Diet and Exercise Interventions in Patients With Pancreatic Cancer
A Scoping Review

Popi Kasvis, MSc*‡ and Robert D. Kilgour, PhD*‡

Abstract: Diet and exercise interventions may help reverse malnutrition and muscle wasting common in pancreatic cancer. We performed a scoping review to identify the knowledge gaps surrounding diet and exercise interventions. We searched PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature, Embase, ProQuest Theses and Dissertations, and Google Scholar using the umbrella terms of “pancreatic cancer,” “diet/nutrition,” and “exercise.” Included were articles reporting on ambulatory adults with diagnosed pancreatic cancer. Excluded were studies examining prevention and/or risk, animal, or cell lines. Of the 15,708 articles identified, only 62 met the final inclusion criteria. Almost half of the articles were randomized controlled studies (n = 27). Most studies were from the United States (n = 20). The majority examined dietary interventions (n = 41), with 20 assessing the use of omega-3 fatty acids. Exercise interventions were reported in 13 studies, with 6 examining a diet and exercise intervention. Most studies were small and varied greatly in terms of study design, intervention, and outcomes. We identified 7 research gaps that should be addressed in future studies. This scoping review highlights the limited research examining the effect of diet and exercise interventions in ambulatory patients with pancreatic cancer.

Key Words: scoping review, pancreatic neoplasm, diet, nutrition, exercise

Pancreatic cancer is a deadly disease, with a 5-year relative survival rate of 9%.1 Canadian projections for 2019 indicate that mortality from pancreatic cancer will surpass that of breast cancer, becoming the third deadliest form of the disease.2 Similarly, it is estimated that in 2020, pancreatic cancer will be the fourth leading cause of all cancer deaths in the United States. The most effective curative treatment is surgical resection with systemic chemotherapy, which seems to improve health-related quality of life (HRQoL) despite possible treatment toxicities.5 The positive effect of palliative treatment in advanced cancer may be muted by poor nutritional status, as a direct relationship with HRQoL has been demonstrated.6 This is of particular concern in patients with pancreatic cancer, as up to 85% experience unintentional weight loss and malnutrition.7,8 The etiology of malnutrition in pancreatic cancer is multifactorial, and includes the following: pancreatic exocrine and endocrine disturbances, cytokine-induced catabolism and altered metabolism, increased energy requirements, anorexia leading to decreased oral intake, and nutrition impact symptoms related to both treatments and the disease.9 These components of malnutrition are related to both muscle wasting and cachexia, commonly seen in patients with pancreatic cancer. Prevalence of muscle wasting in both resectable and nonresectable pancreatic cancer ranges between 19% and 68% at diagnosis.10-12 This is of concern as low muscle mass is associated with worse perioperative outcomes, decreased survival, and increased chemotherapy-induced toxicity.13 There is also evidence that chemotherapy itself may be responsible for muscle wasting.14 In addition, the prevalence of cachexia in patients with pancreatic cancer ranges between 70% and 80% at diagnosis and causes one third of deaths.15 Although it is evident that malnutrition, muscle loss, and cachexia are prevalent in pancreatic cancer, it is unclear if there are interventions that may help counteract these adverse phenomena. It is reasonable to question whether ambulatory diet and exercise interventions, applied either before or during cancer treatment, may help stave off malnutrition and muscle loss and enhance HRQoL. Therefore, we conducted a scoping review to assess the current state of knowledge, and to identify research gaps, in diet and/or exercise interventions previously investigated in ambulatory patients with pancreatic cancer. The outcome of this scoping review may help inform the design of novel interventions.

MATERIALS AND METHODS

The framework of this scoping review was developed based on the method of Arksey and O’Malley.16 Steps for reporting the results of this scoping review follow the 22 items outlined in the “Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation.”17

Search

To identify potentially relevant articles, 6 electronic databases (PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature, Embase, ProQuest Theses and Dissertations, and Google Scholar) were searched from inception to August 4, 2020. The fundamental structure of the search strategy used was as follows: [Pancreatic cancer] AND (diet/nutrition OR exercise). An experienced subject librarian was consulted to ensure completeness and refinement of the search terms and strategy (see Supplementary Table 1, http://links.lww.com/MPA/A869, for the PubMed search strategy used). Hand searching of the citations in review articles deemed to be of interest was performed by P.K. to ensure that no articles were overlooked.7,9,15,18-39 The subject librarian also guided the organization of articles collected and the tracking of selected articles.
articles. Search results were exported into Zotero, and duplicates were removed.

**Inclusion and Exclusion Criteria**

Articles included in this scoping review were published in English and had a diet and/or exercise intervention administered to ambulatory adult patients with pancreatic cancer. Excluded were articles reporting prevention or risk factors of pancreatic cancer, studies in animals, pediatric populations or cell lines, and studies focusing on nonmalignant pancreatic disease (eg, pancreatitis). It was also decided to exclude nonambulatory patients, and thus perioperative nutrition support, as the goal of this review was to assess interventions in ambulatory patients. Articles reporting the results of trials, retrospective studies, case studies, review articles, and gray literature (eg, graduate theses) were all considered in this review. In addition, there were no date limits placed on our search to ensure the most complete results. Inclusion and exclusion criteria for the final selection of the articles are outlined in Table 1.

**Screening and Data Extraction**

The title and abstracts of all articles were screened independently by P.K. and R.D.K. Each article was labeled “yes,” “no,” or “maybe” if there was uncertainty. The independent screening results of each reviewer were compared to identify disagreement. The full text of disputed articles was accessed to allow for discussion and final consensus on inclusion. In addition, the full text of all articles the authors agreed to include in the study was accessed. Data charting tables were developed collaboratively by the reviewers, with variables of interest identified. Data were then charted by P.K. and reviewed by R.D.K. Data of interest included study design; date of publication; country where the intervention took place; antineoplastic treatment modalities; whether the intervention included diet, exercise, or diet and exercise; and overall intervention type (eg, diet, exercise, or diet and exercise) and then by study type (eg, diet, exercise, or diet and exercise) and then by primary outcome identified. Data were then charted by P.K. and reviewed by R.D.K. Each article was labeled “yes,” “no,” or “maybe” if there was uncertainty. The independent screening results of each reviewer were compared to identify disagreement. The full text of disputed articles was accessed to allow for discussion and final consensus on inclusion. In addition, the full text of all articles the authors agreed to include in the study was accessed. Data charting tables were developed collaboratively by the reviewers, with variables of interest identified. Data were then charted by P.K. and reviewed by R.D.K. Data of interest included study design; date of publication; country where the intervention took place; antineoplastic treatment modalities; whether the intervention included diet, exercise, or both; specifics on intervention type and dose; outcomes; and adverse events. Each article was deemed as having a positive or negative result based on whether the primary study objective was achieved. Finally, studies were grouped by the overall intervention type (eg, diet, exercise, or diet and exercise) and then by the specific intervention (eg, omega-3 fatty acids, resistance exercise).

**RESULTS**

A total of 15,708 articles were found: PubMed, 4184; Scopus, 4147; Cumulative Index to Nursing and Allied Health Literature, 1162; Embase, 5876; ProQuest Dissertations and Theses, 149; and Google Scholar, 190. Of these, 8055 articles were duplicates, leaving 7653 articles to be reviewed. After reviewing titles and abstracts, 7489 articles were excluded, and the full text of 164 articles was retrieved and examined for inclusion. Of these, 102 articles were excluded, leaving 62 studies deemed to meet the eligibility criteria of this review. The PRISMA flow diagram outlining the selection process is reported in Figure 1. Of the 62 studies included in this review, 41 reported dietary interventions\(^\text{40–80}\) (see Supplemental Table 2, http://links.lww.com/MPA/A869), 13 exercise interventions\(^\text{81–95}\) (see Supplemental Table 3, http://links.lww.com/MPA/A869), and 8 a combination of both\(^\text{96–101}\) (see Supplemental Table 4, http://links.lww.com/MPA/A869). Almost half of the articles were randomized controlled trials (n = 27), followed closely by prospective cohort studies (n = 26). Five case reports described exercise interventions, with 1 describing a dietary intervention. Most studies were conducted in the United States (n = 20), the United Kingdom (n = 15), and Germany (n = 9). Characteristics of the included studies are reported in Table 2.

**Dietary Interventions**

**Omega-3 Fatty Acids**

A total of 20 (54%) of all dietary intervention studies reported findings related to omega-3 fatty acid supplementation.\(^\text{40–59}\) All studies used products enriched with eicosapentaenoic acid (EPA). Supplementation was delivered in the form of an enriched oral nutritional supplement (ONS) in 12 of these studies,\(^\text{40–51}\) via peripheral intravenous infusion with chemotherapy in 4 studies,\(^\text{52–55}\) and orally in the form of an emulsion or capsule in 4 studies.\(^\text{56–59}\) Eicosapentaenoic acid dosing was 2.2 g/d in the studies using ONS,\(^\text{40–51}\) and 4.3 to 8.6 g/infusion of combined EPA and docosahexaenoic acid.\(^\text{52–55}\) Dosage did not vary among the ONS and infusion studies, as they were performed by the same study groups. However, there were conflicting dosages and sources of omega-3 fatty acids in the studies providing oral EPA, varying from 300 mg of marine phospholipids and fish oil supplements to studies hoping to achieve a maximum intake of 6 to 36 g/d of EPA in participants.\(^\text{56,58,59}\) Primary outcomes of the studies varied widely. Most of the studies reported nutritional status outcomes, such as changes in energy expenditure,\(^\text{42,49}\) weight,\(^\text{44–47,49,53,57–59}\) and body composition.\(^\text{40,46,48}\) The effect of EPA on various cytokines (eg, interleukin-6 [IL-6]) and acute phase proteins (eg, albumin, C-reactive protein) was reported in 6 studies.\(^\text{51,43,45,51,58,59}\) The anticancer effect of EPA was reported in 3 studies.\(^\text{50,52,55}\) Finally, outcomes on safety and tolerability was the focus of 1 study.\(^\text{42}\) Reported improvements in nutritional parameters were mixed. Weight stabilization or gain was reported in 5 of the 8 studies with this primary outcome; however, EPA had no effect on body composition. Although Barber et al.\(^\text{42}\) reported reduced resting energy expenditure and fat oxidation in the fasted state, this was contradicted by Moses et al.\(^\text{40}\) who found that total energy expenditure was greater in those with highest EPA intake. There was no effect of EPA on cytokine reduction or acute-phase protein modulation. After 3 weeks of fish oil supplementation, Barber et al.\(^\text{41}\) reported a decrease in production of IL-6, but not IL-1β or tumor necrosis factor. Overall, there was no change in albumin\(^\text{41,45,51}\) or C-reactive protein\(^\text{51,53,58,59}\) after supplementation; however, an increase in transferrin was reported by Barber et al.\(^\text{41}\)

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<th>TABLE 1. Inclusion and Exclusion Criteria</th>
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<td><strong>Inclusion Criteria</strong></td>
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<td>• Pancreatic cancer, all stages</td>
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<td>• Must report on a diet and/or exercise intervention</td>
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<td>• All treatment types (chemotherapy, surgery, or radiation)</td>
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<td>• Nonpancreatic cancer</td>
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<td>• Prevention or risk factors of pancreatic cancer</td>
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<td>• Animal or cell line studies</td>
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Mixed results were also found supporting the antineoplastic effect of EPA. Arshad et al\textsuperscript{52} reported objective response rate in only 14% of patients, a finding corroborated by Ueno et al,\textsuperscript{50} who found no significant difference in 1-year survival between those receiving an EPA-rich ONS and controls. In another study, Arshad et al\textsuperscript{55} reported that 85.7% of patients receiving concomitant gemcitabine and omega-3 fatty acid–rich lipid infusions had stable disease, with partial response of liver metastases in 41% of patients.

Preoperative Nutrition Interventions (Immunonutrition)

Immunonutrition refers to the modulation of the immune system, and/or the downstream effects of immune activation, by nutrients consumed in amounts greater than what is found in a regular diet.\textsuperscript{102} These nutrients include omega-3 fatty acids, amino acids such as glutamine and arginine, antioxidants, and nucleotides.\textsuperscript{102} Five studies examined the effect of preoperative oral immunonutrition supplementation on various postoperative outcomes.\textsuperscript{60-64} Immunonutrition was delivered per os via an ONS in all 5 studies. All studies had a control group and compared immunonutrition with placebo,\textsuperscript{60} standard care,\textsuperscript{63} or to no particular control intervention.\textsuperscript{62-64} Primary outcomes of interest were postoperative complications, infections, and hospital length of stay for 3 of the studies,\textsuperscript{61-63} with the effect on antioxidant capacity and inflammatory response examined in 2 studies.\textsuperscript{60,64} Results were mostly positive, with reduced length of hospital stay and complications reported in 2 of the 3 studies.\textsuperscript{62,63} Although antioxidant capacity was greater in the immunonutrition group,\textsuperscript{60} there was no significant effect on inflammatory markers.\textsuperscript{50,64}

Dietary Counseling

Dietary counseling by a registered dietitian, with or without the use of ONS, was found in 4 of the included studies.\textsuperscript{65-68} The goals of the dietary interventions varied greatly and included changes in weight, body composition, and HRQoL;\textsuperscript{65} if patients met their protein needs;\textsuperscript{66} nutrition status and survival;\textsuperscript{67} and if a soft diet decreased the occurrence of bowel obstruction.\textsuperscript{68} Two of the studies were retrospective in design.\textsuperscript{67,68} Dietary counseling with the use of an ONS had a positive effect on macronutrient intake and a greater gain of fat mass, compared with only increased protein intake in those who received counseling alone.\textsuperscript{65} However, despite improved protein intake, most of the patients did not meet their protein needs.\textsuperscript{66} Dietary counseling also either stabilized or improved nutritional status, as evaluated by Subjective Global Assessment, in 70% of patients who received counseling.\textsuperscript{67} Nutritional status was found to be an independent predictor of survival.\textsuperscript{67} Finally, dietary counseling promoting a prophylactic soft diet led to no patients developing bowel obstruction, compared with 71% of noncounseled controls.\textsuperscript{68}

Vitamin D

Two studies examined the effect of oral vitamin D supplementation.\textsuperscript{69,70} The first examined the effect of taking calcitriol (0.5 μg/kg) on the day before receiving standard docetaxel treatment
on time to progression. Results demonstrated no improvement on time to progression or overall survival. The second study examined whether vitamin D supplementation (various dosages based on disease status and malabsorption) combined with pancreatic enzyme replacement therapy can normalize serum 25-hydroxy vitamin D levels. This time, results were positive with 25-hydroxy vitamin D status normalized in patients with pancreatic cancer, albeit with a large dosage required (up to 20,000 IU/d).

**Enteral Nutrition**

One prospective, single-arm study examined if weight maintenance could be achieved through peptide-based, jejunal tube feeding in patients with pancreatic cancer with cachexia. Almost 2/3 (n = 10) of patients maintained their weight after 3 months in this small study.

**Parenteral Nutrition**

The effect of overnight, home-based parenteral nutrition on nutritional status was reported in 2 studies. Both studies reported weight maintenance or gain in most of the patients, with Richter et al reporting these positive results in only those with survival more than 5 months. Both studies provided ~25 kcal/kg, with omega-3 fatty acids administered to 76% of patients in the study by Richter et al.

**Supplements and Alternative Interventions**

The effect of oral curcumin supplementation was examined in 2 studies. In both studies, 8 g of curcumin per day was prescribed. The response to the treatment was mostly negative, with most of the participants exhibiting disease progression. There was an anti-inflammatory effect found due to a significant reduction in inflammatory COX-2 expression and pSTAT3 activation. Oral bioavailability was low with significant gastrointestinal toxicity leading to the cessation of treatment in some patients.

One study examined the effect of L-carnitine, a molecule derived endogenously or through diet and involved in the metabolism of fatty acids, on cachexia in patients with pancreatic cancer. Participants were asked to consume a liquid formulation of L-carnitine, providing 4 g/d for 12 weeks, compared with placebo. Results were overall negative, as there were no differences between groups in C-reactive protein, albumin, leukocyte count, carbohydrate antigen 19-9, or survival. Body mass index and fat mass increased in the L-carnitine group, but not lean body mass.

Another study looked at the effect of active hexose correlated compound (AHCC), a functional food extracted from the mycelia of the shiitake mushroom, on reducing adverse events related to gemcitabine. Patients were asked to take 6 g of AHCC orally for 8 weeks, corresponding to 2 cycles of gemcitabine. Results were mostly positive; although there were no differences in hematological outcomes, grade 3 modified Glasgow Prognostic Scale scores, taste disturbances, and C-reactive protein were lower, and albumin is higher, in the AHCC group.

The feasibility of administering another functional food, broccoli sprouts, was examined in a placebo-controlled pilot study. Patients were asked to consume 15 capsules daily of pulverized broccoli sprouts containing 90 mg of sulforaphane and 180 mg of glucophanin for 1 year. Results were disappointing, with 21% of the treatment group dropping out within 1 month of starting the intervention and 72% before the 1 year end point. Taste, possible gastrointestinal discomfort, and the burden of taking numerous capsules each day were some reasons cited for this poor outcome.

A retrospective study of patients who followed an alkaline diet and received bicarbonate therapy reported the effect of this intervention on urinary pH and survival in patients with advanced...
pancreatic cancer. The alkaline diet consisted of patients consuming at least 400 g of fruits and vegetables and the avoidance of meat and dairy products. Participants were also prompted to take 3 to 5 g/d of oral bicarbonate if their urine pH was less than 7. Unsurprisingly, urine pH increased with this treatment. The authors also report that patients with urine pH 7 or higher had greater survival than those whose urine was acidic. It is difficult to extrapolate any effect on cancer by this intervention, given the normal acid-base regulation of the lungs and kidneys.

Finally, 1 pilot case series examined an alternative treatment combining dietary modification (raw or lightly steamed fruits and vegetables, daily vegetable juice, plant-based proteins, with daily freeze-dried thymus or liver supplements, 25 to 40 g of porcine lyophilized pancreas product, and detoxification with twice-daily coffee ememas. The effect of this intervention on survival was positive, with 81% of patients surviving for 1 year, which the authors state is better than those whose urine was acidic. It is difficult to extrapolate any effect on cancer by this intervention, given the normal acid-base regulation of the lungs and kidneys.

Exercise Interventions

Aerobic Exercise

Two studies reported on the effect of a walking program. One study examined safety and feasibility and the other the effect on fatigue, physical function, and HRQoL. Walking programs were well tolerated, with 68% of patients completing the study, and most dropouts were due to declining health. Brisk walking for 90 to 150 minutes per week, divided into 3 to 5 sessions, for a 3-month period had a positive effect on fatigue and reported physical health compared with usual care controls, but not performance status or symptom burden.

Resistance/Strength Training Interventions

Four studies examined the effect of strength training as a monotherapy. One case study described the utilization of ultrasound imaging to guide motor control training in a patient after Whipple surgery. Abdominal muscle training, trunk stretching, spine stabilization exercises, and progressive strengthening exercises were performed and progressed based on performance to address postoperative impairment and functional limitations. The results were positive, with improvements in pain, muscle performance, and functional scores reported at 5 weeks, 12 months, and 18 months postoperatively. The results of a randomized controlled trial produced 2 articles that reported outcomes of a supervised versus home-based resistance training program, versus a usual care control group. The intervention lasted 60 minutes, 2 times/wk, and included the following exercises: leg press, leg extension, leg curl, seated row, latissimus pull-down, back extension, butterfly reverse, and crunch. Each exercise was performed 8 to 12 times for 2 to 3 sets each. Overall adherence to the program was 64.1% in the supervised group and 78.4% in the home-based group, with completion of more than 50% of the intervention in those who completed the study. Maximal isokinetic peak torque improved significantly in the supervised group for elbow flexors and extensors compared with the home-based and control group. Maximal voluntary isometric contraction improved significantly in the supervised group for elbow flexors compared with control. Both intervention groups improved in knee extensors. There was a beneficial effect of the intervention on HRQoL and fatigue in the short term. At 3 months, physical functioning, global HRQoL, cognitive functioning, sleep problems, physical fatigue, and reduced activity were significantly different than controls. This was not the case at 6 months. Finally, a resistance training intervention to improve mobility, strength, and lean body mass in cachectic patients with pancreatic cancer was explored. Over a 12-week period, the intervention group received a twice weekly, 8-exercise, supervised program targeting all major muscle groups, versus a control group who received no intervention. The intervention improved function as measured by the 400-m walk test, 6-m usual walk test, and chair rise, compared with control. In addition, peak torque extension of the knee and both elbow flexor and extensors also improved. Appendicular lean mass was also greater in the intervention group after 12 weeks compared with controls.

Combined Aerobic and Resistance/Strength Training Interventions

The majority of exercise interventions included both an aerobic and resistance training component. Of the 7 studies, 3 were prospective and offered a home-based exercise program, of these, 2 were pilot studies. The remaining 4 articles were case studies/reports, one of which was designed as a randomized controlled trial but reported as a case series due to poor recruitment. All of the case studies offered supervised exercise interventions, whereas the prospective studies examined home-based exercise programs. Frequency of exercise interventions varied from 2 times/wk to daily at a duration of approximately 60 minutes/session. Targeted resistance exercises of both upper and lower body muscle groups were explored in 4 studies, with 1 study only assigning lower body exercises and 2 studies not reporting which muscle groups were targeted. Three studies reported that patients were asked to perform 2 to 3 sets of between 8 and 12 repetitions. Aerobic exercises were performed with ergometers, with gym equipment (treadmill, elliptical, and rowing machine), or by bicycling or walking. Study outcomes varied widely and included feasibility, adherence and safety, changes in vascular function, improvements in physical function, muscle mass, HRQoL, and fatigue. All of these exercise studies had positive results. Exercise can be safely prescribed, with good overall adherence to aerobic programs but mixed results on reported adherence to resistance exercise.

In the case studies, both subjective (eg, patient-reported physical function as assessed by the Functional Assessment of Cancer Therapy-General [FACT-G] questionnaire, Godin Leisure-Time Exercise questionnaire, Global Questionnaire of Physical Activity) and objective measures (eg, 400-m walk test, 1-repetition maximum, 1-repetition maximum, chair sit-to-stand, and stair climb) showed improvement. In addition, muscle mass, as measured by both dual-energy X-ray absorptiometry and bioelectrical impedance analysis, also improved. However, in the study by Marker et al, the positive effect on lean mass was only seen in the preoperative period, with losses experienced postoperatively. Health-related quality of life measurements (FACT-G, FACT-Hepatobiliary, EORTC-C30, and Short Form-36) improved in all case studies. In addition, fatigue, as reported using the Functional Assessment of Chronic Illness–Fatigue questionnaire, improved over the intervention periods.

Diet and Exercise Interventions

There were 8 studies reporting on interventions that included both a diet and exercise components. All study participants were awaiting pancreatic surgery and underwent prehabilitation, with the intervention applied in the preoperative period. Three of the studies were subanalyses of a larger prehabilitation study. The nutrition interventions included protein supplementation (whey and leucine-rich essential amino acids), EPA-rich ONS, 5 days of immunonutrition ONS preoperatively, and nutritional
counseling (high energy–protein diet and management of nutrition impact symptoms).93–95,99–101 Protein recommendations and goals varied and included recommending dietary intake of 1.3 to 1.5 g/kg per day,7,99–101 having a protein-rich meal or snack (at least 20 g) within 1 hour of strength training,93,95 or consuming a leucine-rich amino acid supplement within 30 minutes pre/postexercise.98 The exercise component of the intervention included both aerobic and strength training in all studies but one;96 in which attaining a step count was the goal. The exercise prescriptions were not always detailed; however, 3 studies reported strengthening exercises included upper and lower body large muscle groups and ranged from 2 to 3 sets of 8 to 12 repetitions of each exercise.95,96,98 Primary outcomes of the studies also varied widely, with feasibility and adherence reported in 2 studies.94,95 Changes in physical function (measured using the 6-minute walk test)96–98 and body composition (as measured by bioelectric impedance analysis)99–101 were reported in 3 studies each. Nutritional status,98 HRQoL,96 and surgical outcomes98 were examined in only one study each. Of the 8 studies, 5 reported positive results.94–96 Exercise and nutrition interventions were feasible, with greatest adherence reported for the nutritional and aerobic components of the intervention.94,95 Prescribed strengthening exercises were least adhered to,97 mirroring the results of other studies.97 Results of functional outcomes were positive, with increased distance walked in the 6-minute walk test from baseline to the preoperative assessment in the 3 studies that examined this outcome.96–98 However, body composition was not improved in the preoperative period, and decreased weight, fat mass, and fat-free mass were found 6 weeks postsurgery.99–101 The study by Nakajima et al98 was the only one reporting outcomes on nutritional status beyond body composition; the prognostic nutritional index improved in the treatment group, with preoperative albumin dropping only in the control group. In addition, Nakajima et al98 reported fewer postoperative bile leaks and shorter hospital length of stay in the intervention group compared with controls. Finally, HRQoL as measured by the FACT-G and FACT-Hepatobiliary was not different from baseline at the preoperative assessment.96

**DISCUSSION**

A summary of dietary and exercise interventions provided to ambulatory, adult patients with pancreatic cancer have been outlined in this scoping review. Our review included articles with a variety of study designs, originating from many different countries and with no date restriction. Despite our wide search criteria, only 62 articles were identified. As the goal of this review was to identify gaps in the literature, specifics on the intervention, assessments, and outcomes were examined.

**Research Gaps**

Of the 62 articles, most described a nutrition-centered intervention (n = 41), of which the effect of omega-3 fatty acids was most widely examined (n = 20), followed by preoperative nutrition intervention (including immunonutrition); dietary counseling by a registered dietitian; the use of vitamin D supplementation; home-based enteral and parenteral nutrition; supplements such as curcumin, L-carnitine, AHCC, and broccoli sprouts; and finally, 2 alternative therapies. It is difficult to determine which, if any, of these dietary interventions should be explored further for a multitude of reasons: 1) most studies were small, single-center studies, 2) not all studies had a true control group, and 3) the heterogeneity of the patient population (eg, resectable versus nonresectable, patients receiving antineoplastic treatment versus those who were not). An additional difficulty was identified in the omega-3 studies, as there was a wide variety of doses and/or modes of administration (eg, ONS versus parenteral versus oral) and/or substances (eg, EPA rich versus EPA alone versus marine phospholipids versus fish oil) that were used in each intervention. The greatest amount of evidence seems to suggest that dietary counseling with the use of an ONS (regardless of EPA content) may improve overall macronutrient intake, nutritional status, and body composition.94,95–97,99–101 The questionable benefit of an EPA-rich ONS was demonstrated by Fearon et al.94 In a randomized, placebo-controlled trial where almost 200 participants consumed either an EPA-rich or an isocaloric standard ONS, no difference between groups was found in the attenuation of weight loss, improved performance, or HRQoL scores. However, these negative results may be due to difficulty in compliance, rather than the EPA-rich ONS being ineffective. Noncompliance to ONS prescription was also reported by Akita et al.94 because of the poor taste of the supplement. Therefore, it seems clear that a measure of compliance when interventions include ONS should be included in future studies. In addition, compliance would be improved if care is taken with ONS palatability and prescribed in small volumes.65 Future interventions should be randomized in nature, with a placebo-controlled group, offering dietary counseling along with an ONS. Furthermore, the ability of immunonutrition to improve surgical outcomes would also require further study, as no study compared immunonutrition to a standard ONS as a placebo-control.

Thirteen studies described exercise interventions, which were a mix of aerobic (n = 2), resistance (n = 4), or combined aerobic and resistance exercise programs (n = 7); there is a paucity of data on all these types of exercise interventions in patients with pancreatic cancer. Available evidence may be considered weak solely based on study design, as 5 of the studies reported either a case report or series. The types of aerobic (walking and ergometers) exercises prescribed as well as the tools used to perform resistance training (free weights, elastic tubes, and weight machines) varied widely. In addition, as with the dietary interventions, patients studied were heterogeneous in nature, based on treatments and stage of disease. Multiple outcomes were assessed and included adherence, safety and feasibility, physical function, muscle strength and cardiovascular fitness, body composition, fatigue, and psychological well-being: any of these outcomes can be reexamined in future studies to strengthen available evidence. Five studies examined home-based interventions, 6 examined a supervised intervention (only 1 of which was a randomized controlled trial, with the rest being case studies), and 2 compared home-based with supervised exercise sessions (these 2 studies reported outcomes from the same cohort). Therefore, with the current state of knowledge, it cannot be determined whether home-based or supervised interventions are best in this patient population. However, clinical practice guidelines recommend that supervised exercise is preferable for people living with cancer.103

This review demonstrated that very few studies examined a combined exercise and nutrition intervention (n = 8). Of these 8 studies, all described prehabilitation interventions designed to support patients through neoadjuvant treatments and improve functional and nutritional reserves in preparation for surgery. Unlike the previously described nutrition interventions, those combined with exercise often included amino acid/protein supplementation, either with L-leucine or whey protein, to promote muscle protein synthesis. There were a variety of main outcomes reported, including feasibility, adherence, relationships between physical activity and HRQoL, functional capacity, postoperative complications, length of hospital stay, and body composition. There were no multimodal studies examining the effect of diet and exercise on patients with advanced pancreatic cancer who were not surgical candidates but receiving palliative chemotherapy. The application of a multimodal intervention in patients whose treatment goals

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are noncurative is challenging. The presence of both tumor and host-derived proinflammatory cytokines in patients with cachexia leads to metabolic disturbances promoting lipolysis and proteolysis.104 As such, anabolic resistance may be present despite targeted diet and exercise treatments. Recent guidelines by the American Society of Clinical Oncology suggest only moderate benefit of nutritional counseling and unknown benefit of exercise in patients with cancer cachexia, with the strength of evidence determined to be low.105 Other challenges in designing multimodal studies targeting patients with advanced pancreatic cancer are treatment related. For example, achieving adequate oral intake is difficult for patients receiving palliative chemotherapy due to common treatment adverse effects, such as anorexia, dysgeusia, nausea, and vomiting. Nutrient malabsorption related to pancreatic exocrine insufficiency, as an adverse effect of a Whipple procedure or due to the tumor itself, also leads to malnutrition and wasting. Finally, exercise in this patient population may not be feasible due to pain, which is present in up to 80% of patients with advanced pancreatic cancer.106 Despite these difficulties, it is worth investigating the role of early multimodal interventions as an adjunct to chemotherapy.107 Preliminary evidence suggests an anti-inflammatory benefit of resistance and aerobic exercise108 and the capacity of resistance exercise and dietary protein, in particular the essential branched-chain amino acid leucine, to stimulate muscle protein synthesis.109 A systematic review recently demonstrated that exercise interventions seem to maintain physical function and may improve quality of life in patients with advanced cancer, although improvements in fatigue remain unclear.110

Implications for Future Research

This scoping review revealed a scarcity of studies examining the effect of dietary and exercise interventions in patients with pancreatic cancer. Of particular note, we recommend the following be examined more closely in well-designed, randomized, placebo-controlled (where applicable) trials:

1) A combined nutrition and exercise intervention
2) The nutrition component should include dietary counseling and supplementation (consider ONS, protein)
3) Alternatively, a nutrition intervention examining immunonutrition versus a standard ONS should be examined in patients awaiting pancreatic surgery
4) The exercise intervention should include both aerobic and resistance training
5) Supervised versus home-based exercise programs should be studied specifically in patients with pancreatic cancer
6) The effect of a multimodal intervention in nonsurgical patients undergoing palliative chemotherapy has yet to be reported
7) As outcomes measured in all reported studies are very heterogeneous, any can be chosen. The following are proposed examples:
   a. Trial design in which patient-reported outcomes and HRQoL measures are outcomes of interest, considering the palliative nature of treatments
   b. Relationships between nutritional status, muscle mass, and chemotherapy tolerance

Strengths and Weaknesses of the Review

The strength of this review was the use of the PRISMA-ScR methodology to identify a research question, create our search strategy, and choose the final articles included herein. The clearly defined inclusion and exclusion criteria and the inclusion of gray literature allowed for the maximal number of studies and interventions to be identified. The weakness of this scoping review, as in all scoping reviews, is the inability to evaluate the quality of each study. It may also be argued that a weakness of this study was to not include pancreatic enzyme replacement therapy (PERT) as a sole nutritional intervention. This was done intentionally as the authors felt that PERT may warrant a scoping review of its own and that our search criteria were not broad enough to ensure the capture of all relevant articles. Interventions with a nutrition intervention that included PERT were reviewed in this study, but not PERT on its own.

CONCLUSIONS

This scoping review has helped elucidate the current state of knowledge and identified gaps in the literature regarding diet and/or exercise interventions in ambulatory patients with pancreatic cancer. At the present time, there are a limited number of studies examining such interventions, with a particular lack of information on multimodal approaches. A striking gap in the literature is that a combined diet and exercise intervention in patients receiving palliative treatments has yet to be examined. As such, this may be of particular interest to researchers, given the overall poor survival rate, multiple treatment and surgical adverse effects, and overall disease burden in these patients. Dietary and exercise interventions may help improve HRQoL while supporting patients through palliative treatments.

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