Persistent Posttreatment Fatigue in Thyroid Cancer Survivors
A Scoping Review

Anna M. Sawka, MD, PhD, FRCPC\(^a,b\), Asima Naeem, BSc\(^a\), Jennifer Jones, PhD\(^c,d\), Julia Lowe, MBChB, MMedSci\(^b,e\), Philip Segal, MD, FRCPC\(^a,b\), Janette Goguen, MD, MEd, FRCPC\(^b,g\), Jeremy Gilbert, MD, FRCPC\(^b,e\), Afshan Zahedi, MD, FRCPC\(^b,f,h\), Catherine Kelly, MD, FRCPC\(^b,h\), Shereen Ezzat, MD, FRCPC\(^i\)

**KEYWORDS**
- Thyroid cancer
- Fatigue
- Vitality
- Quality of life
- Survivorship

**KEY POINTS**
- There is evidence that long-term fatigue is a common problem among thyroid cancer (TC) survivors.
- It is challenging to make specific recommendations on the treatment of persistent post-treatment fatigue (PPF) in TC survivors, because of a paucity of randomized controlled trials in this population.

Funding: This work was funded in part by a University of Toronto Department of Medicine Strategic Innovation Fund grant. A.M. Sawka currently holds a Chair in Health Services Research from Cancer Care Ontario, funded by the Ontario Ministry of Health and Long-term Care.

Disclosures: Other than the academic funding listed earlier, the authors have no relevant disclosures to declare.

\(^a\) Division of Endocrinology, Department of Medicine, University Health Network, 200 Elizabeth Street, 12th Floor, Toronto, Ontario M5G 2C4, Canada; \(^b\) Division of Endocrinology, Department of Medicine, University of Toronto, 200 Elizabeth Street, 12 EN-243, Toronto, Ontario M5G 2C4, Canada; \(^c\) Department of Psychiatry, University of Toronto, 250 College Street, 8th Floor, Toronto, Ontario M5T 1R8, Canada; \(^d\) Cancer Survivorship Program, Princess Margaret Hospital, University Health Network, 200 Elizabeth Street, BcS-045, Toronto, Ontario M5G 2C4, Canada; \(^e\) Division of Endocrinology, Department of Medicine, Sunnybrook Health Sciences Center, 2075 Bayview Avenue, H Wing, Toronto, Ontario M4N 3M5, Canada; \(^f\) Division of Endocrinology, Department of Medicine, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada; \(^g\) Division of Endocrinology, Department of Medicine, St. Michael’s Hospital, 61 Queen Street East, 6th Floor, Toronto, Ontario M5C 2T2, Canada; \(^h\) Division of Endocrinology, Department of Medicine, Women’s College Hospital, 76 Grenville Street, Toronto, Ontario M5S 1B2, Canada; \(^i\) Endocrine Oncology Site Group, Princess Margaret Hospital, University Health Network, 200 Elizabeth Street, 12NU-1200, Toronto, Ontario M5G 2C4, Canada

* Corresponding author. Toronto General Hospital, 200 Elizabeth Street, 12 EN-212, Toronto, Ontario M5G 2C4, Canada.

**E-mail address:** Annie.Sawka@uhn.ca

Endocrinol Metab Clin N Am 43 (2014) 475–494
http://dx.doi.org/10.1016/j.ecl.2014.02.007 endo.theclinics.com

0889-8529/14/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
INTRODUCTION

There are currently more than a half a million thyroid cancer (TC) survivors in the United States.\(^1\) Furthermore, TC incidence rates are increasing.\(^1,2\) It is thus important to address any long-term problems in this growing population. Persistent posttreatment fatigue (PPF) is one of the most common problems encountered in general oncology populations,\(^3–11\) with an estimated prevalence of about 19% to 38%.\(^4\) There is no universally accepted definition of PPF (also referred to as cancer-related fatigue) in cancer survivors, but some generally accepted concepts include a multidimensional nature (eg, physical and mental components), symptoms out of proportion to exertion, incomplete relief with rest, and interference with usual functioning.\(^3,4,7\) Cancer-related fatigue may occur as a consequence of malignancy or its treatment,\(^3,7\) or in association with related conditions (eg, psychological distress).\(^6\) The prevalence or severity of PPF in TC survivors is not known.

Our objective was to examine the volume, breadth, and type of research published on PPF in TC survivors. As a secondary objective, we identified some research gaps. The study design was that of a scoping review, with the intention of performing a preliminary search and mapping a broad range of literature on the topic.\(^12–17\)

METHODS

The general method followed was that of a scoping review, which typically involves (1) identifying a broad research question, (2) identifying relevant studies, (3) study selection, (4) abstracting data, (5) summarizing the results (including key themes), and (6) an optional stakeholder consultation phase.\(^13\) A scoping review typically does not include an in-depth critical appraisal of methodological data (found in systematic reviews), nor pooled quantitative data synthesis (found in meta-analyses).\(^12–17\)

Research Questions

Our primary research question was: what is the current scope of published literature, relating to PPF in TC survivors? Our secondary research aim was to identify research gaps in this field.

Inclusion and Exclusion Criteria for Studies

Our focus for this review was TC survivors who had completed primary oncologic treatment such as surgery, with or without radioactive iodine remnant ablation/treatment or external beam radiation treatment. Short-term fatigue associated with current or recent radioactive iodine treatment, surgery, radiation treatment, or systemic oncologic treatment (such as chemotherapy or targeted molecular therapy) was not a focus of this review. For the purpose of this review, we defined PPF as fatigue that is experienced more than 6 months after completion of any combination of such TC treatment(s). Input on a meaningful time frame for measurement of PPF was received.
from a clinical content expert (SE) as well as an expert in measurement of fatigue in oncology populations (JJ). Short-term fatigue associated with preparation for radioactive iodine treatment or scanning (eg, thyroid hormone withdrawal, or short-term studies comparing thyroid hormone withdrawal with the use of recombinant human thyrotropin) was not a focus of this review. Our target study population was TC survivors (any primary histologic subtype). For inclusion in the review, it was required that more than half the study population meets all inclusion criteria (ie, for studies of mixed populations) or that data on respective subgroups of interest were reported. Furthermore, fatigue measurements more than 6 months after primary treatment were required to be reported in more than half of the study population (ie, for studies reporting a mixture of short-term and long-term fatigue data in 1 outcome analysis). There was no methodological inclusion restriction. Only published English language articles were included, because of resource limitations for translation of articles. We excluded duplicate publications reporting the same outcome measurements in the same TC survivors, at the same time point.

Search for Relevant Studies

The details of our electronic searches are listed in Table 1. In summary, we searched the following electronic databases from inception until September, 2013: EMBASE, Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, and PubMed. The search terms incorporated the condition of thyroid carcinoma as well as the general concept of fatigue, with no restrictions on age, language, or methodology. All electronic searches were conducted by a librarian with expertise in electronic database searching. The hand searches were divided between reviewers, and these included reviews of reference lists from team members with content expertise (AMS), potentially relevant cross-references of included articles (AMS), and tables of contents from January 2008 to September 2013 from some key journals (ie, Thyroid and The Journal of Clinical Endocrinology and Metabolism) (AN).

Study Selection

Two team members (AMS and AN) independently reviewed the citations retrieved from electronic searches for relevance as well as any full-text articles deemed relevant by either reviewer from either the citation review phase or hand searching. A kappa statistic (with 95% confidence intervals [CIs]) was calculated for estimation of agreement between reviewers on (1) citations retrieved from the electronic database search for inclusion in full-text review, and (2) full-text review for inclusion in the study (using Confidence Interval Analysis Software, Version 2.2.0; T.N. Bryant, PhD, of the University of Southampton).18 Consensus was achieved between reviewers on the final full-text articles for inclusion in the review, after discussion and rereview of the articles in question.

Data Abstraction and Reporting of Results

The flow of information through various phases of the review process was summarized using a flowchart that was adapted from a published template intended for systematic reviews.19 Data abstraction was independently performed by 2 reviewers (AMS and AN) on standardized data abstraction forms. For studies collecting data at multiple time points, we abstracted only the long-term fatigue data (ie, more than 6 months following completion of TC treatment). Each abstracted data set was checked (by the other reviewer), and a final consensus data set was created. Key aspects of the published research were identified by both reviewers, using
the abstracted data sets. Relevant themes from abstracted data sets were then extracted by both reviewers. Abstracted data, including relevant themes, were summarized in tabular and narrative form within the article. For statistical comparisons performed in the primary studies, we assumed that a $P$ value of less than .05 was statistically significant.

**Consultation Phase**

Our completed article was reviewed by a group of University of Toronto endocrinologists from various academic hospitals. We specifically sought feedback on the key points/research gaps identified in the review. Feedback was received via e-mail, and any necessary edits were made to the article.
RESULTS

Studies Included in the Scoping Review

The process of study selection is shown in Fig. 1. Two reviewers independently screened 898 unique citations from the electronic search. In-depth, full-text review was performed by 2 independent reviewers for 43 articles (19 of which originated from the electronic search, and 24 from the hand search). We included 24 articles in the review. The reasons for exclusion of other full-text articles were that 2 studies had TC population data that overlapped with that of another included publication, 8 studies focused on short-term (acute) fatigue, 7 studies provided insufficient or no extractable raw data on fatigue, and most of the study population in 2 of the studies were not TC survivors. The 2 studies that overlapped already included studies were used as a supplement, to clarify any missing or unclear information from the respective included studies. One of the citations that had insufficient extractable fatigue data was limited by being a published meeting abstract, and complete details, as would be found in a fully published article, were not available at the time of our review. The kappa scores for agreement between reviewers for various stages of the review process were as follows: (1) electronic database citation review, kappa 0.729 (95% CI, 0.542, 0.916); (2) full-text review 0.580 (95% CI, 0.336, 0.824).

Fig. 1. Summary of the process of study selection for this scoping review.
Description of Studies According to Thematic Content

The studies included in this review, as well as TC survivor and control group characteristics, and instruments used to measure fatigue-related outcomes, are shown in Table 2. After abstracting the data, we reviewed the included study characteristics, and agreed on several broad study design themes (categories), as well as relevant subcategories. Studies that provided multiple comparators or multiple outcome analyses are listed in more than one category. The 2 broad categories were: (1) epidemiologic studies, and (2) randomized controlled trials (RCTs) of therapeutic interventions. The epidemiologic analyses were subdivided as follows: (1) 9 studies providing descriptive quantitative data on fatigue in TC survivors at 1 time point (eg, symptom prevalence, fatigue prevalence ranking relative to other symptoms, or measure of fatigue on some form of quantitative measurement instrument), without any non-TC population control comparison; (2) 16 studies providing quantitative comparisons of fatigue-related outcomes between TC populations and non-TC populations, at 1 time point; and (3) 8 studies providing explanatory data on risk factors or associations for the presence or increasing severity of fatigue-related outcomes at 1 time point.

Three RCTs examined the following types of respective interventions: (1) thyroid hormonal treatment (2 studies; one trial of a combination of synthetic triiodothyronine [T3] with levothyroxine [LT4] substitution for LT4 alone, and another trial of restoration of euthyroidism after prolonged thyroid-stimulating hormone [TSH] suppressive therapy), and (2) supervised exercise.

We could not find various other categories of study designs. For example, we found no long-term prospective studies providing data on the natural history of fatigue in TC survivors at multiple time points beyond 6 months (ie, excluding short-term fatigue measurements in relation to thyroid hormone withdrawal or recombinant human thyrotropin administration for diagnostic surveillance). Furthermore, we found no qualitative studies examining experience descriptions of long-term fatigue, from the perspective of TC survivors. We found no quantitative or qualitative studies examining life impact specifically in relation to severity of PPF (eg, social functioning, missed time from paid work, work productivity, or finances).

Epidemiologic studies

Descriptive fatigue-related data without non-TC control group comparisons

This category included descriptive, quantitative data on fatigue in TC survivors at 1 time point (eg, symptom prevalence, fatigue prevalence ranking relative to other symptoms, or measure of fatigue on some form of quantitative measurement instrument), without any non-TC population control group comparison, and consisted of data from 9 studies, including a combined total of 1129 TC survivors. In 4 respective clinical samples of TC survivors, fatigue was the most commonly reported physical symptom. The overall prevalence rates of long-term fatigue in clinical populations of TC survivors were reported to be 54.4% and 62.1% in respective studies. Huang and colleagues reported that the prevalence of fatigue in the past month was 41.1% (reported as part of the Quality-of-life Index questionnaire, which was administered 6 to 36 months after TC surgery). Gning and colleagues reported that severe fatigue was experienced by 28.3% of TC survivors, whereas the same percentage of respondents had no fatigue. In a cancer registry–based survey study from the Netherlands, 50% of TC survivors reported experiencing abrupt attacks of fatigue on the Thyroid Cancer Survivors’ Association Quality of Life (THYCA-QoL) questionnaire, and this was the third most common complaint, after pain in the joints or muscles (64%) and feeling chilly (52%). In another clinic-based study from Columbia, South America, tiredness, with or without decay or dry
skin, was reported as a posttreatment effect in 20% of TC survivors (although the definition of decay was unclear).²⁷ Four respective studies described a single time point measurement for fatigue-related outcomes from generic quality-of-life instruments, without any control comparison, including 2 studies²⁶,²⁷ reporting the Vitality subscale of the Short Form 36 (SF-36), another study³⁷ reporting fatigue symptom data from the European Organization for Research and Treatment of Cancer (EORTC)-QLQ-C30 questionnaire, and a fourth study⁴¹ reporting the Vigor-Vitality and Fatigue-Inertia subscales data from the Profile of Mood States (POMS).

Case-control comparisons of fatigue-related outcomes at 1 time point There was a total of 16 studies,²⁰,²²⁻²⁴,²⁸,³⁰⁻³⁴,³⁶,³⁹⁻⁴³ including a combined total of 2122 TC survivors, that reported 1 or more case-control comparisons of fatigue-related outcome data on TC survivors compared with non-TC controls. For 15 of these studies, the comparator group was a general population or healthy (variably defined) control population.²⁰,²²⁻²⁴,²⁸,³⁰⁻³²,³⁴,³⁶,³⁹⁻⁴³ Of the 15 studies (N = 1982 TC survivors) reporting 1 or more case-control comparisons with population or healthy controls, fatigue was reported to be significantly worse in the TC group in 1 or more analyses in 10 of the studies.²⁰,²²,²³,²⁸,³⁰⁻³²,⁴¹⁻⁴³ For this descriptive summary, the number of participants in the 2 different outcome studies by Husson and colleagues³⁰,³¹ was only counted once. More information, according to type of fatigue-related outcome measured in the study, is detailed later.

There were 7 studies reporting quantitative comparisons of fatigue-related outcomes in TC survivors compared with non-TC population control groups, using dedicated fatigue questionnaires (at 1 time point).²³,²⁴,²⁸,³¹⁻³³,³⁴,⁴³ In 6 of the studies, fatigue questionnaire data from TC survivors was compared with general population or healthy control data (variably defined),²³,²⁴,²⁸,³¹,³²,³⁴ whereas in 1 study the comparator group contained individuals treated for autoimmune hypothyroidism.³³ The specific fatigue questionnaires used in these studies included the Brief Fatigue Inventory (1 study), the Chalder Fatigue Scale (2 studies), the Fatigue Assessment Scale (1 study), and the Multidimensional Fatigue Inventory-20 (MFI-20) (3 studies).²³,²⁴,²⁸,³¹,³²,³³ In 5 of the 6 studies comparing fatigue levels in TC survivors with population or healthy controls (variably defined), fatigue levels were statistically significantly worse in the TC group. In 1 of these studies, the prevalence of Fatigue Assessment Scale classification in the fatigued or very fatigued category ranged from 39% to 47% in TC survivors out to more than 15 years after diagnosis, whereas the prevalence was 25% in age-matched and sex-matched population controls (P<.001).³¹ In 1 study comparing MFI-20 scores between TC survivors and individuals treated for autoimmune hypothyroidism, fatigue levels were reported to be significantly worse in the latter group (P<.001).³³ However, the autoimmune thyroid group had a significantly shorter mean LT4 treatment period, significantly higher mean TSH measurements, and significantly higher mean body mass index compared with the TC survivors.³³ In this study, the median TSH level was 0.07 mIU/L in the TC survivors, and 1.20 mIU/L in the treated autoimmune hypothyroid group (P<.001 for the difference in TSH).³³

There were 10 studies that reported quantitative comparisons of fatigue-related outcomes between TC populations and non-TC populations using generic quality-of-life or general symptom questionnaires.²⁰,²²,²³,³⁰,³⁴,³⁶,³⁹⁻⁴² All of these studies used general population or health control group (variably described) comparator groups.²⁰,²²,²³,³⁰,³⁴,³⁶,³⁹⁻⁴² The questionnaires and relevant subscales/symptom domains used in these studies included the Vitality subscale of the SF-36 (8 studies), the Fatigue subscale of the EORTC-QLQ-C30 (1 study)³⁰,
<table>
<thead>
<tr>
<th>First Author (Year, Country)</th>
<th>TC Population</th>
<th>Control Population</th>
<th>Fatigue-Related Outcome Measurement Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botella-Carretero (2003, Spain)</td>
<td>18 women with DTC, Mean age 44 y, All had suppressed TSH level, No active SR</td>
<td>18 healthy, euthyroid women (patients' relatives or hospital employees), Mean age 43 y</td>
<td>SF-36 (Vitality), POMS (Vigor-Activity), Visual Analog Mental Scales (Tiredness), Nottingham Health Profile (Energy)</td>
</tr>
<tr>
<td>Bunevicius (2003, Lithuania)</td>
<td>15 women, history TC, Mean age 46 y, Mean TSH 0.09 mU/L</td>
<td>Crossover design randomized trial (so same as TC population)</td>
<td>POMS (Vigor-Activity, Fatigue-Inertia)</td>
</tr>
<tr>
<td>Crevenna (2003, Austria)</td>
<td>150 DTC survivors, both sexes, Mean age 52 y, TSH not reported, but free thyroxine normal, No active SR</td>
<td>Age-matched and sex-matched reference values</td>
<td>SF-36 (Vitality) (German version)</td>
</tr>
<tr>
<td>De Oliveira Chachamovitz (2013, Brazil)</td>
<td>38 DTC survivors, both sexes, Mean age 45 y, Mean TSH 0.23 mIU/L (inclusion criterion of TSH &lt;0.4 mIU/L), No active SR</td>
<td>54 healthy individuals known to TC group, similar sex to TC group, Mean age 43 y, Mean TSH 1.70 mIU/L</td>
<td>Chalder Fatigue Scale (Portuguese version), SF-36 (Vitality Subscale), Portuguese version</td>
</tr>
<tr>
<td>Eustatia-Rutten (2006, Netherlands)</td>
<td>For baseline measures for the nonrandomized case-control comparison, total 24 DTC survivors, both sexes, Mean age 49 y, Median TSH 0.058 mIU/L, No active SR</td>
<td>For the nonrandomized case-control comparison: age-related reference Dutch values were used for a comparison with the baseline measures</td>
<td>MFI-20</td>
</tr>
</tbody>
</table>

Sawka et al.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country/Year</th>
<th>Study Population</th>
<th>Mean Age</th>
<th>TSH</th>
<th>Active SR</th>
<th>Measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gning</td>
<td>United States (2009)</td>
<td>60 TC survivors, both sexes</td>
<td>51 y</td>
<td>NA</td>
<td>No active SR</td>
<td>MD Anderson Symptom Inventory – TC Module (core symptom of fatigue)</td>
</tr>
<tr>
<td>Golger</td>
<td>Canada (2003)</td>
<td>181 DTC survivors, both sexes</td>
<td>43 y</td>
<td>0.19 mIU/L</td>
<td>No active SR</td>
<td>SF-36 (Vitality)</td>
</tr>
<tr>
<td>Gomez</td>
<td>Columbia (2010)</td>
<td>75 TC survivors, both sexes</td>
<td>Central age range 45–61 y</td>
<td>NA</td>
<td>No active SR</td>
<td>SF-36 (Vitality)</td>
</tr>
<tr>
<td>Hoftijzer</td>
<td>Netherlands (2008)</td>
<td>153 DTC survivors, both sexes</td>
<td>49 y</td>
<td>0.1 mIU/L</td>
<td>No active SR</td>
<td>Two separate control groups: 1. 113 controls selected by the patients with TC, of comparable age, sex, and socioeconomic status 2. Data pooled from 336 age-matched and gender-matched controls from other Leiden quality-of-life studies MFI-20</td>
</tr>
<tr>
<td>Huang</td>
<td>Taiwan (2004)</td>
<td>146 TC survivors, both sexes</td>
<td>48 y</td>
<td>NA</td>
<td>TSH and current disease status not reported</td>
<td>Quality-of-Life Index</td>
</tr>
<tr>
<td>Husson</td>
<td>Netherlands (2013)</td>
<td>306 TC survivors, both sexes</td>
<td>Mean age 56.4 y</td>
<td>TSH and current disease status not reported</td>
<td>800 age-matched and sex-matched cancer-free controls from the Netherlands THYCA-QOL (fatigue symptom) (only TC group) EORTC-QLQ-C30</td>
<td></td>
</tr>
<tr>
<td>Husson</td>
<td>Netherlands (2013)</td>
<td>See row above</td>
<td>530 age-matched and sex-matched controls from the Netherlands</td>
<td>Fatigue Assessment Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>South Korea (2010)</td>
<td>316 DTC survivors, both sexes</td>
<td>Mean age 46 y</td>
<td>Mean TSH 0.49 MIU/L</td>
<td>Sex-matched and age-matched reference control group data adopted from previously published study of the general Korean population</td>
<td>Brief Fatigue Inventory</td>
</tr>
</tbody>
</table>

(continued on next page)
Table 2 (continued)

<table>
<thead>
<tr>
<th>First Author (Year, Country)</th>
<th>TC Population</th>
<th>Control Population</th>
<th>Fatigue-Related Outcome Measurement Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louwerens33 (2012, Netherlands)</td>
<td>140 DTC survivors, both sexes Mean age 49 y Mean TSH 0.07 mIU/L No active SR</td>
<td>138 patients treated for autoimmune hypothyroidism, both sexes Mean age 48 y Mean TSH 1.20 mIU/L</td>
<td>MFI-2096</td>
</tr>
<tr>
<td>Malterling34 (2010, Sweden)</td>
<td>52 TC survivors, both sexes Median age 61 y No TSH data 6% had active TC</td>
<td>Healthy Swedish population reference data SF-36 (Vitality)87-89</td>
<td></td>
</tr>
<tr>
<td>Mendoza35 (2004, United States)</td>
<td>54 DTC survivors, both sexes No TSH data Although some had history of treated TC recurrence, current active SR status not reported</td>
<td>NA</td>
<td>Symptom inquiry</td>
</tr>
<tr>
<td>Peltarri36 (2009, Finland)</td>
<td>341 DTC survivors, both sexes, with low-risk TC at diagnosis Mean age 52 y No TSH measurements</td>
<td>Published reference control group data for the Finnish population from a national health survey</td>
<td>15D Instrument90</td>
</tr>
<tr>
<td>Roberts37 (2010, United States)</td>
<td>62 TC survivors, both sexes Mean age 53 y No TSH data No data on active SR</td>
<td>NA</td>
<td>EORTC-QLQ-C3082</td>
</tr>
<tr>
<td>Roerink38 (2013, Netherlands)</td>
<td>145 DTC survivors, both sexes Mean age 40 y Mean TSH 0.42 mIU/L Active SR in 6.2%</td>
<td>NA</td>
<td>Distress Thermometer and Problem List (Dutch version)91,92</td>
</tr>
<tr>
<td>Schroeder39 (2006, United States)</td>
<td>228 DTC survivors, both sexes Mean age 47 y Median baseline TSH 0.08–0.10 mIU/L49 21% had radioactive iodine scan positivity outside the thyroid bed49</td>
<td>Published general United States population norms (not reported if any specific age or sex adjustment performed in the analysis)</td>
<td>SF-36 (Vitality)75,77</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Population Details</td>
<td>Follow-Up Details</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Shah 40 (2006, Canada)</td>
<td>Canada</td>
<td>55% of population had TC, the rest benign thyroid disorder; all had thyroid surgery, both sexes</td>
<td>Mean age 46 y, No TSH data, No data on active SR</td>
</tr>
<tr>
<td>Tagay 41 (2005, Germany)</td>
<td>Germany</td>
<td>100 DTC survivors, both sexes</td>
<td>Mean age 50 y, Median TSH &lt;0.01 mIU/L, No data on active SR</td>
</tr>
<tr>
<td>Tan 42 (2007, Singapore)</td>
<td>Singapore</td>
<td>144 DTC survivors, both sexes</td>
<td>Mean age 48 y, No TSH data, No data on active SR</td>
</tr>
<tr>
<td>Vigario 43 (2011, Brazil)</td>
<td>Brazil</td>
<td>For the nonrandomized case-control comparison: 36 DTC survivors, both sexes (in case-control comparison)</td>
<td>Median age 48 y, Median TSH 0.02 mIU/L, No active SR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age 51 y, Median TSH 1.56 mIU/L</td>
<td>For the randomized trial, 17 of the individuals in the preceding column were randomized to be physically inactive</td>
</tr>
</tbody>
</table>

**Abbreviations:** DTC, differentiated TC; EORTC-QLQ, European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire; MFI-20, Multidimensional Fatigue Inventory 20; NA, not applicable; POMS, Profile of Mood States; SR, structural recurrence; THYCA-QOL, Thyroid Cancer Survivors’ Association Quality of Life; TSH, thyroid-stimulating hormone.

a Randomized controlled trial.
b Some blinding in the randomized controlled trial.
c Retrospective chart review.
d No blinding in the randomized controlled trial.

Data from Refs. 20–43
the Vitality subscale of the 15D questionnaire (1 study), the Fatigue-Inertia and the Vigor-Activity subscales of the POMS, the Energy subscale of the Nottingham Health Profile, and the Fatigue symptom on the Visual Analog Mental Scales (all in 1 study).

Three of the 8 analyses of the Vitality subscale of the SF-36 questionnaire showed statistically significantly worse vitality scores in TC survivors, compared with controls. The only study that used the Fatigue subscale of the EORTC-QLQ-C30 reported a statistically significant difference in fatigue levels between TC survivors and age-matched and sex-matched cancer-free controls. There were no significant differences between TC survivors and controls in respective analyses on fatigue-related subscales of the POMS, 15D, or the Visual Analog Mental Scales.

In summary, of the 10 respective studies comparing fatigue-related outcomes between TC survivors and non-TC controls using generic quality-of-life or symptom questionnaires, 5 of the studies reported that fatigue was worse in TC survivors, in at least 1 such analysis.

**Explanatory studies** We identified 8 explanatory studies including a total of 1247 TC survivors, that explored risk factors or associations for the presence or increasing severity of fatigue-related outcomes at 1 time point. Crevenna and colleagues reported that, in a multiple regression analysis, time since initial diagnosis was significantly associated with reduced SF-36 Vitality subscale score, but not gender, age, number of concomitant diseases, or partnership status. Furthermore, Hoftijzer and colleagues reported that, using a stepwise univariable linear regression, longer duration of differentiated TC (DTC) cure was associated with statistically significantly less fatigue on the MFI-20 subscales of General Fatigue, Physical Fatigue, and Mental Fatigue. Husson and colleagues reported no statistically significant difference between Fatigue subscale scores of the EORTC-QLQ-C30 between TC survivors at less than 5 years after diagnosis, compared with those 5 to 10 years after diagnosis, and those more than 10 years after diagnosis, but having one or more comorbidities was associated with more fatigue. Furthermore, in the same population, Husson and colleagues reported that Fatigue Assessment Scale Questionnaire scores were not significantly different between survivors according to time since diagnosis (ie, <5 years, 5–10 years, 10–15 years, or >15 years), but there was some variability in statistical significance of fatigue associations with age, comorbidity, presence of psychological problems, and marital status, among various multivariable logistic regression models explored. Some variables that were not statistically significantly associated with higher Fatigue Assessment Scale score in any of the multivariable models in this study included sex, clinicopathologic stage of disease, or the presence of any additional TC treatment after TC surgery. De Oliveira Chachamovitz and colleagues reported in respective secondary subgroup analyses of 30 female and 8 male TC survivors whose TSH was less than 0.4 mIU/L (with normal free thyroxine measurements) that levels of fatigue measured by Chalder Fatigue Scale were not significantly different when the mean TSH value was less than 0.1 mIU/L, compared with those when the mean TSH was greater than or equal to 0.1 mIU/L. Furthermore, in this study, Vitality subscale measurements were not significantly different between these two TSH categories in an analysis of 30 women (male vitality data not reported for this subgroup analysis). In a univariate analysis, Lee and colleagues reported no significant difference in Brief Fatigue Inventory scores between TC survivors who were treated with TC surgery alone, compared with those
groups treated with TC surgery with various dose activities of radioactive iodine. Tan and colleagues\(^\text{42}\) reported that, in a multivariable analysis, reduced Vitality score on the SF-36 questionnaire was statistically significantly predicted by the presence of more than 5 medical appointment days in the past 12 months, but not level of education or employment status. Furthermore, age, race, and the presence of 2 or more TC surgeries did not significantly predict this outcome in univariable analyses in this study.\(^\text{42}\) In a univariable analysis, Louwerens and colleagues\(^\text{33}\) suggested that the presence of the TSH receptor–Asp727Glu polymorphic allele was associated with significantly more fatigue in DTC survivors on 4 out of 5 subscales of the MFI-20 (ie, General Fatigue, Physical Fatigue, Reduced Activity, and Reduced Motivation) compared with the wild type for the allele. The Asp/Glu polymorphism was present in 10.7% of the DTC survivors in this study.\(^\text{33}\) It was hypothesized in this study that the Asp/Glu polymorphism was more sensitive than the wild-type TSH receptor, thereby theoretically increasing neuronal ability to modulate intracellular thyroid hormone levels in patients with the polymorphism.\(^\text{33}\) There was reported to be no significant difference in biochemical parameters between genotypes in the patients with DTC in this study.\(^\text{33}\)

**RCTs of interventions**

There were 3 RCTs, examining the effect of interventions on fatigue-related outcomes, in a combined total of 75 TC survivors.\(^\text{21,24,43}\) None of these trials had a specific eligibility criterion, requiring participants to have any degree of fatigue before enrollment in the study. Bunevicius and colleagues\(^\text{21}\) reported a subgroup analysis in 15 female TC survivors who had been enrolled as part of a larger, single-center, blinded, crossover design RCT,\(^\text{44}\) in which the use of the usual LT4 dose was compared with the combination of T3 and LT4 (where 50 µg of the usual LT4 dose was substituted with 12.5 µg of T3) for 5 weeks, and vice versa. The results of the POMS questionnaire subscales were conflicting, showing statistically significant improvements in the Fatigue-Inertia subscale, but no significant difference in the Vigor-Activity subscale of the same questionnaire, for the combination therapy group compared with the LT4 group (secondary subgroup analyses in the RCT).\(^\text{21}\) In a single-blinded parallel-design RCT of 6 months’ duration, Eustatia-Rutten and colleagues\(^\text{24}\) compared the use of the usual LT4 dose (with a target TSH <0.4 mIU/L) with a reduced dose of LT4 with placebo with the intention of achieving euthyroidism (target TSH 0.4–4.8 mIU/L). This RCT included 24 DTC survivors who had been on TSH-suppressive therapy for more than 10 years (mean of 12 years, standard deviation 1 year).\(^\text{24}\) Eustatia-Rutten and colleagues\(^\text{24}\) compared the baseline and 6-month subscale scores from the Multidimensional Fatigue Index 20 (ie, subscales of General Fatigue, Physical Fatigue, Reduced Activity, Reduced Motivation, and Mental Fatigue) for respective study arms. There was no significant change in all of these fatigue-related subscales in participants who had been maintained on TSH-suppressive therapy, and no significant change in most of the subscales in the euthyroid group, with the exception of statistically significant improvement in the Reduced Motivation subscale (\(P = .003\)).\(^\text{24}\) In a third, unblinded, RCT, Vígario Pdos and colleagues\(^\text{43}\) randomized 36 DTC survivors who were on TSH-suppressive therapy (TSH <0.4 mIU/L) to an individually prescribed supervised exercise program (treadmill-based aerobic activity with warm-up and cool-down, for a total 60 minutes, twice a week, for 12 weeks), compared with prescribed physical inactivity (ie, participants instructed to do as little as possible for 12 weeks). Fatigue (measured by the Chalder Fatigue Scale) was significantly reduced in the exercise group, and significantly worsened in the inactivity group, at 3 months.\(^\text{43}\)
SUMMARY

In this scoping review, we found that most of the published literature on PPF in TC survivors is epidemiologic in nature, and there is a paucity of RCTs. Most of the epidemiologic literature is focused on cross-sectional comparisons of fatigue-related outcome measurements relative to control populations. Furthermore, the control group comparisons are largely composed of general population or healthy individuals (variably defined). In uncontrolled clinical studies, fatigue seems to be one of the most frequently reported problems. Also, most studies evaluating levels of fatigue in TC survivors compared with the general population or healthy controls suggest that fatigue is worse in the TC group on at least one measurement. However, there is some variability in study findings, which may be partly caused by variability in measurement tools. We found little research examining the prevalence of fatigue according to severity levels. Furthermore, risk or explanatory factors for fatigue were inconsistent among the studies examining this issue. The relationship between fatigue and thyroid hormone biochemical indices was not clear in the limited data for this issue. Some limitations of this review include exclusion of unpublished literature, a modest level of agreement between reviewers for study inclusion at the full-text review stage (largely caused by challenges in interpreting the minimum threshold for data that could be abstracted for inclusion, from studies in which outcomes of interest were not clearly reported), abstraction of limited clinical details, limited methodological appraisal of primary studies, and no quantitative meta-analyses of abstracted data. However, our intention was to provide a broad general overview of the topic in TC populations, rather than a systematic review of specific details of the individual studies, or any pooled statistical analysis. In the process of performing this scoping review, we have determined that there are sufficient data for one or more in-depth systematic reviews in this area, which could provide more detailed, in-depth insights on the results.

There are many research gaps PPF in TC survivors that may be identified from this review. For example, there is a need for more RCTs for the treatment of fatigue in affected TC survivors. There is also a need for more research examining fatigue severity, modifying factors, natural history, and associated life impact in TC survivors. Qualitative research examining the experience of fatigue from TC survivors’ perspectives would also be valuable.

The results of this scoping review may be considered in the broader findings of other reviews, summarizing the knowledge and research priorities in cancer-related fatigue, and cancer survivorship. Some research priorities recently identified by experts in cancer-related fatigue that may be relevant to TC include examining the biology and behavioral mechanisms of fatigue (ideally using long-term, prospective cohort studies), clarifying the minimal clinically important differences in the measurement of fatigue (ie, the smallest difference that is perceived to be important by patients), establishing fatigue severity thresholds for participation in intervention RCTs, and conducting dissemination trials of effective management strategies. Moreover, as part of a scoping review of research in cancer survivorship care, Richardson and colleagues suggested that research priorities (including in management of PPF), should incorporate (1) large-scale prospective cohort studies, describing the needs of long-term survivors and predicting those at highest risk; (2) RCTs of specific delivery-ready interventions; and (3) research identifying the most effective and efficient ways to guide organization of care. Such goals have not yet been met in TC survivorship research, and it is likely that this scoping review will generate more questions than answers. Nevertheless, we hope that this work will broaden thoughtful consideration by stakeholders on PPF in a significant subset of TC survivors.
ACKNOWLEDGMENTS

We thank Ms Junhui Zhang, MEd, MLIS, an Information Specialist at the Princess Margaret Hospital, for assistance with the electronic database searches. We also acknowledge the research administrative assistance of Mrs Coreen Marino for retrieving many of the articles for review.

REFERENCES


