a traditional chinese medicine, using a 3-dimensional cell culture model of oral mucositis. *Evid Based Complement Alternat Med* 2015;2015:425760.
56 Witenberg B, Kletter Y, Kalir HH, *et al*. Ascorbic acid inhibits apoptosis induced by X irradiation in HL60 myeloid leukemia cells. *Radiat Res* 1999;152:468–78.
57 Lonkvist CK, Lønbro S, Vinther A, *et al*. Progressive resistance training in head and neck cancer patients during concomitant chemoradiotherapy -- design of the DAHANCA 31 randomized trial. *BMC Cancer* 2017;17:400.