Received: 23 May 2022 | Accepted: 28 June 2022

DOI: 10.1002/hed.27142

CLINICAL REVIEW

WILEY

Interventions for head and neck cancer survivors: Systematic review

Danielle N. Margalit MD, MPH[1] | **Talya Salz PhD**[2] | **Rebecca Venchiarutti PhD**[3,4] | **Kristi Milley PhD**[5,6] | **Mairead McNamara BAppSc MDietPrac**[5,6,7] | **Sophie Chima BS**[5] | **Jamieson Wong BS**[5] | **Paige Druce Msc(Epi)**[5,6,8] | **Larissa Nekhlyudov MD, MPH**[9]

[1]Department of Radiation Oncology, Head and Neck Oncology Program, Dana-Farber Cancer Institute/Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[3]Sydney Head and Neck Cancer Institute, Department of Head and Neck Surgery, Chris O'Brien Lifehouse, Camperdown, New South Wales, Australia

[4]School of Public Health, Faculty of Medicine and Health, The University of Sydney, New South Wales, Australia

[5]Primary Care Collaborative Cancer Clinical Trials Group (PC4), Centre for Cancer Research, Melbourne, Victoria, Australia

[6]Department of General Practice, University of Melbourne, Melbourne, Victoria, Australia

[7]Department of Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

[8]Central Clinical School, Monash University, Melbourne, Victoria, Australia

[9]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence
Danielle N. Margalit, Department of Radiation Oncology, Head and Neck

Abstract

Background: Interventions for head/neck cancer (HNC) survivors may not address their cancer-related and general health needs.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guided this systematic review of studies from 2000 to 2021 of interventions targeting cancer survivors treated with curative-intent, using MEDLINE, Embase, Emcare, and PsycINFO. Interventions were categorized into domains of the Quality of Cancer Survivorship Care Framework to characterize the scope and quality of interventions.

Results: We identified 28 studies for inclusion: 13 randomized and 15 non-randomized. Most targeted surveillance/management of physical effects ($n = 24$) including 13 that also targeted psychosocial effects. Four studies addressed prevention/surveillance for recurrence/new cancers, one addressed health promotion/disease prevention, and one addressed chronic medical conditions. Most studies ($n = 27$) had medium-high risk of bias.

Conclusions: There are few high-quality studies addressing HNC survivorship. Future rigorously designed studies should address broader areas of care, including chronic disease management and health promotion/disease prevention.

KEYWORDS

cancer treatment effects, head and neck cancer, oropharynx cancer, radiation therapy, survivorship

This study was accepted for presentation at ASCO 2022.

Oncology Program, Dana-Farber Cancer Institute/Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA.
Email: danielle_margalit@dfci.harvard.edu

1 | INTRODUCTION

The population of head and neck cancer (HNC) survivors is growing, due to both improvements in treatment and the changing epidemiology of the disease. Human papillomavirus (HPV)-associated HNC, which is rising in incidence, has a better prognosis than non-HPV related HNC.[1] With improvements in patient survival, there is a growing population of HNC survivors that have cancer-related effects that extend years beyond treatment.[2] Survivors of HNC have unique needs compared to survivors of other cancers. The aerodigestive anatomic location of the tumor influences eating, breathing, speaking, and appearance. Long-term effects of HNC treatment are wide-ranging and often serious, encompassing numerous physical conditions that are critical to daily functioning. Psychosocial effects are also significant, with HNC survivors experiencing high rates of depression and suicide,[3] fear of cancer recurrence,[3] and financial toxicity.[4–7] Both recurrence and subsequent malignancies are common, especially among HNC survivors with heavy alcohol and tobacco use.[8] Furthermore, HNC survivors may have pre-existing comorbidities that require ongoing medical management and health promotion to reduce risk. With such complex ongoing health issues, HNC survivors require coordinated care beyond treatment completion.

The recently developed *Quality of Cancer Survivorship Care Framework* describes five domains of cancer survivorship care, all of which are relevant to HNC survivors.[9] The domains include: (1) surveillance and management of physical effects; (2) surveillance and management of psychosocial effects; (3) prevention and surveillance for recurrences and new cancers; (4) chronic disease management; (5) health promotion and disease prevention. The framework also includes contextual domains of the health care delivery system that influence cancer survivorship care quality including clinical structure, communication and decision making, care coordination, and patient/caregiver experience. The effect of survivorship care across these domains can be ascertained by health outcomes, which include function/health-related quality of life, emergency/hospitalization, costs, and mortality. Even though HNC survivors represent a complex population that require high-quality survivorship care across all domains, it is unclear how to address these needs, particularly in long-term follow-up after treatment and acute recovery. We performed a systematic review of the literature to identify, characterize, and assess the evidence, and identify gaps for interventions.

2 | METHODS

The protocol for this review was registered on PROSPERO (registration ID: CRD42021269566), and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed.[10] Electronic searches were conducted across four databases (MEDLINE, Embase, Emcare, and PsycINFO) for primary studies published in English between January 1, 2000 and November 12, 2021. The search strategy (Supplementary Data S1) included key words and MeSH terms related to head and neck neoplasms, survivorship, symptom management, and survivorship needs captured in the quality framework (Supplementary Data S1).

2.1 | Study selection

The patient population included adults (≥18 years) without active disease who completed curative-intent treatment for HNC. Tumors could be of any histology from the following cancer sites: larynx, hypopharynx, oropharynx, oral cavity, nasopharynx, nasal cavity, salivary glands, and paranasal sinuses. Eligible studies included randomized and non-randomized primary studies of interventions that began after completion of treatment with a study endpoint assessed at least 12 months following completion of therapy or cancer diagnosis (when date of treatment completion was not available). Studies were included if some patients had <12-month follow-up since cancer treatment, if details were given on the proportion of patients with at least 12 months follow-up. Studies could have a control group, comparison with standard of care or with another intervention, no comparator/control group, or pre-intervention/historical controls. We excluded editorials, reviews, meta-analyses, opinion pieces, case reports, study protocols, conference abstracts and retrospective reviews of interventions or practices.

Covidence systematic review software[11] was used to facilitate article screening, study selection and data extraction. Two reviewers (any two of PD, KM, MM, LN,

TABLE 1 Characteristics of included trials ($n = 28$)

Study	Country	Study design	Number of participants	Intervention type	Outcome	Disease site	Setting	Risk of bias
Randomized trials ($n = 13$)								
Alamoudi 2018[12]	Canada	Randomized controlled trial	20	Submental liposuction	Lymphedema	Oropharynx, oral cavity, larynx, neck, nasal cavity,	Hospital	High
Bhatia 2017[13]	United States	Randomized controlled trial	176	13 Cis-retinoic acid	Prevention of second primary cancer	Oropharynx, oral cavity, larynx, hypopharynx	Hospital	Medium
Cramer 2021[14]	United States	Randomized controlled trial, post hoc analysis	171	Lung cancer screening	Incidence of second primary lung cancer	Oropharynx, oral cavity, larynx, nasal cavity, sinus	Hospital	Medium
Guglielmo 2020[15]	Italy	Randomized controlled trial	32	Ginseng	Fatigue	Oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, paranasal sinus, salivary, unknown primary	Hospital	High
Jansen 2020[16]	Netherlands	Randomized controlled trial	92	Guided self-help program	Swallow/ communication	HNC NOS	Hospital	Medium
Kaae 2020[17]	Denmark	Randomized controlled trial	91	Chewing gum	Dry mouth	Oropharynx, oral cavity	Hospital	High
McNeely 2015[18]	Canada	Randomized controlled trial	52	Resistance exercise	Shoulder dysfunction	Oropharynx, oral, larynx, hypopharynx, thyroid, other.	Hospital	Medium
Millgard 2020[19]	Sweden	Randomized controlled trial	74	Voice rehabilitation	Voice quality	Larynx	Hospital	High
Pereira 2020[20]	Brazil	Randomized controlled trial	40	Pilocarpine spray	Dry mouth	HNC NOS	Hospital	Medium
Schutte 2021[21]	Netherlands	Randomized controlled trial	134	Stepped care program	Sexual interest/ enjoyment	Oropharynx, oral cavity, larynx, hypopharynx, other	Hospital	High
Tang 2011[22]	China	Randomized controlled trial	43	Rehab therapy	Trismus and dysphagia	Nasopharynx	Hospital and home	High
Vadcharavivad 2013[23]	Thailand	Randomized controlled trial	50	Saliva substitute	Dry mouth	HNC NOS	Hospital	High
Wu 2019[24]	Australia	Randomized controlled trial	41	Endoscopic dilation	Dysphagia	HNC NOS	Hospital	Low

(Continues)

TABLE 1 (Continued)

Study	Country	Study design	Number of participants	Intervention type	Outcome	Disease site	Setting	Risk of bias
Non-randomized prospective studies ($N = 15$)								
Al-Bazie 2016[25]	Saudi Arabia	Single arm prospective study	89	Perioperative antibiotics and antibacterial mouthwash	Prevention of osteoradionecrosis after dental extractions	Nasopharynx, oral cavity, maxilla	Hospital	High
Chan 2004[26]	China	Non-randomized experimental study	29	Alpha-tocopherol	Cognitive function for temporal lobe necrosis	Nasopharynx	Hospital	Medium
Chen 2020[27]	Taiwan	Single-arm prospective study	175	Endoscopic surveillance	Metachronous esophageal squamous cell carcinoma	Oropharynx, oral cavity, larynx, hypopharynx	Hospital	High
DeLeeuw 2013[28]	Netherlands	Non-randomized experimental study	160	Nurse-led additional follow-up consults	Psychosocial adjustment and HRQOL	Oropharynx, oral cavity, larynx, hypopharynx, other	Hospital	Medium
Dholam 2011[29]	India	Single arm prospective study	12	Implant-retained dental prosthesis into reconstructed maxillae and mandibles	Quality of life questionnaires and speech assessment software	HNC NOS	Hospital	High
Fong 2014[30] Fong 2014[31]	Hong Kong	Non-randomized experimental study	52	Qigong training	HRQOL, physical	Nasopharynx	Community and home-based	Medium
Kraaijenga 2017[32]	Netherlands	Single-arm prospective study	18	Swallowing exercise program	Dysphagia	Oropharynx, oral cavity, hypopharynx, larynx, neck, parotid	Hospital	High
Liu 2021[33]	Taiwan	Parallel arm prospective study	217	Carotid duplex ultrasound	Carotid artery stenosis progression	Nasopharynx, HNC NOS	Hospital	High
Manne 2020[34]	United States	Single-arm prospective study	66	Web-based tool	Feasibility, preliminary impact on health/QOL outcomes	Oropharynx, oral cavity	Hospital, community	High
Martin-Harris 2015[35]	United States	Single-arm prospective study	30	Respiratory-swallow training	Dysphagia related QOL, spirometry	Oropharynx, oral cavity, nasopharynx, larynx/hypopharynx	Hospital	High
Montalvo 2020[36]	Sweden	Single-arm prospective study	15	Therabite	Trismus	HNC NOS	Hospital	High
Mozzati 2014[37]	Italy		20		Healing post-extraction		Hospital	High

TABLE 1 (Continued)

Study	Country	Study design	Number of participants	Intervention type	Outcome	Disease site	Setting	Risk of bias
		Non-randomized experimental study		Plasma rich growth factors		Oropharynx, oral cavity, larynx, 'bone'		
Nativ-Zelter 2021[38]	United States	Single-arm prospective study	10	Autologous muscle-derived cell therapy	Safety, dysphagia (secondary)	Oropharynx	Hospital	High
Pauli 2016[39]	Sweden	Cohort study	100	Therabite®	Trismus	Oropharynx, oral cavity, nasopharynx, HNC NOS	Hospital and community (control)	High
Sterba 2019[40]	United States	Single arm prospective study	52	SNAP (Survivorship Needs Assessment Planning Tool)	Feasibility and short-term change in psychosocial outcomes	Oropharynx, oral cavity, larynx, other	Hospital	High

Abbreviations: HNC, head and neck cancer; HRQOL, health-related quality of life; NOS, not otherwise specified.

TS, DM, RV, SC, or JW) screened titles and abstracts. Full-text articles were also independently evaluated for inclusion by two reviewers (any two of the aforementioned), and disagreements were resolved by consensus. When more than one paper was published from a single trial, the endpoints were reviewed, critically appraised, and the data combined, such that each trial is listed only once in Table 1.

2.2 | Data extraction

The Quality of Cancer Survivorship Care Framework[9] was used to inform the development of the data extraction fields. Information on the following was extracted: study characteristics (country, year, study aim, study design, methods), study population (tumor site, number of participants, treatment modality), intervention information (aim, targeted symptom or concern, survivorship framework domain and health care outcome measures, type of intervention, components, timing and duration) and outcome (outcomes measured, timing of outcome measurement, effect of intervention). Data extraction was pilot tested by all authors to ensure consistency. Thereafter, data were extracted independently, and then collated and checked for consistency and inaccuracies.

2.3 | Data synthesis and critical appraisal

Due to the anticipated heterogeneity of the included studies, narrative synthesis was used to summarize the data. Studies were critically appraised by two reviewers to assess for bias using the Joanna Briggs Institute (JBI) critical appraisal tools corresponding to each study design.[41] Each of these tools evaluates elements of study design and reporting of findings that may reflect the quality and rigor of the original research.

3 | RESULTS

3.1 | Study selection

A flow diagram of study identification is provided in Figure 1. The search identified 7395 studies. After

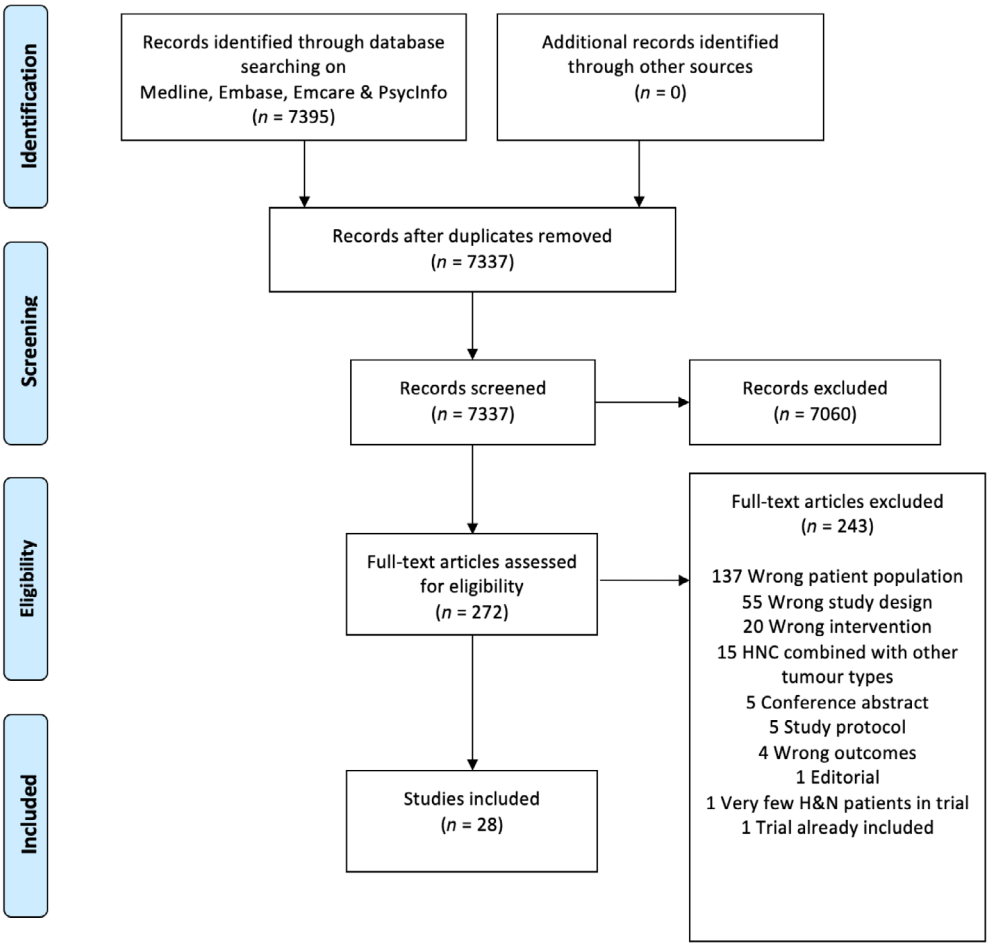

FIGURE 1 PRISMA flowchart [Color figure can be viewed at wileyonlinelibrary.com]

removal of duplicates and screening of titles and abstracts and subsequent full text review, 28 studies were included for critical appraisal and are shown in Table 1. These include 13 randomized trials (including one post hoc analysis[14]) and 15 non-randomized studies.

TABLE 2 Quality of cancer survivorship care framework domains

Study	Surveillance and management of physical effects	Surveillance and management of psychosocial effects	Prevention and surveillance for recurrence and new cancers	Surveillance and management of chronic medical conditions	Health promotion and disease prevention
Alamoudi 2018[12]	✓	✓			
Al-Bazie 2016[25]	✓				
Bhatia 2017[13]			✓		
Chan 2004[26]	✓	✓			
Chen 2020[27]			✓		
Cramer 2021[14]			✓		
DeLeeuw 2013[28]	✓	✓			
Dholam 2011[29]	✓	✓			
Fong 2014,[31] Fong 2014[30]	✓	✓		✓	✓
Guglielmo 2020[15]	✓	✓			
Jansen 2020[16]	✓	✓			
Kaae 2020[17]	✓				
Kraaijenga 2017[32]	✓	✓			
Liu 2021[33]	✓				
Manne 2020[34]	✓	✓	✓		
Martin-Harris 2015[35]	✓				
McNeely 2015[18]	✓	✓			
Millgard 2020[19]	✓				
Montalvo 2020[36]	✓				
Mozzati 2014[37]	✓				
Nativ-Zeltzer 2021[38]	✓				
Pauli 2016[39]	✓	✓			
Pereira 2020[20]	✓	✓			
Schutte 2021[21]	✓	✓			
Sterba 2019[40]		✓			
Tang 2011[22]	✓				
Vadcharavivad 2013[23]	✓				
Wu 2019[24]	✓				

3.2 | Study population

Most studies included patients with heterogeneous cancer types or did not specify the HNC subsites: six studies were limited to the specific sites of the nasopharynx,[22,26,30,31] larynx[19] and oropharynx.[38] Receipt of cancer treatment, including radiation therapy (RT), surgery, or chemotherapy, was reported for most studies. Among the 28 studies, 17 included patients treated with radiation therapy with or without surgery/chemotherapy,[12,15,17,19,20,22–26,30,31,33,36–39] and 3 included patients treated with surgery with combinations of RT/chemotherapy[16,18,29]; other studies included a combination of treatment modalities[28,35,40] or did not specify.[27] Hospital/academic setting was the site of patient recruitment and intervention training for all studies except for two that had a community-based component of the intervention.[30,31,34] Eligible patients were generally identified from records at head and neck oncology clinics. The studies were most commonly from North America, Europe, and Asia, mainly the United States ($n = 6$), Netherlands ($n = 5$), Sweden ($n = 3$), Canada ($n = 2$), China ($n = 2$), and Italy ($n = 2$).

3.3 | Quality of the evidence

Studies were appraised for risk of bias as shown in Table 1 and Supplementary Tables 1–3. Most had a medium to high risk of bias. Among the 13 randomized studies, there were 12 with a medium[13,14,16,18,20] to high[12,15,17,19,21–23] risk of bias, and only one study with a low[24] risk of bias. The most common sources of bias were lack of concealment of allocation, heterogeneity of baseline participant characteristics, or unclear/lack of blinding of the participants, assessors, or those delivering the study intervention. Additional reasons for introduction of bias included incomplete information on follow-up of participants,[15] limited information on power calculations,[14,21,22] and lack of target accrual[13] or patient attrition.[19]

The 15 non-randomized studies included 12 with a high risk of bias[25,27,29,32–40] and three with a medium risk of bias.[26,28,30,31] Common reasons for introducing bias included lack of planned sample size/power calculations or pre-specified endpoints. Follow-up was frequently incomplete due to low participation in the intervention or loss to follow-up with lack of adequate description or analysis to account for loss to follow-up.[28,30–32,34–36]

3.4 | Survivorship domains

Interventions were grouped into the domains as specified by the Quality of Cancer Survivorship Care Framework[9] (Table 2) and described below.

3.4.1 | Surveillance and management of physical effects

Most interventions ($n = 24$) focused on surveillance and management of physical effects, with 13 of those studies also addressing surveillance and management of psychosocial effects (described below). The physical domains targeted by the 11 randomized studies included: speech and swallow function and trismus,[16,19,22,24] dry mouth,[17,20,23] fatigue,[15] shoulder dysfunction,[18] sexual function[21] and lymphedema.[12] Of these, seven randomized controlled trials (RCTs) reported statistically significant results, including one trial with a low-risk of bias showing an improvement in dysphagia after endoscopic dilatation for patients treated with RT with or without total laryngectomy.[24] Two studies had a medium risk of bias, and showed improvements in shoulder pain and function with a progressive resistance exercise training program,[18] and swallowing-related QOL measures after a guided self-help exercise program.[16] Four additional studies had a high risk of bias[12,17,22,23] focusing on appearance after submental liposuction,[12] dry mouth after chewing gum intervention,[17] trismus and dysphagia after speech and swallow rehabilitation exercise therapy,[22] and dry mouth with use of a hospital prepared saliva substitute.[23]

The 13 non-randomized studies targeting physical effects of cancer therapy focused on improving trismus and dysphagia,[32,35,36,38,39] carotid stenosis surveillance,[33] prevention of dental complications and osteoradionecrosis,[25,37] cognitive function,[26] health-related quality of life after implant-retained dental prostheses into reconstructed mandibles,[29] and patient-reported physical symptoms and role functioning.[28,30,31,34] All non-randomized studies had a medium to high risk of bias. Included non-randomized studies examined the effect of an oral opening device on trismus,[36,39] antibiotic use around teeth extraction after RT,[25] healing in post-extraction sockets treated with plasma-rich growth factors,[37] dysphagia following autologous muscle derived stem cell therapy,[38] and swallowing following respiratory-swallow training.[35] Additional non-randomized studies reported the use of alpha-tocopherol use on neurocognitive function,[26] and carotid ultrasound in predicting progressive carotid artery stenosis.[33]

3.4.2 | Surveillance and management of psychosocial effects

Thirteen studies targeted surveillance and management of psychosocial effects (Table 2). Four studies focused on psychosocial outcomes of cancer treatment as the primary study outcome, including one RCT with a high risk of bias[21] and three non-randomized studies with a medium[28] to high risk of bias.[34,40] The RCT studied sexual interest

TABLE 3 Detailed study outcomes of randomized and non-randomized studies ($n = 28$)

Study	Interval from treatment to intervention[c]	Comparison	Intervention type	Outcomes	Measures	Results	Conclusions
Randomized trials ($n = 13$)							
Alamoudi 2018[12]	30 ± 12 months	Intervention versus observation	Submental liposuction	Appearance/ Lymphedema	MBOE[a] DAS-59 (Derriford Appearance Scale)	SS improvement in both scales	Submental liposuction vs. no intervention associated with improvement in patient-reported appearance
Bhatia 2017[13]	1-61 months	Intervention versus placebo	13 Cis-retinoic acid	Prevention of second primary cancer	Number of secondary primary tumors (SPT) & time to diagnosis of SPT[a] OS	N-SS difference in SPT or time to SPT	13-CRA did not reduce SPT in underpowered trial
Cramer 2021[14]	Intervention group: median 9 years (IQR 6–13 years) CXR: median 10 years (IQR 6–17 years)	Low-dose CT (LDCT) versus chest-x-ray (CXR)	Lung cancer screening	Incidence of second primary lung cancer	Incidence of second primary lung cancer (SPLC)[a] Incidence of a second primary HNC, combined SPHNC or SPLC, OS, incidence of abnormal imaging findings	N-SS difference in SPLC identified on LDCT compared to CXR SS-higher incidence of SPLC in HNC survivors compared to other	Post hoc analysis of a RCT did not show SS difference in SPLC in LDCT in HNC subgroup; SS higher SPLC in HNC survivors
Guglielmo 2020[15]	≥12 months	Intervention versus placebo	Ginseng	Fatigue	BFI[a]	No SS difference in BFI from baseline to post-intervention	Ginseng did not reduce patient-reported fatigue
Jansen 2020[16]	78%: 6 months–5 years 22%: <6 months	Intervention versus self-care education program alone	Guided self-help exercise program and self-care education program	Swallow/ communication	SWAL-QOL[a] SHI (speech handicap index) Shoulder problems (SDQ) PAM EORTC QLQ-C30 EORTC QLQ-H&N35	SS improvement in SWAL-QOL in intervention group N-SS improvement in other domains Time since cancer treatment moderated effectiveness of intervention on speech problems	Guided self-help exercise program improvement patient-reported swallowing function

(Continues)

TABLE 3 (Continued)

Study	Interval from treatment to intervention[c]	Comparison	Intervention type	Outcomes	Measures	Results	Conclusions
Kaae 2020[17]	75%: 6–24 months 25%: 36–60 months	Intervention versus CAU	Chewing gum	Dry mouth	EORTC QLQ-H&N35 "dry mouth" question[a] GRIX UWS and SWS sialometry	SS reduction improvement in primary endpoint N-SS difference in other measures	Chewing gum associated with improvement with dry mouth question on EORTC-QLQ-HN35
McNeely 2015[18]	44%: ≥18 months 42%: <9 months 15%: 9–17 months	Intervention versus CAU, option to crossover	Progressive resistance exercise training	Shoulder dysfunction	SPADI[a] Upper extremity strength Shoulder ROM FACT-An NDII	SS improvement in all measures	Progressive resistance exercise training reduced patient-reported shoulder pain and disability and improved muscle strength/endurance
Millgard 2020[19]	Follow-up extended to 2 years	Intervention versus CAU	Voice rehabilitation	Voice quality	CPPS[a] GRBAS sale	N-SS differences in measures	Voice rehab may have positive effects but N-SS correlation found between CPPS and perceptual parameters of GRBAS
Pereira 2020[20]	2–6 years	Intervention versus placebo	Pilocarpine spray	Dry mouth	SWSF[a] XI OHIP-14	N-SS difference in measures	Topical pilocarpine spray did no lead to SS difference in measures of xerostomia
Schutte 2021[21]	46%: >12 months 37%: >7 months 18%: 7–12 months	Intervention versus CAU	Stepped care program targeting psychological distress	Sexual interest/enjoyment	Sexuality symptom subscale of EORTC QLQ-H&N35[a]	N-SS improvement	SC targeting psychological distress did not reduce problems with sexuality. Interventions specifically targeting sexuality are recommended

TABLE 3 (Continued)

Study	Interval from treatment to intervention[c]	Comparison	Intervention type	Outcomes	Measures	Results	Conclusions
Tang 2011[22]	Mean 4.6 years for intervention versus 4.8 years for control	Intervention versus CAU	Rehabilitation exercise therapy	Trismus and dysphagia	Water swallow test[b] LENT/SOMA IID	SS-improvement in all measures	Swallow and trismus therapy improved swallow function and reduced severity of trismus
Vadcharavivad 2013[23]	≥1 year	Intervention versus commercially available saliva substitute	In-hospital prepared saliva substitute	Dry mouth	XeQoLS[a]	SS inferior score in intervention group	Commercially available saliva substitute was better than the hospital-prepared formulation
Wu 2019[24]	≥1 year	Intervention versus sham	Endoscopic dilation	Dysphagia	SSQ score + satisfactory global assessment by swallow therapist[a] SAE Dysphagia relapse	SS improvement in all measures, no SAEs	Dilation improves swallowing function
Non-randomized prospective studies ($N = 15$)							
Al-Bazie 2016[25]	12–33 months	None	Perioperative antibiotics (oral amoxicillin) and antibacterial mouthwash	Prevention of osteoradionecrosis after dental extractions	No. extracted teeth[b] Osteoradionecrosis (no further definition)	232 extractions (average 2.6 teeth/patient) and no ORN	No patients using the antibiotic protocol had ORN after extractions
Chan 2004[26]	Intervention: mean 15.47 years (SD 5.3 years) Control: 13.80 years (7.45)	Matched control group	Alpha-tocopherol	Cognitive function for temporal lobe necrosis	Cantonese MMSE[b] Category Fluency Test Hong Kong List Learning Test (HKLLT) Visual Reproduction subtest of the Wechsler Memory Scale-III (WMS-III VR) Cognitive Flexibility Test Self-evaluation questionnaire	SS improvement in MSSE, and verbal and visual memory, and executive function N-SS difference between groups in attention, language, or self-reported improvement	Alpha-tocopherol may improve cognitive function

(Continues)

TABLE 3 (Continued)

Study	Interval from treatment to intervention[c]	Comparison	Intervention type	Outcomes	Measures	Results	Conclusions
Chen 2020[27]	Mean 33 months	None	Endoscopic surveillance	Metachronous esophageal squamous cell carcinoma	Biospy-proven dysplasia or squamous cell carcinoma	Metachronous esophageal squamous cell neoplasms ESCN) developed in 11.4% patients (17 low-grade dysplasia, 3 squamous cell carcinoma. Median time to ESCN was 33 ± 22.9 months	Endoscopic surveillance can detect ESCN
DeLeeuw 2013[28]	Intervention extended to 12 months post-treatment	CAU group recruited in preceding year	Nurse-led additional follow-up consults	Psychosocial adjustment and HRQOL	PAIS-SR[b] EORTC QLQ-C30 and QLQ-H&N35	N-SS difference between groups	Nurse-led consultations had a positive but not SS effect on HRQOL
Dholam 2011[29]	≥1 year	No	Implant-retained dental prosthesis into reconstructed maxillae and mandibles	HRQOL, and speech	EORTC QLQ-H&N 35 and EORTC QLQ-C30[b] Dr. Speech Software	N-SS improvement in pre-intervention versus post-intervention assessment, even if numerically improved	QOL parameters did not markedly change after implant retained prosthesis reconstruction even if individual parameters numerically improved
Fong 2014[31] Fong 2014[30]	Mean 12.5 years in intervention group versus 8.4 years in control group	Self-selected volunteers who did CAU	Qigong training	HRQOL, physical	EORTC QLQ-H&N, QLQ-C30[b] Blood flow velocity Arterial resistance by Doppler ultrasound Functional aerobic capacity measured by walking distance and self-report of fatigue	NS-SS difference between intervention and control group for EORTC QLQ measures SS higher diastolic blood flow, lower arterial blood flow resistance, and higher palmar skin temperature, and	Tai Chi Qigong program may improve arterial hemodynamics and functional aerobic capacity

TABLE 3 (Continued)

Study	Interval from treatment to intervention[c]	Comparison	Intervention type	Outcomes	Measures	Results	Conclusions
					Palmar skin temperature measurement	functional aerobic capacity	
Kraaijenga 2017[32]	≥88%: ≥2 years	None	Swallowing exercise program	Dysphagia	Feasibility and compliance[a] SWAL-QOL EQ-5D Interincisal opening FOIS VFS parameters PAS IOPI Dynamometer for jaw muscle strength	High compliance (97%) and completion rate (88%) SS-not reported, but descriptive statistics for numeric improvements in strength in various muscles	Feasibility and compliance for a swallowing exercise program can be high with some objective and subjective effects of muscle strength and swallow function despite most being at least 2 years post-treatment
Liu 2021[33]	Mean 8.81 years (SD 4.66) in high plaque (HP) group and 9.56 years (SD 3.67) in low plaque (LP) group	At enrolment, 2 groups created: high-plaque group versus low-plaque group	Carotid duplex ultrasound (CDU)	Carotid artery stenosis (CAS) progression	>50% stenosis on B-mode CDU with compatible hemodynamic pattern in any ICA or CCA on a follow-up CDU study[b]	HP group had a SS higher frequency of CAS progression and N-SS increased future ischemic stroke	Patients with total plaque sore of ≥7 on CDU are susceptible to CAS progression and should have close monitoring
Manne 2020[34]	1–3 years	None	Web-based tool: "Empowered Survivor"	Feasibility, preliminary impact on health/QOL outcomes	22-item scale composed for the study to represent confidence in managing different aspects of self-care[a] 10-item scale used previously by study group for assessing preparedness for oral and oropharyngeal survivorship EORTC QLQ-HN35 Study-specific measure for	82% pts viewed intervention Descriptive statistics showed increased self-efficacy, preparedness for survivorship, HRQOL, rates of oral self-exam, and other secondary endpoints	The web-based survivorship empowerment tool showed a beneficial impact on multiple domains

(Continues)

TABLE 3 (Continued)

Study	Interval from treatment to intervention[c]	Comparison	Intervention type	Outcomes	Measures	Results	Conclusions
					performance and thoroughness of oral self-exam, maintenance of exercise, and action/coping planning, activation, and information needs Supportive Care Needs Survey		
Martin-Harris 2015[35]	>1 year	None	Respiratory-swallow training	Dysphagia related QOL, spirometry	Respiratory-swallow phase pattern[b] MBSImP PAS MDADI	SS improvement in optimal phase swallowing patterning, and component scores of MBSimP including laryngeal vestibular closure, tongue base retraction, and pharyngeal residue SS improvement in PAS and MDADI	Improvements in respiratory-swallowing coordination can be trained in patients with chronic dysphagia with favorable effects on airway protection and bolus clearance
Montalvo 2020[36]	Mean 6.2 years (range 0.7–14.8)	None	Therabite	Trismus	MIO[b] Gothenburg Trismus Questionnaire (GTQ) EORTC QLQ C30 and EORTC QLQ-H&N35	SS improvement in MIO and individual domains in the other questionnaires	Structured exercise with the jaw-mobilizing device was beneficial for patients with trismus
Mozzati 2014[37]	Mean 4.1 ± 2.5 years	Same patient, contralateral extraction sockets with CAU	Plasma rich growth factors	Healing post-extraction	Healing index (HI), residual socket volume (RSV), postoperative complications[b]	Intervention showed SS-better RSV and HI and no postoperative complications (bone exposure)	Plasma rich in growth factors accelerated mucosal healing and avoided post-extraction bone exposure

TABLE 3 (Continued)

Study	Interval from treatment to intervention[c]	Comparison	Intervention type	Outcomes	Measures	Results	Conclusions
Nativ-Zelter 2021[38]	Mean 11.5 years, (SD 7.6)	No	Autologous muscle-derived cell therapy	Safety (phase I trial with efficacy measurements), dysphagia	IOPI[a] PAS Pharyngeal constriction ratio Pharyngo-esophageal segment (PES) opening Pharyngeal transit time Pharyngeal peak pressure EAT-10 VHI-10	No SAEs SS increase in tongue pressure. N-SS change in other metrics	Injection with autologous muscle-derived cell therapy was feasible and safe and was accompanied by increase in tongue strength
Pauli 2016[39]	Includes 2-year f/u The 10-week Intervention was 3–6 months post-treatment	Control group receiving CAU (no structured trismus-focused program	Therabite®	Trismus	MIO[a] Gothenburg Trismus Questionnaire (GTQ) EORTC QLQ C30 and EORTC QLQ-H&N35	SS higher MIO and GTQ at 2-year follow-up in intervention group. Individual domains in other questionnaires had SS differences	There is a positive persistent effect of jaw opening exercises on trismus and patient reported outcomes
Sterba 2019[40]	9 patients: >12 months 6 patients: 6–12 months 11 patients: 0–6 months	No	SNAP (Survivorship Needs Assessment Planning Tool)	Feasibility and short-term change in psychosocial outcomes	PROMIS (depression)[a] Cancer Survivors/ Partners Unmet Needs instruments PLANS Dyadic coping inventory Zarit Burden Inventory FOCUS—2 single items Other study-specific surveys	SS improvement in scores for depression, unmet needs, and survivorship knowledge in survivors and caregivers NS-SS change in symptom distress and management	The SNAP tool is feasible and able to address dyads' needs; the tool merits further testing in a clinical trial

Abbreviations: BFI, brief fatigue inventory; CAU, care as usual; CPPS, smoothed cepstral peak prominence; EAT-10, Eating Assessment Tool; EORTC-QLQ, European Organization for Research and Treatment of Cancer generic and HNC-specific health-related quality of life measures; EQ-5D, European Quality of Life 5 Dimensional Questionnaire; FACT-An scale, Functional Assessment of Cancer Therapy-Anemia scale; FOCUS, National Cancer Institute Follow-up Care Use and Health Outcomes of Cancer Survivors; FOIS, functional oral intake scale; GRBAS, Grade, Roughness, Breathiness, Asthenia and Strain scale; GRIX, Groningen Radiation-Induced Xerostomia questionnaire; HNC, head and neck cancer; HRQOL, health-related quality of life; IID, interincisal distance; IOPI, Iowa Oral Performance Instrument; LENT/SOMA, Late Effects Normal Tissue/Subjective, Objective, Management, Analytic scales; MBOE, Modified blepharoplasty Outcomes Evaluation; MBSImP, Modified Barium Swallow Impairment Profile; MDADI, MD Anderson Dysphagia Inventory; MIO, maximal interincisal opening; MMSE, Mini-Mental Status Examination; NDII, neck dissection impairment index; No., number; NOS, not otherwise specified; N-SS, non-statistically significant; OHIP-14, Oral Health Impact Profile; PAIS-SR, Psycho-social Adjustment to Illness Scale-Self Report; PAM, patient activation measure; PAS, penetration aspiration scale; PLANS, Preparing for Life As a New Survivor; PROMIS, Patient-Reported Outcomes Measure Information System; ROM, range of motion; SAE, serious adverse event; SDQ, shoulder disability questionnaire; SHI, speech handicap index; SPADI, shoulder pain and disability index; SS, statistically significant; SSQ, Sydney Swallow Questionnaire; SWAL-QOL, swallowing quality of life questionnaire; SWSF, stimulated whole saliva flow; UWS, unstimulated whole saliva; VFS, video fluoroscopy; VHI, Voice Handicap Index; XeQoLS, Xerostomia Quality of Life Scale; XI, Xerostomia Inventory.

[a]Primary endpoint.

[b]Primary endpoint not specifically stated in methods.

[c]Time from treatment to intervention is given, time from diagnosis is given if specific time from treatment not given.

after a stepped care program intervention targeting psychological distress; this trial did not show a statistically significant effect.[21] The non-randomized studies looked at the effect of a nurse-led intervention on psychosocial adjustment and health-related quality of life (HRQOL) showing no statistically significant difference between groups,[28] the effect on self-efficacy with a web-based tool showing an improvement with descriptive statistics but no tests of significance,[34] and a statistically significant improvement in depression, unmet needs, and survivorship knowledge in both survivors and care-givers.[40] Of note, this was the only study identified by this systematic review that targeted an intervention to the patient-caregiver dyad rather than the survivor alone. Most of the 13 studies assessed psychosocial effects as secondary outcomes using surveys such as the EORTC-QLQ-H&N35 to ascertain the multi-dimensional effect of an intervention targeting physical effects of cancer treatment (see Table 3 for measures of outcome).

3.4.3 | Prevention and surveillance for recurrence and new cancers

Four interventional studies, including two RCTs with a medium risk of bias,[13,14] and two non-randomized experimental studies with a high risk of bias[27,34] reported on prevention and surveillance for recurrence and new cancers. The two RCTs were both underpowered and did not show a statistically significant benefit of the intervention. One of these was the ECOG-ACRIN chemoprevention trial that closed early due to slow accrual and did not show a benefit of a synthetic vitamin A derivative for prevention of second primary cancers in HNC survivors.[13] The other was a post hoc analysis of the National Lung Screening Trial, which demonstrated the high incidence of second primary lung cancer among HNC survivors.[14] In this study, there was a non-statistically significant increase in detection of lung cancer and survival with low-dose CT compared to chest x-ray surveillance.

The two non-randomized trials with a high risk of bias included a single-arm study designed to assess detection of metachronous esophageal squamous cell neoplasms in HNC survivors using endoscopic surveillance.[27] The other was an eHealth intervention to teach patients to self-screen for recurrent or second primary oral or skin lesions, showing increased engagement in oral self-exams to screen for recurrence or second primary tumors.[34]

3.4.4 | Chronic medical conditions/health promotion and disease prevention

We found only one study that touched on the general health-related domains. This study, with a high risk of

bias, examined the effect of Tai Chi Qigong on improving measures of arterial hemodynamics and functional aerobic capacity. Tai Chi had a statistically significant benefit for physical measures,[30] but no significant benefit on quality-of-life measures (using the EORTC QLQ-C30 and QLQ-H&N35 instruments).[31]

3.5 | Health care outcomes

Study outcome measures were categorized according to four previously described outcome measures identified in the Quality of Cancer Survivorship Care Framework including health-related quality of life/function, emergency services/hospitalizations, costs, and mortality.[9] All studies assessed the HRQOL/function outcomes (Table 3). Only two studies assessed mortality outcomes as secondary endpoints.[13,14] No studies assessed outcomes of emergency services/hospitalizations and costs.

4 | DISCUSSION

This systematic review identified 13 randomized trials and 15 non-randomized prospective studies, mostly with medium to high risk of bias, focusing on interventions for HNC survivors at least 1 year after curative-intent treatment. These survivorship interventions were characterized into the five quality domains of the Quality of Cancer Survivorship Care Framework demonstrating an emphasis on surveillance and management of physical and psychosocial effects of cancer treatment, with particular focus on management rather than surveillance. Few studies evaluated interventions addressing surveillance and management of chronic medical conditions and health promotion and disease prevention. Outcomes almost exclusively addressed HRQOL/function rather than costs, financial toxicity, health care utilization, or mortality. We identified numerous gaps in HNC survivorship research including under-represented domains of survivorship care, and methodologic gaps in study design, conduct, and analysis that introduce risk of bias.

Our findings emphasize a lack of prospective data with low risk of bias regarding interventions for HNC survivors that span beyond the acute phase of treatment. Our identification of so few high quality interventions highlights the lack of evidence in the current guidelines for HNC survivorship care,[42,43] in which most of the supporting evidence is based on level three data (case control or prospective cohort studies) or expert opinion.[42] However, we did identify a few studies with low to medium risk of bias that have clinical implications and may be considered for incorporation into survivorship guidelines. Specifically, endoscopic dilation can lead to improvement in dysphagia in select patients at risk of pharyngo-esophageal junction stricture.[24] Tailored rehabilitation exercises targeting shoulder dysfunction can improve function and HRQOL,[18] which aligns with a recent systematic review identifying the beneficial effects of physical rehabilitation in cancer survivorship.[44] And a self-help exercises program suggested that dysphagia-related QOL may improve modestly, even among long-term survivors.[16] Even a few studies with a high risk of bias may be considered as routine components of survivorship care, due to the relatively low risk of harm. These include oral opening exercises for trismus and specific swallowing exercise programs. Unfortunately, variations between studies in dysphagia-targeted interventions limit generalizability of interventions. Integration of movement-based programs such as Tai Chi in a survivorship program may also have beneficial effects on general health maintenance and chronic disease prevention through reduction in measures of hypertension and improved aerobic capacity.[30]

We identified very few studies targeting common HNC psychosocial symptoms and conditions, specifically fatigue, neurocognitive function, depression, sexual health, and coping. Only two small studies of Internet-based tools specifically targeted depression and unmet survivorship needs, both showing favorable effects, but requiring more definitive clinical trials with longer follow-up to demonstrate benefit.[34,40] Additionally, we did not identify interventions addressing hearing loss[45] and renal dysfunction associated with cisplatin-induced kidney injury,[46] which are both important side effects of treatment with chemotherapy that impact long-term physical health and function. Additionally, despite the prevalence of sleep-related breathing disorders in patients with HNC after treatment,[47,48] we did not find studies targeting obstructive sleep apnea or other causes of sleep complaints.

We found health outcomes to address function and quality of life, rather than costs, health care utilization and mortality. Studies are needed that investigate and intervene on cost and financial toxicity, a recognized concern for HNC patients that are particularly vulnerable given the high rate of workforce exit[4,5] and gaps in dental coverage.[49] Due to the high prevalence of chronic medical conditions, subsequent cancers, smoking and other symptoms specific to HNC survivors, hospitalization and emergency-department utilization, and mortality are needed.

In addition to characterizing the limited high-quality clinical evidence for the existing HNC survivorship literature, we uncovered a number of methodological gaps, including study design (e.g., integrity of randomization and concealment, lack of blinding of participants and/or outcome assessors), study populations (e.g., small sample sizes, patient heterogeneity), intervention (e.g., limited in

scope, hospital based rather than community-based), and outcome measures (e.g., lack of pre-specified clinically meaningful endpoints, and loss to follow-up without characterization or analysis of impact). These methodological gaps are described below with recommendations for future study design.

First, most of the identified studies enrolled survivors in a hospital-based or academic setting, with few focused on patients in their home/community. As such, the findings may not be generalizable to the population of HNC survivors in a rural or community-based setting. Recruitment and study conduct may have the highest yield of eligible patients in the clinic setting. However, as time from treatment completion increases, some patients may be lost to follow-up for various reasons including discharge, travel time or distance to clinic, and competing health or social circumstances. This may limit participation of follow-up in trials that study endpoints that may occur years after treatment.

Second, study retention and attrition are major limitations to many of the studies we identified. Attrition among HNC survivors and caregivers was characterized in a recent study that identified the most common causes as mortality, logistical, physical, and psychological-related reasons.[50] As patients become less mobile or have more comorbidities, there is a lower likelihood of travel to the hospital setting or participation in multi-timepoint surveys or interventions. Future studies may address these gaps of follow-up by engaging survivors in the community using web-based recruitment and interventions.[51] Another proposed solution to loss-to-follow-up is to oversample specific subgroups such as those with higher comorbidity or higher risk of mortality.[50]

Third, most of the studies we reviewed were relatively small, ranging from 10 to 217 (median 52) participants. This is of particular importance due to the heterogeneity of HNC survivors that receive a range of treatments with physical, psychological, socioeconomic, and other late effects that differ substantially based on patient-factors, cancer-extent and treatments. For example, patients that received laryngectomy may face more difficulty with communication and social isolation than patients treated for early-stage tonsil cancer who are expected to have good swallowing and speech outcomes when treated appropriately.[52] A patient treated with radiation for early glottic larynx cancer would be expected to have limited dental complications from treatment which is focused just on the larynx, compared to a patient treated with surgery and radiation to the mandible for an oral cavity cancer. Sample size and heterogeneity present challenges that limit study power. Including patients with multiple tumor sites, stages, and treatments into the same study may bias the study, most often toward the null, depending on the outcome and study design. Use of large-scale clinical research networks such as PCORnet®, a US-based infrastructure bridging multiple health care systems, may enhance the ability to conduct patient-centered research in the "real-world" setting and may facilitate enrollment of larger patient cohorts. Further, collaborative groups and consortiums may improve the ability to conduct large well-powered studies. Unfortunately, we found that even the largest published randomized control trial in our review, the ECOG chemoprevention trial, was underpowered due to slow-accrual.[13]

As mentioned earlier, a major challenge to studying HNC survivorship is the long latency between the treatment and some targeted health outcomes, including stroke, critical carotid stenosis, hypertension, pituitary endocrinopathy, and other potential late effects. This requires very long follow-up, and it is difficult to design a feasible interventional trial with an outcome that may take more than a decade to manifest. Therefore, trials are needed with intermediary endpoints, such as optimization of cardiac risk factors, specifically targeting chronic disease management, including diabetes, dyslipidemia, and hypertension as well as health promotion and disease prevention, which could include interventions targeting reduction in tobacco, alcohol, weight management, and age-appropriate cancer screening.

Limitations to our study should be acknowledged. It is possible that our pre-specified study inclusion criteria may have excluded informative interventions. For example, studies that intervened on multiple cancer survivor populations were excluded if there were no results shown specifically for HNC survivors. For interventions to reduce distress, increase smoking cessation activities, or target other behavioral outcomes, we may have excluded interventions that are equally relevant to and beneficial for HNC survivors. However, without demonstrating effects in HNC survivors, the relevance to this population is still untested and should be demonstrated in future research. In addition, the purpose of the study was to focus on interventions of HNC survivors without active cancer and beyond the acute toxicity phase of therapy. Therefore, we excluded studies that either did not specify the time from treatment to the study intervention, or that did not include a study time point at least 12 months after HNC treatment. One excluded study that both included too broad of a population over too wide a time window since treatment was a recent trial looking at eHealth self-management application termed "Oncokompas" that evaluated the impact of a computer-based intervention on 625 cancer survivors, including 185 HNC survivors.[53] Because the time from diagnosis or treatment to intervention was not specified for the HNC survivors, we could not ascertain the relevance of this intervention to our population of interest. To inform the care of long-term HNC survivors, a focus on the post-treatment

stage of survivorship is critical and should be included in eligibility and stratification criteria for future trials on survivorship interventions. Our English language restriction may have resulted in under-representation of some studies in our review, especially given high rates of oral cancers in South Central and East Asia.[53] Most studies were from the United States, Canada, Europe, China, and India. Global survivorship care for HNC is clearly a topic that needs more representation in the research domain.

Lastly, our systematic review focused on interventions directed at HNC survivors and not health care providers. For example, an excluded paper showed that thyroid function testing to detect hypothyroidism within a year after radiation completion could be increased through clinician education and maintenance of an institutional database.[54] However, in reviewing the literature, we did not find much attention to such interventions in HNC survivorship.

5 | CONCLUSION

Most studies identified by this systematic review focused on surveillance and management of physical and psychosocial effects of HNC treatment, though we found significant gaps in addressing common symptoms and conditions within these domains. Surveillance and management of chronic medical conditions as well as health promotion and disease prevention were not addressed. Health care outcomes mainly addressed function and quality of life, rather than mortality, costs, and health care utilization. Studies were medium to high risk of bias and limited by lack of blinding, sample size/power calculations, heterogeneity of patients, and loss to follow-up. While there are unique challenges to HNC survivorship research related to heterogeneity of cancer types and treatment, comorbidity, and long latency from treatment to health care outcomes, future rigorously designed studies should address broader areas of care, including chronic disease management and health promotion/disease prevention.

AUTHOR CONTRIBUTIONS

All work was performed by the authors only.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

This systematic review adheres to the guidelines provided by the PRISMA report.

ORCID

Danielle N. Margalit https://orcid.org/0000-0002-8281-0829

Talya Salz https://orcid.org/0000-0002-4515-6004

REFERENCES

1. Mahal BA, Catalano PJ, Haddad RI, et al. Incidence and demographic burden of HPV-associated oropharyngeal head and neck cancers in the United States. *Cancer Epidemiol Biomarkers Prev*. 2019;28(10):1660-1667.
2. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. *Oncologist*. 2010;15(9):994-1001.
3. Osazuwa-Peters N, Simpson MC, Zhao L, et al. Suicide risk among cancer survivors: head and neck versus other cancers. *Cancer*. 2018;124(20):4072-4079.
4. Baddour K, Fadel M, Zhao M, et al. The cost of cure: examining objective and subjective financial toxicity in head and neck cancer survivors. *Head Neck*. 2021;43(10):3062-3075.
5. Mott NM, Mierzwa ML, Casper KA, et al. Financial hardship in patients with head and neck cancer. *JCO Oncol Pract*. 2022;18:e925-e937.
6. Casswell G, Gough K, Drosdowsky A, et al. Fear of cancer recurrence in survivors of human papillomavirus-associated oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2021;111(4):890-899.
7. Kar A, Asheem MR, Bhaumik U, Rao VUS. Psychological issues in head and neck cancer survivors: need for addressal in rehabilitation. *Oral Oncol*. 2020;110:104859.
8. Fullerton ZH, Butler SS, Mahal BA, et al. Short-term mortality risks among patients with oropharynx cancer by human papillomavirus status. *Cancer*. 2020;126(7):1424-1433.
9. Nekhlyudov L, Mollica MA, Jacobsen PB, Mayer DK, Shulman LN, Geiger AM. Developing a quality of cancer survivorship care framework: implications for clinical care, research, and policy. *J Natl Cancer Inst*. 2019;111(11):1120-1130.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
11. Covidence Systematic Review Software, by Veritas Health Innovation, Melbourne, Australia [computer program]. https://www.covidence.org. Accessed January 05, 2022.
12. Alamoudi U, Taylor B, MacKay C, et al. Submental liposuction for the management of lymphedema following head and neck cancer treatment: a randomized controlled trial. *J Otolaryngol Head Neck Surg*. 2018;47(1):22.
13. Bhatia AK, Lee JW, Pinto HA, et al. Double-blind, randomized phase 3 trial of low-dose 13-cis retinoic acid in the prevention of second primaries in head and neck cancer: long-term follow-up of a trial of the Eastern Cooperative Oncology Group-ACRIN Cancer Research Group (C0590). *Cancer*. 2017;123(23):4653-4662.
14. Cramer JD, Grauer J, Sukari A, Nagasaka M. Incidence of second primary lung cancer after low-dose computed tomography vs chest radiography screening in survivors of head and neck cancer: a secondary analysis of a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2021;28:28.

15. Guglielmo M, Di Pede P, Alfieri S, et al. A randomized, double-blind, placebo controlled, phase II study to evaluate the efficacy of ginseng in reducing fatigue in patients treated for head and neck cancer. *J Cancer Res Clin Oncol*. 2020;146(10):2479-2487.
16. Jansen F, Eerenstein SEJ, Cnossen IC, et al. Effectiveness of a guided self-help exercise program tailored to patients treated with total laryngectomy: results of a multi-center randomized controlled trial. *Oral Oncol*. 2020;103:104586.
17. Kaae JK, Stenfeldt L, Hyrup B, Brink C, Eriksen JG. A randomized phase III trial for alleviating radiation-induced xerostomia with chewing gum. *Radiother Oncol*. 2020;142:72-78.
18. McNeely ML, Parliament MB, Seikaly H, et al. Sustainability of outcomes after a randomized crossover trial of resistance exercise for shoulder dysfunction in survivors of head and neck cancer. *Physiother Can*. 2015;67(1):85-93.
19. Millgard M, Tuomi L. Voice quality in laryngeal cancer patients: a randomized controlled study of the effect of voice rehabilitation. *J Voice*. 2020;34(3):486.e413-486.e422.
20. Pereira RMS, Bastos MDR, Ferreira MP, et al. Topical pilocarpine for xerostomia in patients with head and neck cancer treated with radiotherapy. *Oral Dis*. 2020;26:1209-1218.
21. Schutte LER, Melissant HC, Jansen F, et al. Effect of stepped care on sexual interest and enjoyment in distressed patients with head and neck cancer: a randomized controlled trial. *Sex Med*. 2021;9(1):100304.
22. Tang Y, Shen Q, Wang Y, Lu K, Wang Y, Peng Y. A randomized prospective study of rehabilitation therapy in the treatment of radiation-induced dysphagia and trismus. *Strahlenther Onkol*. 2011;187(1):39-44.
23. Vadcharavivad S, Boonroung T. Effects of two carboxymethylcellulose-containing saliva substitutes on post-radiation xerostomia in head and neck cancer patients related to quality of life. *Asian Biomed*. 2013;7(2):193-202.
24. Wu PI, Szczesniak MM, Maclean J, et al. Endoscopic dilatation improves long-term dysphagia following head and neck cancer therapies: a randomized control trial. *Dis Esophagus*. 2019;32(6):1.
25. Al-Bazie SA, Bahatheq M, Al-Ghazi M, Al-Rajhi N, Ramalingam S. Antibiotic protocol for the prevention of osteoradionecrosis following dental extractions in irradiated head and neck cancer patients: a 10 years prospective study. *J Cancer Res Ther*. 2016;12(2):565-570.
26. Chan AS, Cheung MC, Law SC, Chan JH. Phase II study of alpha-tocopherol in improving the cognitive function of patients with temporal lobe radionecrosis. *Cancer*. 2004;100(2):398-404.
27. Chen YH, Wang YK, Chuang YS, et al. Endoscopic surveillance for metachronous esophageal squamous cell neoplasms among head and neck cancer patients. *Cancer*. 2020;12(12):18.
28. De Leeuw J, Prins JB, Teerenstra S, Merkx MAW, Marres HAM, Van Achterberg T. Nurse-led follow-up care for head and neck cancer patients: a quasi-experimental prospective trial. *Support Care Cancer*. 2013;21(2):537-547.
29. Dholam KP, Bachher GK, Yadav PS, Quazi GA, Pusalkar HA. Assessment of quality of life after implant-retained prosthetically reconstructed maxillae and mandibles postcancer treatments. *Implant Dent*. 2011;20(1):85-94.
30. Fong SSM, Ng SSM, Luk WS, Chung JWY, Leung JCY, Masters RSW. Effects of a 6-month Tai Chi Qigong program on arterial hemodynamics and functional aerobic capacity in survivors of nasopharyngeal cancer. *J Cancer Surviv*. 2014;8(4):618-626.
31. Fong SS, Ng SS, Luk WS, Chung LM, Wong JY, Chung JW. Effects of qigong training on health-related quality of life, functioning, and cancer-related symptoms in survivors of nasopharyngeal cancer: a pilot study. *eCAM*. 2014;2014:495274.
32. Kraaijenga SAC, Molen LV, Stuiver MM, et al. Efficacy of a novel swallowing exercise program for chronic dysphagia in long-term head and neck cancer survivors. *Head Neck*. 2017;39(10):1943-1961.
33. Liu CH, Chang JT, Lee TH, et al. Total plaque score helps to determine follow-up strategy for carotid artery stenosis progression in head and neck cancer patients after radiation therapy. *PLoS One*. 2021;16(2):e0246684.
34. Manne S, Hudson S, Frederick S, et al. e-Health self-management intervention for oral and oropharyngeal cancer survivors: design and single-arm pilot study of empowered survivor. *Head Neck*. 2020;23:23-3388.
35. Martin-Harris B, McFarland D, Hill EG, et al. Respiratory-swallow training in patients with head and neck cancer. *Arch Phys Med Rehab*. 2015;96(5):885-893.
36. Montalvo C, Finizia C, Pauli N, Fagerberg-Mohlin B, Andrell P. Impact of exercise with TheraBite device on trismus and health-related quality of life: a prospective study. *Ear Nose Throat J*. 2020;145561320961727:014556132096172.
37. Mozzati M, Gallesio G, Gassino G, Palomba A, Bergamasco L. Can plasma rich in growth factors improve healing in patients who underwent radiotherapy for head and neck cancer? A split-mouth study. *J Craniofac Surg*. 2014;25(3):938-943.
38. Nativ-Zeltzer N, Kuhn MA, Evangelista L, et al. Autologous muscle-derived cell therapy for swallowing impairment in patients following treatment for head and neck cancer. *Laryngoscope*. 2021;14:14.
39. Pauli N, Svensson U, Karlsson T, Finizia C. Exercise intervention for the treatment of trismus in head and neck cancer - a prospective two-year follow-up study. *Acta Oncol*. 2016;55(6):686-692.
40. Sterba KR, Armeson K, Zapka J, et al. Evaluation of a survivorship needs assessment planning tool for head and neck cancer survivor–caregiver dyads. *J Cancer Surviv*. 2019;13(1):117-129.
41. Institute JB. *Checklist for Systematic Reviews and Research Syntheses*; 2017. Accessed April 26, 2022. https://jbi.global/critical-appraisal-tools
42. Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society head and neck cancer survivorship care guideline. *CA Cancer J Clin*. 2016;66(3):203-239.
43. Nekhlyudov L, Lacchetti C, Siu LL. Head and neck cancer survivorship care guideline: American Society of Clinical Oncology clinical practice guideline endorsement summary. *J Oncol Pract*. 2018;14(3):167-171.
44. Sleight AG, Gerber LH, Marshall TF, et al. A systematic review of functional outcomes in cancer rehabilitation research. *Arch Phys Med Rehabil*. 2022. doi:10.1016/j.apmr.2022.01.142
45. Theunissen EA, Zuur CL, Bosma SC, et al. Long-term hearing loss after chemoradiation in patients with head and neck cancer. *Laryngoscope*. 2014;124(12):2720-2725.
46. Bhat ZY, Cadnapaphornchai P, Ginsburg K, et al. Understanding the risk factors and long-term consequences of cisplatin-

associated acute kidney injury: an observational cohort study. *PLoS One*. 2015;10(11):e0142225.
47. Faiz SA, Balachandran D, Hessel AC, et al. Sleep-related breathing disorders in patients with tumors in the head and neck region. *Oncologist*. 2014;19(11):1200-1206.
48. Saesen K, van der Veen J, Buyse B, Nuyts S. Obstructive sleep apnea in head and neck cancer survivors. *Support Care Cancer*. 2021;29(1):279-287.
49. D'Souza RN, Collins FS, Murthy VH. Oral health for all - realizing the promise of science. *N Engl J Med*. 2022;386(9):809-811.
50. Jansen F, Brakenhoff RH, Baatenburg de Jong RJ, et al. Study retention and attrition in a longitudinal cohort study including patient-reported outcomes, fieldwork and biobank samples: results of the Netherlands quality of life and biomedical cohort study (NET-QUBIC) among 739 head and neck cancer patients and 262 informal caregivers. *BMC Med Res Methodol*. 2022;22(1):27.
51. Kelly R, Gordon P, Thompson R, Semple C. Availability and use of web-based interventions for patients with head and neck cancer: a scoping review. *J Cancer Surviv*. 2022;1-18. doi:10.1007/s11764-022-01168-1
52. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. *Lancet Oncol*. 2019;20(10):1349-1359.
53. van der Hout A, van Uden-Kraan CF, Holtmaat K, et al. Role of eHealth application Oncokompas in supporting self-management of symptoms and health-related quality of life in cancer survivors: a randomised, controlled trial. *Lancet Oncol*. 2020;21(1):80-94.
54. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
55. Bhatt N, Taufique Z, Kamen E, et al. Improving thyroid function monitoring in head and neck cancer patients: a quality improvement study. *Laryngoscope*. 2019;28:28.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Margalit DN, Salz T, Venchiarutti R, et al. Interventions for head and neck cancer survivors: Systematic review. *Head & Neck*. 2022;44(11):2579-2599. doi:10.1002/hed.27142