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# Prehabilitation for adults diagnosed with cancer: a systematic review of long-term physical function, nutrition and psychological outcomes



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**Title:** Prehabilitation for adults diagnosed with cancer: a systematic review of long-term physical function, nutrition and patient reported outcomes

**Abstract:**

Prehabilitation is increasingly being used as an intervention to mitigate treatment-related complications and enhance recovery. An individual's state of health at diagnosis including; obesity, physical fitness and comorbidities, are influencing factors for the occurrence of adverse effects. This review explores whether prehabilitation works in improving health outcomes at or beyond the initial 30-days post treatment and considers the utility of prehabilitation before cancer treatment. A database search was conducted for articles published with prehabilitation as a pre cancer treatment intervention between 2009-2017. Studies with no 30-day post treatment data were excluded. Outcomes post prehabilitation were extracted for physical function, nutrition and patient reported outcomes. Sixteen randomised controlled trials with a combined 2017 particpants and six observational studies with 289 particpants were included. Prehabilitation interventions provided multi-modality components including exercise, nutrition and psycho educational aspects. Prehabilitation improved gait, cardio pulmonary function, urinary continence, lung function and mood 30-days post treatment but was not consistent across studies. When combined with rehabilitation, greater benefits were seen in 30 day gait and physical functioning compared to prehabilitation alone. Large scale randomized studies are required to translate what is already known from feasibility studies to improve overall health and increase long-term cancer patient outcomes.

**Key words:** Prehabilitation, Rehabilitation,Cancer, Exercise, Nutrition, Survivorship

**Title:** Prehabilitation for adults diagnosed with cancer: a systematic review of long-term physical function, nutrition and patient reported outcomes

## Introduction

Prehabilitation offers a route to improving patient's physical status and buffering treatment-related deconditioning between the time of cancer diagnosis and post treatment recovery. Prehabilitation includes physical and psychological assessments that establish baseline functioning and identify impairments that can impact on cancer treatment-related morbidity, as well as providing targeted interventions to maximize patient function prior to treatment onset (Silver and Baima, 2013). The primary goal of prehabilitation is "*to prevent or reduce the severity of anticipated treatment-related impairments that may cause significant disability (page2)* (Silver and Baima, 2013). There are several systematic reviews of prehabilitation for those receiving cancer surgery (Boereboom et al., 2016, Carli et al., 2017, Singh et al., 2013) and all suggest that prehabilitation enhances early discharge from hospital and reduces surgical adverse effects. There is a growing requirement to include prehabilitation as part of the cancer pathway with three recent reports advising the value of prehabilitation, two in the USA (National Academies of Sciences, 2018, Stout et al., 2016) and one in the UK (Macmillan Cancer Support, 2018). However evidence that prehabilitation translates into better long-term patient outcomes beyond the initial 30-day post treatment complications is lacking.

Challenges to providing prehabilitation are that cancer patients are highly likely to have comorbidities that complicate treatment delivery and reduce physical fitness (Sarfati et al., 2016, Stairmand et al., 2015). Comorbid conditions associated with aging and particularly excess body weight are common in patients presenting with cancer (Goodwin and Chlebowski, 2016) and evidence from epidemiological studies suggests that comorbidities and poorer health are correlates of poorer survival (Land et al., 2012, Land et al., 2012). There is compelling evidence for the link between obesity and cancer outcomes (Calle et al., 2003) with particular associations in the following tumour sites breast

(Jiralerspong and Goodwin, 2016), gastrointestinal (Brown and Meyerhardt, 2016), endometrial (Onstad et al., 2016), prostate (Vidal et al., 2014) as well as haematological cancers, including multiple myeloma and leukaemia (Yang et al., 2016). Obesity is an important risk factor for cardiovascular, kidney disease, diabetes and some musculoskeletal disorders (Collaboration). These obesity-related comorbidities contribute to the adverse effects of cancer treatment (Bradley et al., 2014, Søgaard et al., 2013) and combined with an aging demographic, where more than 60% of cancer patients are over 65, comorbidity and poorer physical and functional health will impact upon future cancer treatment delivery and outcomes (Greenlee et al., 2016). These co exisiting health problems are strong indicators for providing prehabilitation to maximise cancer treatment outcomes.

Rehabilitation interventions such as exercise, weight reduction and pharmacotherapy are recognised ways of managing comorbity-related conditions after cancer treatment (Alamuddin et al., 2016) and there is evidence that smoking cessation (Sitas et al., 2014) reduces adverse treatment effects and improves survival. Preparing patients prior to cancer therapy by improving their overall health status as in prehabilitation could optimise their response to treatment and has important implications for future service delivery (Silver and Baima, 2013). Prehabilitation has been espoused as a key component of early recovery in cancer patients and is a term that has been traditionally used to describe interventions for optimising cardiopulmonary reserve prior to cancer surgery, with the aim of improving post-operative recovery outcomes (Carli et al., 2017, Silver, 2015, Silver and Baima, 2013). However, prehabilitation programs are also targeting this pre-treatment period to improve chemotherapy adherence (Le Roy et al., 2016), reduce anxiety (Tsimopoulou et al., 2015), and to provide a stronger platform for post-treatment rehabilitation aimed at reversing treatment-related side effects and symptoms, managing comorbidities and enhancing longer-term health-related quality of life (Alfano et al., 2012, Boereboom et al., 2015, Shun, 2016, Silver, 2014). While fewer studies have been undertaken outside of the surgical context, a growing number of studies are focusing on different cancer treatments and modes of prehabilitation using exercise, psychological support and nutritional interventions. These studies need to look at longer-term outcomes beyond the traditional enhanced recovery 30-day post treatment outcomes, to understand treatment adherence, mortality, disease prognosis or impact on health economics (Stout et al., 2018). This is the first systematic review to critically review the impact of different prehabilitation interventions on long-term health outcomes (at or beyond 30-days post-treatment completion) in cancer patients and explore the utility of prehabilitation as a platform for risk management before and after all cancer treatments.

This review addressed two questions:

1. What is the effect of prehabilitation on ≥ 30 day post treatment outcomes including; physical functioning, nutrition and patient-reported outcomes ?
2. How can prehabilitation be used to optimise the management of cancer patients with comorbidity or pre-existing risk factors that are associated with poorer cancer treatment outcomes?



**Methods**

*Data Sources and search method*

The review was registered on PROSPERO (CRD42016050296) international prospective database of systematic reviews. The search was conducted in two stages. In stage one, studies were identified via abstracts through a systematic search strategy for Medline (Pub med), CINAHL (with full text) Embase and Cochrane central register of controlled trials. The databases were chosen to identify potentially relevant published studies in the field of medicine, exercise, health and psychosocial care. Search terms were split into two categories "prehabilitation combined with cancer" and terms to identify the nature of prehabilitation such as "exercise, nutrition, psychology and other behavioural interventions". The full search strategy and MESH terms are provided in supplementary materials. In stage two, other relevant publications were retrieved by reviewing the reference lists of these studies against the eligibility criteria.

Studies selected were published from the period 2000 to February 2017. The following were all excluded from the review; prehabilitation studies with no reported post-treatment outcomes at 30-days or longer; studies that combined data from previously published studies; abstracts, case studies, conference abstracts and those not in English. Participants included were cancer patients who were treated with any treatment modality and received any form of prehabilitation either in the home or hospital setting. Prehabilitation was defined as a single or multi-modality intervention that could include exercise, nutritional support, patient education and/or psychological therapy. Control was defined as those participant's receiving usual care as defined in the clinical pathway. Identification of objective clinical, patient reported and delivery outcomes were described at 30-days post treatment completion. Comorbidity data at baseline and at completion were also reviewed. Efficacy in relation to 30 day post treatment objective physical functioning was explored through meta-analysis but data was not of sufficient quality to make a comparison. The quality of eligible studies was assessed using the PRISMA critical appraisal methods (Shamseer L et al., 2015). Risk of bias was assessed by an interdisciplinary research team using the Cochrane Collaboration's tool for assessing risk of bias ROBINS-I tool (Sterne et al., 2016). Observational or quasi-experimental studies were included as they provided additional information as to the use of prehabilitation interventions.



**Results**

Sixteen randomised controlled trials (RCT) and six observational studies were included in the narrative synthesis (Figure 1). The quality of the RCT studies varied considerably with 7 of the 16 studies being considered as having a high risk of bias. Studies were not sufficiently consistent in intervention or outcome data to be included in a meta-analysis. In many studies reporting of the randomization processes, lack of allocation concealment to those enrolling, blinding of outcome assessors and poor reporting of missing data may have impacted on study quality (Table 1). Most studies were single centre studies. However, one of two multi-site studies was a 3-arm trial comparing psychological prehabilitation strategies, with participants randomized to stress management, a support group or usual care (Parker et al., 2009). Other studies compared different prehabilitation components head to head as nutritional interventions or psychological approaches. The number of participants within the RCTs ranged from 48 to 652, with a median of 88 with a total number of subjects in the review of 2017 (Table 1). Most individual RCTs analysed fewer than 60% of the sample originally recruited in the study, excluding participants due to comorbidity or inability to undergo cardio pulmonary exercise testing. Participants were adults with colorectal (Carli et al., 2010, Cheville et al., 2015, Gillis et al., 2014, Gillis et al., 2016, Moriya, 2015) lung (Barlési et al., 2008, Stefanelli et al., 2013), head and neck (Van Bokhorst-de Van der Schuer et al., 2000), breast (Garssen et al., 2013), bladder (Jensen et al., 2015, Jensen et al., 2014) and prostate (Bales et al., 2000, Burgio et al., 2006, Parker et al., 2009) cancer or included individuals with a range of cancers (Schmidt et al., 2015). Trial designs were primarily feasibility studies and therefore the studies were rarely powered to determine the efficacy of prehabilitation on post-treatment recovery outcomes. The primary endpoint was predominantly objective physical function prior to treatment with the secondary endpoints described at 1 to 6 months post intervention. Only four (25%) of the authors fully reported participant comorbidities at baseline (Burgio et al., 2006, Jensen et al., 2015, Schmidt et al., 2015, Van Bokhorst-de Van der Schuer et al., 2000) whilst two actively excluded participants with comorbidities possibly due to the intensity of the exercise programme (Carli et al., 2010, Stefanelli et al., 2013).

The designs of the 6 observational studies were either case controlled cohort, historical controls or quasi experimental. Studies were primarily feasibility studies and participant numbers were small, ranging from 35 to 87 with a total of 289 particpants. Studies included individuals with breast cancer (Baima et al., 2015), lung cancer (Jones et al., 2007, Peddle et al., 2009, Sekine et al., 2005), colorectal cancer (Li et al., 2013) and prostate cancer (Sueppel et al., 2001).

Comorbidities were only reported in three of the studies at baseline, with ill health being cited as a contributing factor to difficulties with recruitment rather than this being recorded as an outcome. Several studies did not report attrition (Sekine et al., 2005, Sueppel et al., 2001), and among those that did attrition rates ranged from 0 to 52%. The number and combination of prehabilitation modalities varied considerably across studies, ranging from 1 to 3 across individual RCTs and observational studies (Table 2 & 3).

Most (16/22) studies included an *exercise modality*, either as a stand-alone prehabilitation intervention or in combination. Four studies examined the effects of pelvic floor training in men with prostate cancer over a varying number of weeks before radical prostatectomy (Bales et al., 2000, Burgio et al., 2006, Centemero et al., 2010, Sueppel et al., 2001). These were predominantly home-based exercise programmes with some level of instruction and supervision and/or biofeedback training. Two studies incorporated supervised therapeutic pulmonary exercises (in conjunction with more conventional conditioning exercise) in lung cancer patients in the 2-3 weeks prior to surgery (Sekine et al., 2005, Stefanelli et al., 2013). These exercises were performed on 5-7 days per week and included incentive spirometry, abdominal breathing, huffing and coughing, and respiratory exercises on a bench, mattress pad and wall bars. Finally, a study in breast cancer patients investigated the feasibility of therapeutic shoulder mobility exercises in the 2-4 weeks before surgery, comparing in-person teaching with video-only teaching (Baima et al., 2015). Both methods were shown to be feasible with high adherence (≥75%). Other studies investigated the effects of conventional forms of exercise conditioning for improving cardiopulmonary fitness and/or muscular strength over durations of 2-8 weeks, though most programmes were of 2-4 weeks duration (Table 2 & 3). All but one of these studies implemented exercise prehabilitation in the time period before colorectal, lung or bladder cancer surgery, whereas the remaining study (Cheville et al., 2015) focused on adherence to chemo radiotherapy in patients with gastrointestinal cancers. Home-based programmes generally consisted of aerobic and resistance exercise on at least three days per week with varying degrees of face to face supervision and telephone support (Carli et al., 2010, Gillis et al., 2014, Jensen et al., 2015, Jensen et al., 2014, Li et al., 2013). Instructions on both the frequency and intensity of aerobic exercise were generally provided and in some cases participants used heart rate monitors and perceived exertion scales to self-assess their level of effort (Gillis et al., 2014, Li et al., 2013). Studies of more closely supervised 2-6 week programs of exercise prehabilitation involved vigorous intensity cycle ergometry in lung (Jones et al., 2007, Peddle et al., 2009) and rectal cancer patients (West et al., 2015) prior to surgery and isokinetic muscle strengthening exercises in patients with gastrointestinal cancers during chemo radiotherapy (Cheville et al., 2015). Two further studies included vigorous gym-based aerobic exercise (Stefanelli et al., 2013) or walking exercise (5000 steps/day)(Sekine et al., 2005) in combination with therapeutic pulmonary exercises in patients with lung cancer prior to surgery. The short timelines prior to therapy made a progressive programme difficult to achieve. Although adherence to the home exercise program was reported in most of these studies, adherence to exercise at the prescribed intensity and progression of the exercise programme were poorly reported.

Only five of the studies provided a *nutritional modality* as part of the prehabilitation package. Some of the interventions were purely nutrition based (Gillis et al., 2016, Moriya, 2015, Van Bokhorst-de Van der Schuer et al., 2000), however, two of the studies used nutrition as part of multi-component prehabilitation intervention (Gillis et al., 2016, Li et al., 2013). The nutritional interventions were varied with 5-10 days preoperative feeding plus a supplemental arginine formula (Van Bokhorst-de Van der Schuer et al., 2000) or whey protein (Gillis et al., 2014, Li et al., 2013) or a low or high dose immune-enhancing diet (Moriya, 2015). Multi-modal prehabilitation interventions provided 90-min of nutritional counselling with daily whey protein supplementation (Gillis et al., 2016) in comparison to a control group which received nutritional counselling without supplementation. The timing of nutritional interventions varied between 5-10 days (Gillis et al., 2016, Moriya, 2015) and 3-6 weeks pre-operatively (Gillis et al., 2014, Li et al., 2013). The nutritional intervention did not continue beyond surgery, with one exception (Gillis et al., 2016) which continued the nutritional intervention 4 weeks' post-surgery. Nutritional therapies were primarily targeted on individuals with cancer who were malnourished, receiving treatment for head and neck (Van Bokhorst-de Van der Schuer et al., 2000) or colorectal cancer (Gillis et al., 2014, Gillis et al., 2016, Li et al., 2013, Moriya, 2015). Van Bokhorst (Van Bokhorst-de Van der Schuer et al., 2000) excluded adults from the study if they were well nourished (10% excluded), whereas Gillis (Gillis et al., 2016) screened for malnutrition using the Patient Generated – Subjective Global Assessment (PG-SGA) which is a validated tool for nutritional assessment in oncology. Adherence to nutritional intervention is reported in only one study with researchers contacting participants on a weekly basis to encourage them to record their whey protein ingestion. This study noted that adherence was higher in the prehabilitation group compared to the rehabilitation group both pre and post-surgery.

Studies involving a *psychoeducation modality* as part of prehabilitation programmes have focused primarily on anxiety and stress reduction(Cheville et al., 2015, Garssen et al., 2013, Parker et al., 2009, Schmidt et al., 2015), patient education and lifestyle advice (Baima et al., 2015, Barlési et al., 2008) (Jensen et al., 2015) and/or counselling (Parker et al., 2009) as part of the intervention; however, few studies report any detail of the therapeutic components of the intervention. Psycho educational prehabilitation strategies have been studied as single mode counselling interventions (Barlési et al., 2008, Cheville et al., 2015) or by comparing a variety of psychological and educational approaches prior to cancer treatment (Parker et al., 2009). Psycho educational strategies have also been studied as part of multi component prehabilitation programmes (Gillis et al., 2014, Jensen et al., 2015, Jensen et al., 2014). Psycho educational interventions prior to surgery for lung and gastrointestinal cancer provided written and verbal information to participants which described the disease and associated surgery outcomes (Barlési et al., 2008, Schmidt et al., 2015). An alternative psycho therapeutic approach involved weekly group sessions with a psychiatrist, focused on individuals' social, cognitive and emotional care in conjunction with relaxation exercises 30-days prior to chemotherapy(Cheville et al., 2015). Similarly, Garsen (Garssen et al., 2013) provided 4 sessions over 5 days to women with breast cancer, including stress management, relaxation, guided imagery techniques and counselling. Parker(Parker et al., 2009) investigated the effects of a similar programme on post-operative recovery outcomes in men with prostate cancer.  These interventions were all compared to usual or supportive care. Adherence to the intervention was not always reported in the observational studies with attrition 25-52% respectively (Baima et al., 2015) (Jones et al., 2007).

*Objective clinical outcomes following prehabilitation*

Studies that included an exercise modality investigated the effects of prehabilitation regimens on cancer treatment recovery outcomes and cardiopulmonary fitness (table 4). Three studies reported favourable effects of home-based pelvic floor training on post-operative urinary continence outcomes in prostate cancer patients undergoing radical prostatectomy up to 12 months of follow-up (Burgio et al., 2006, Centemero et al., 2010, Sueppel et al., 2001) and a fourth study (Bales et al., 2000) showed no urinary continence benefits of including biofeedback training. Similarly, a study of female breast cancer patients reported no additional post-operative benefits when home-based shoulder exercise prehabilitation included an in-person teaching session versus video-based instruction (Baima et al., 2015). Supervised exercise prehabilitation programmes in lung cancer patients have generally been more intensive than home-based programmes and have resulted in improvements in pre-operative cardiopulmonary fitness measures, including six minute walk test (6MWT) (Jones et al., 2007) and peak $VO_2$ (Jones et al., 2007, Stefanelli et al., 2013). However, the improvements in peak $VO_2$ were modest (2-3 ml kg min$^{-1}$) and it is unclear whether improvements of this magnitude translate to improved post-operative recovery outcomes or longer-term outcomes, such as quality of life. It is of interest to note that intensive cycle ergometry prehabilitation had no impact on quality of life pre-surgery or at 2-months post surgery (Peddle et al., 2009). Nevertheless, Sekine (Sekine et al., 2005) reported a reduction in post-operative pulmonary complications and hospital length of stay in lung cancer patients after a prehabilitation programme that involved daily pulmonary therapeutic exercises and walking (5000 steps/day) in the two weeks prior to lobectomy when compared to historical controls. In other studies, prehabilitation programs involving exercise have yielded equivocal results. A supervised programme involving cycling + strengthening exercises in patients with gastrointestinal cancer compared to those in a walking + breathing exercise group showed no differences in 6MWT distance (Carli et al., 2010). Similarly, home-based exercise programs involving aerobic and/or resistance exercise 4 weeks prior to surgery have had minimal impact on post-operative hospital length of stay or severity of complication (Gillis et al., 2014, Jensen et al., 2015, Jensen et al., 2014), although Jensen (Jensen et al., 2015) reported improved post-operative 6MWT distance in bladder cancer patients receiving prehabilitation, 4806m (95%CI 4075m-5536m) compared to 2906m (95%CI 2408-3404m) in those receiving usual care. Gillis (Gillis et al., 2014) reported higher submaximal cardiopulmonary fitness + 23.4m (6MWT) in a prehabilitation/ rehabilitation group compared to rehabilitation alone -21.8m (80.7) at 8 weeks after colorectal cancer surgery.

Studies that included nutritional outcomes were few and reported no significant differences between the intervention and control groups at ≥30 days (Moriya, 2015) on post treatment physical functioning (table 4). However, preoperative nutritional modality groups showed a significant improvement in physical functioning and initial symptoms post operatively (Gillis et al., 2014, Li et al., 2013, Van Bokhorst-de Van der Schuer et al., 2000). Only one study measured upper-body strength (Gillis et al., 2016) and this improved pre-surgery but was not sustained post-surgery. Participants who received arginine supplementation with feeding pre-and post-surgery showed reduced appetite at 6 months (Van Bokhorst-de Van der Schuer et al., 2000) and serum albumin remained stable in a small (n=17) pre-post intervention study (Li et al., 2013). However, prehabilitation studies nutritional outcomes are compromised by the lack of consistency in measuring nutritional intake and adherence (mainly through self-report tools) or objective sarcopenia measures. Such limitations could have important implications for assessing treatment fidelity and the sensitivity of outcome measures.



*Patient reported outcomes (PRO) of prehabilitation*

PRO in the studies reviewed included health related quality of life using the Short Form Health Survey (SF36) and Prostate Cancer Index (PCI), which incorporate physical and emotional subscales. Symptom specific measures such as the International Continence Scale for men (ICS male), the Hospital Anxiety and Depression Scale (HADs) and (PCI) and Activities of Daily Living (ADL) tool were also reported in some studies (Table 4). Quality of life scores were comparable between prehabilitation and control groups at 3 months post-intervention in most studies (Barlési et al., 2008, Burgio et al., 2006, Garssen et al., 2013, Peddle et al., 2009). However, in two studies, self-reported physical function was higher in the prehabilitation group at 1 year (Li et al., 2013, Parker et al., 2009) and in the study by Li (Li et al., 2013), an increase in self-reported physical activity persisted 8 weeks after surgery. Post-treatment improvements in mood, anxiety and depression have been reported immediately post-operatively following prehabilitation involving walking + breathing exercises and psychological support (Carli et al., 2010, Parker et al., 2009, Schmidt et al., 2015) but effects were small and between group differences were not sustained long-term (Parker et al., 2009, Schmidt et al., 2015). Behavioural change techniques, such as smoking cessation, were rarely reported in studies, this can impact on radiotherapy side-effects and subsequent post-treatment cancer outcomes (Warren et al., 2014).

*Patient reported and service outcomes for prehabilitation*

Complication rates and length of hospital stay post-surgery were the most frequent service delivery measures reported for ≥30-days post treatment (Table 4). There was no difference in length of stay, between prehabilitation and control groups in five studies (Gillis et al., 2014, Gillis et al., 2016, Jensen et al., 2014, Li et al., 2013, Schmidt et al., 2015), with the exception of Sekines (Sekine et al., 2005), where the intervention group had a reduced length of stay after a 4-6 week prehabilitation program. Post-operative complications such as wound healing, seroma formation and bleeding were shown to be comparable between intervention and control groups but Moriya (Moriya, 2015) found that those receiving a prehabilitation nutritional intervention had fewer post-operative site infections . Prehabilitation has been shown to improve initial post-operative mobilisation (Jensen et al., 2015) and the number of patients completing chemotherapy (Cheville et al., 2015). Furthermore, in the latter study, those receiving the intervention had significantly fewer treatment hospitalisations.

**Discussion**

Overall this systematic review suggests prehabilitation impacts on select 30-day outcome measures for some people with cancer but few studies have measured or reported overall long-term health benefits. The results of the review are summarised pictorially as a diagram describing the multi-modality intervention and linked physical function, nutrition and patient reported outcomes used in the reviewed studies (Figure 2). Many of these studies report service or process data measures such as length of stay and post-operative complications, but do not consistently capture changes in physical functioning or patient reported outcomes. The only exception is pre-operative therapeutic pelvic floor exercises for men undergoing prostatectomy for prostate cancer where prehabilitation improved long-term urinary continence. This reflects the differentation between general prehabilitation versus targeted exercise or nutrition interventions and the greater specificity of their effect. There is insufficient evidence for demonstration of long-term benefits in other cancer patient populations beyond the initial 30 day post treatment complications. Even vigorous intensity pre-operative aerobic exercise conditioning programmes have only resulted in modest improvements in peak oxygen uptake pre-operatively (of the order of 2-3 $ml/kg/min^{-1}$), possibly a factor of the short duration of programs, and these gains are lost post-operatively. Not surprisingly then, prehabilitation combined with rehabilitation was the most effective approach in improving outcomes longer than 30-days.

It is now recognised that a physically active lifestyle is inversely related to the risk of certain cancers and mortality (Brown JC et al., 2012, Schmid and Leitzmann, 2014). Surprisingly few prehabilitation studies measured or reported participant comorbidities and how they changed over time. Therefore we were unable to address our second question, how prehabilitation can optimise the management of cancer patients with comorbidity? Comorbidities in participants in prehabilitation studies were considered exclusion criteria rather than as predictors of physical functioning that could be mediated by exercise or nutrition and that could change as a response to intervention (Brown JC et al., 2012). Those participants with high levels of comorbidities and poor fitness were often not eligible to be included, which suggests those people most in need to improve physical function were less likely to receive prehabilitation. The multi-modality approach of prehabilitation could optimise the management of cancer patients with low baseline scores and who have been shown to gain greater benefits (Minnella et al., 2016). Rather than trying to demonstrate the efficacy of multi-modality prehabilitation on the fittest patients, we should consider using the approach to optimise the management of the more complex and least fit cancer patients who have most to gain. This requires more sophisticated tailoring of intervention to personalise and target prehabilitation. For example, current exercise guidelines for cancer survivors recommend muscle strengthening exercises for overall conditioning (Schmitz KH et al., 2010) but this may not be sufficient to manage specific deficits. A more task-specific approach incorporating functional movements using strength and mobility may be optimal for prehabilitation regimens (Winters-Stone et al., 2015).

In some studies, the high attrition of participants suggests a balance is required between intensity and duration of exercise to be able to meet the needs of those with greater limitations. This highlights the need for continuity and support in establishing exercise habits and expectations around exercise for people with cancer (Brown JC et al., 2012, Mayo et al., 2011). The content of exercise programmes is poorly described in some papers, and have not followed the FITT principle of reporting Frequency, Intensity, Timing and Type of exercise and/or how the exercise programme is personalised or progressed over time (Thompson et al., 2010). These oversights make it challenging to understand whether or not the exercise program was insufficiently designed and/or how to revise programs to optimize adherence and outcomes in the future.

The inclusion of nutritional support as part of prehabilitation improved short-term physical function. The pre-surgical interventions were necessarily short (2-3 weeks) primarily due to treatment target times. Indications from one study suggest that longer term patient outcomes could benefit with additional post-surgical rehabilitation. Given the rising proportion of cancer patients who are obese at diagnosis, the prehabilitive and rehabilitative window is potentially an opportunity to embed new lifestyle behaviours. Malnutrition is associated with a poorer response to cancer treatment and hypoalbuminaemia is associated with post-surgical mortality, increased morbidity and length of stay (Hu W-H et al., 2015). Patients with colorectal cancer are more malnourished than other patients groups (28% colorectal compared to 4% prostate cancer) (Hu W-H et al., 2015) hence the wide number of prehabilitation studies in this population. In the nutrition components of prehabilitation programs surrogate measures were used for the combined interventions rather than specific targets such as, serum values or anthropometric measures. If we are tackling obesity in cancer and its risks, then a greater focus on adiposity, fat distribution and sarcopenia should be included in prehabilitation studies. With emerging therapies and earlier diagnosis techniques, for example of low dose computerised imaging in lung cancer (Smith et al., 2017), the opportunitiy for prehabilitation becomes more feasible as patients are less likely to be burdened by advanced disease or chronic illness.

Understanding how prehabilitation components work together is a challenge as few studies used a theoretical or conceptual frameworks to guide design. Exploring how the multi-modality components work; such as exercise, nutrition, psychoeducational components is essential to maximize outcomes (Figure 2). The use of factorial research designs in future studies is recommended in evaluating prehabilitation components (Montgomery et al., 2003). Whilst pre-operative exercise programmes have incorporated both aerobic and resistance training, most emphasis has been on aerobic exercise. The effect of resistance exercise on pre-operative muscular function and how this impacts upon post-operative recovery outcomes has received less attention (Singh et al., 2013). The relationship between psychological health and exercise behaviour has been well established. Short and long term adherence may be optimized if anxiety and depression are also addressed during an exercise program, however the focus on anxiety and depression management at the expense of evidence based behaviour change strategies may not be the best strategy for long-term adherence (Stacey FG et al., 2015).

A limitation of this review is that conclusions have to be considered in the context of a limited number of studies, the majority of which are underpowered feasibility studies. The importance of feasibility studies is recognized in the Medical Research Council (MRC) complex interventions framework and that they should now be used to inform fully powered RCTs. The review highlighted the need for improved quality of studies for example following consort or strobe reporting guidance and this has also been described in previous prehabilitation systematic reviews (Singh et al., 2013). It's imperative that future studies take a more ambitious approach to test efficacy by building on the current evidence base using a conceptual framework to guide intervention design and robust evaluation.

Can prehabilitation programmes impact on longer-term cancer health outcomes? The answer is currently unclear especially in relation to changing comorbiditiy. Prehabilitation is now an integral part of many cancer surgical preparatory pathways as part of early recovery but there is scope for greater targeting to include nutrition and psychoeducational components, as well as considering how prehabilitative interventions may buffer symptoms such as fatigue and pain during adjuvant therapies. Sophisticated research designs incorporating economic evaluation and longer-term measures are essential to guide service development and support implementation if the concept of cancer prehabilitation is to emulate cardiac rehabilitation services.

In conclusion, prehabilitation strategies may have an important role to play in addressing the rising complexity of health needs of those diagnosed with cancer. Forty-percent of all those diagnosed with cancer have one co-morbid condition and 15% at least two concurrent health problems (Sarfati et al., 2016). This systematic review highlights that single and multi-modal prehabilitation programmes are feasible and some approaches confer short-term benefits in the post-surgical recovery period. The next stage is to design robust efficacy studies to test carefully defined prehabilitative/prehabilitative-rehabilitative interventions at the time of first cancer treatment (be that surgery, systemic anti-cancer therapy or radiotherapy) and measure clinical outcome, PRO, patient benefit and service delivery outcomes throughout the care pathway.

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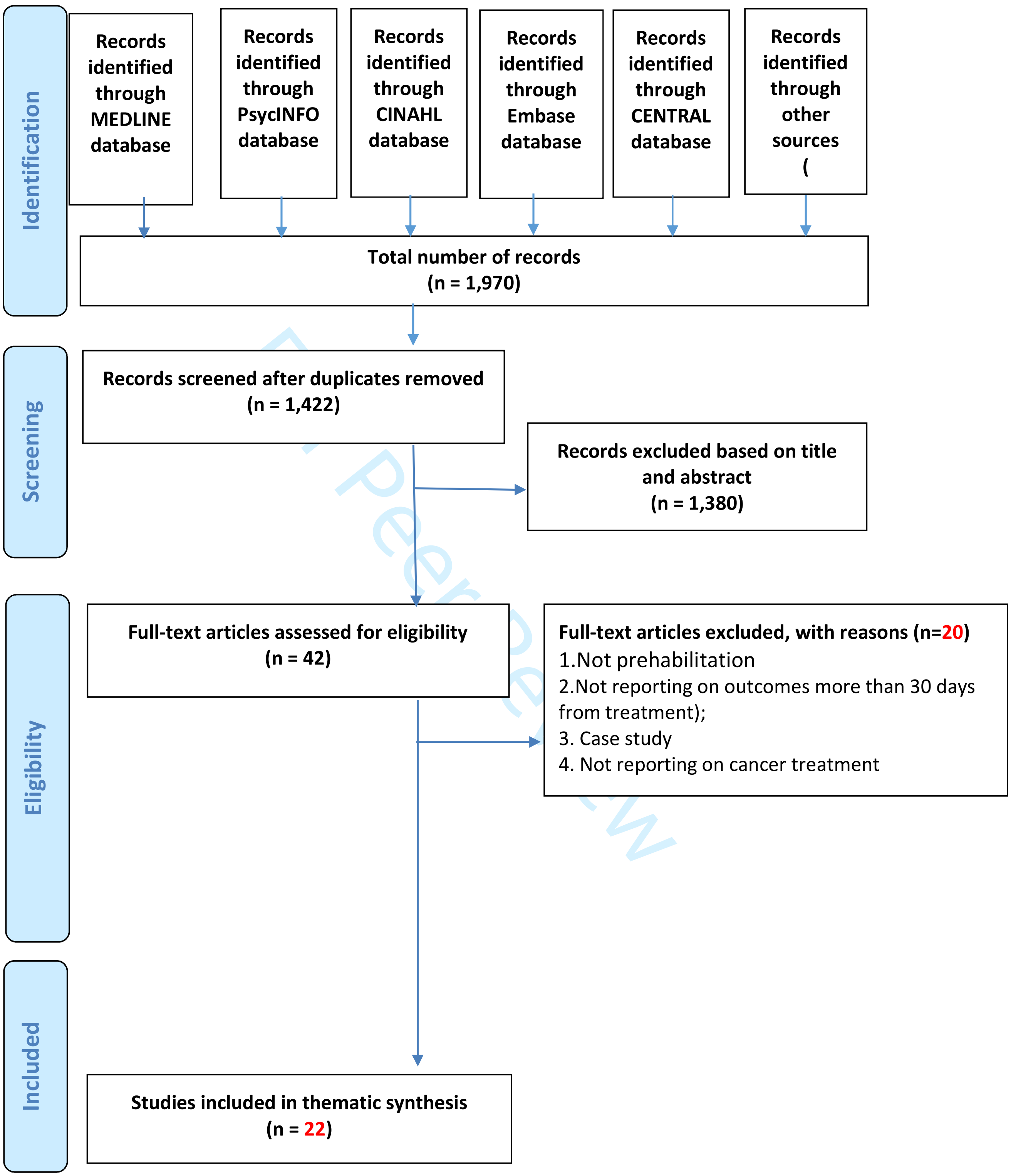
**Figure 1. PRISMA study selection flowchart**



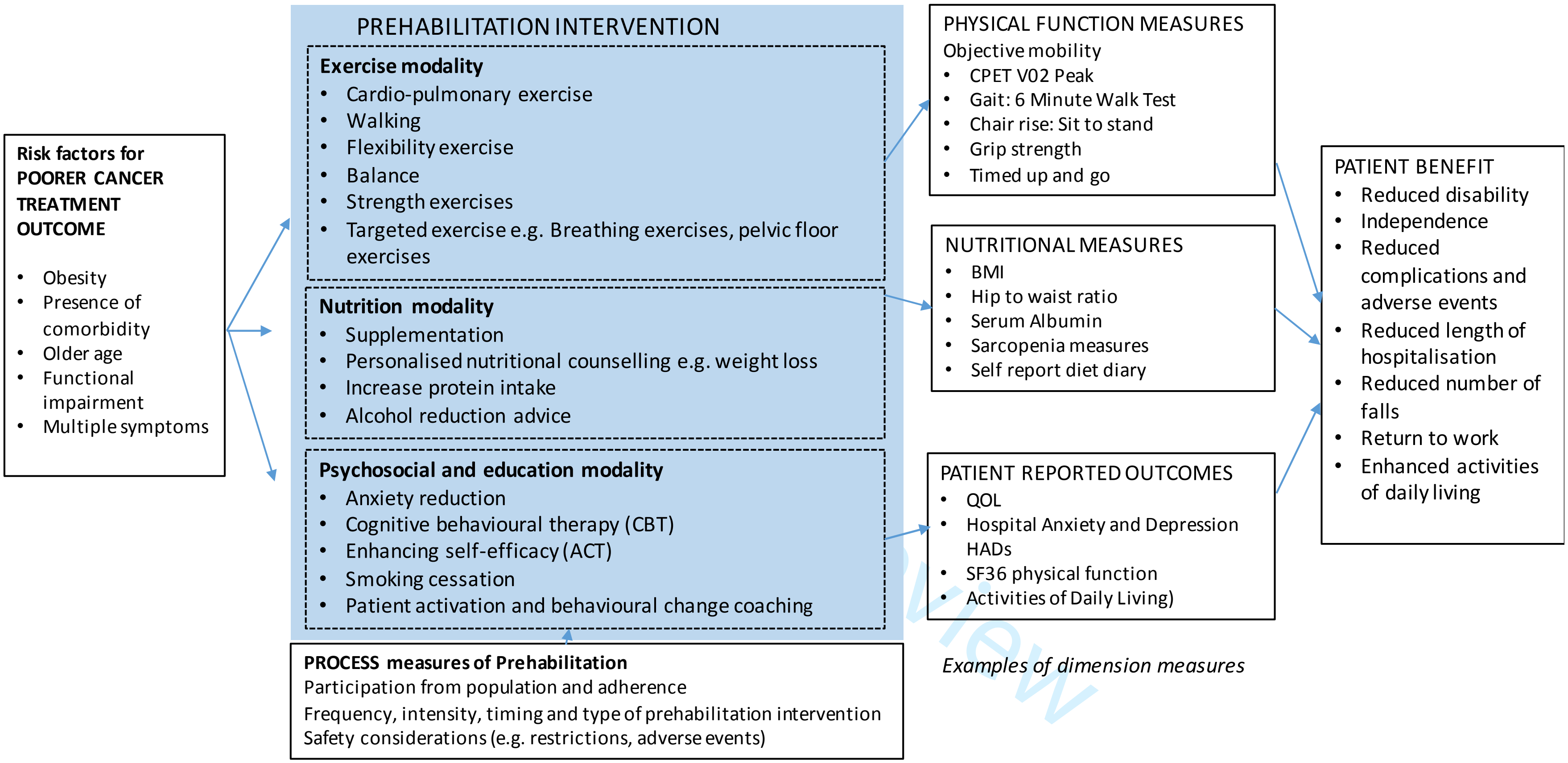

PREHABILITATION INTERVENTION
Exercise modality
Cardio-pulmonary exercise
Walking
Flexibility exercise
Balance
Strength exercises
Targeted exercise e.g. Breathing exercises, pelvic floor exercises
Nutrition modality
Supplementation
Personalised nutritional counselling e.g. weight loss
Increase protein intake
Alcohol reduction advice
Psychosocial and education modality
Anxiety reduction
Cognitive behavioural therapy (CBT)
Enhancing self-efficacy (ACT)
Smoking cessation
Patient activation and behavioural change coaching
Risk factors for POORER CANCER TREATMENT OUTCOME
Obesity
Presence of comorbidity
Older age
Functional impairment
Multiple symptoms
PROCESS measures of Prehabilitation
Participation from population and adherence
Frequency, intensity, timing and type of prehabilitation intervention
Safety considerations (e.g. restrictions, adverse events)
PHYSICAL FUNCTION MEASURES
Objective mobility
CPET V02 Peak
Gait: 6 Minute Walk Test
Chair rise: Sit to stand
Grip strength
Timed up and go
NUTRITIONAL MEASURES
BMI
Hip to waist ratio
Serum Albumin
Sarcopenia measures
Self report diet diary
PATIENT REPORTED OUTCOMES
QOL
Hospital Anxiety and Depression HADs
SF36 physical function
Activities of Daily Living)
Examples of dimension measures
PATIENT BENEFIT
Reduced disability
Independence
Reduced complications and adverse events
Reduced length of hospitalisation
Reduced number of falls
Return to work
Enhanced activities of daily living

Table 1 Risk of bias was assessed by an interdisciplinary research team using the Cochrane Collaboration's tool for assessing risk of bias ROBINS-I tool

| | | **Random Sequence Generation** | **Allocation concealment** | **Blinding of participants and personnel Blinding of** | **Incomplete outcome data** | **Selective outcome reporting** |
|---|---|---|---|---|---|---|
| | | random eg. random number table, computer | participants and investigators enrolling participants could not forsee assignment | outcome and the outcome measurement are not likely to be | no missing outcome data, reasons for missing data similar across groups | study protocol available and all pre-specified outcomes are |
| x | Research Design | **Criteria 1** | **Criteria 2** | **Criteria 3** | **Criteria 4** | **Criteria 5** |
| Bales, 2000 | RCT | unclear | high | unclear | unclear | low |
| Burgio, 2006 | RCT | low | high | low | unclear | low |
| Carli, 2010 | RCT Stratified randomisation | unclear | unclear | high | multiple imputations | low |
| Centemero, 2010 | RCT | low | low | low | low | low |
| Gillis, 2014 | RCT | low | low | low | multiple imputations | low |
| Jensen, 2014 | RCT | unclear | unclear | unclear | unclear | high |
| Jensen, 2015 | RCT | low | low | unclear | low | low |
| Stefanelli, 2013 | RCT | unclear | unclear | unclear | unclear | low |
| Barlesi, 2008 | RCT | unclear | unclear | unclear | high | low |
| Cheville, 2015 | RCT | unclear | unclear | low | low | low |
| Garssen, 2013 | RCT Block Randomised | unclear | unclear - block randomizat | low | unclear | high |
| Parker, 2009 | RCT | unclear | unclear | low | unclear/high | low |
| Schmidt, 2015 | RCT Block randomised | low | unclear | unclear | high | low |
| Gillis, 2015 | RCT | low | low | low | low | low |
| Moriya, 2015 | RCT | low | low | unclear | low | low |
| Van Bokhorst, 2000 | RCT | unclear | unclear | low | high | low |

*Table 2 Randomized Controlled Trials (RCTs) of Prehabilitation and critical analysis*

| Author and date | Intervention description | Control group description | Sample | Follow-up after intervention | Attrition | Critical analysis |
|---|---|---|---|---|---|---|
| Bales, 2000 | *Frequency*:2-4 weeks prior to surgery<br>*Intensity:* nurse-led biofeedback,10-15 repetitions Advised to practice 4x per day<br>*Timing* 45 minutes<br>*Type:* pelvic floor muscle exercise plus biofeedback followed by post-op PFM exercises | Written and brief verbal instructions on how to perform pelvic floor muscle exercises | 100 men undergoing radical prostatectomy Mean age intervention 60.9yrs and control 59.3yrs.<br><br>Prostate cancer stages T1c-T2c<br><br>Comorbidity not reported | Every month for 6-months post-surgery | 3%<br>6% | By 6 months following radical prostatectomy, the incidence of urinary continence in the biofeedback and control groups was 94% and 96%, respectively.<br><br>No difference in patients who received biofeedback pre op and those who did not There was no objective measure, just number of wet diapers (vs weight of diaper); unclear about characteristics of those who dropped out, unknown pelvic floor muscle strength prior to undertaking study |
| Barlesi, 2008 | *Frequency:* unclear<br>*Intensity:* unclear<br><br>*Timing:* Prior to surgery<br>*Type:* Additional oral plus written information including associated symptoms | Oral information only describing the disease and its associated surgery and outcomes | 75 patients with NSCLC undergoing thoracic surgery<br><br>Comorbidity not reported | Baseline and 3 months | 26% | QoL scores (baseline, 3 months) were comparable between both groups. Patients receiving oral plus written information were significantly dissatisfied related to several aspects of care regarding staff as well as the structure.<br><br>The information group significantly influenced satisfaction levels at multivariate analysis (standardized beta coefficient, 0.26, $p = 0.04$). |

| | | | | | | |
|---|---|---|---|---|---|---|
| Burgio, 2006 | *Frequency*: initiated 1 week prior to surgery<br>*Intensity* Daily 45 pelvic floor exercises<br>*Timing:* One preoperative session<br>*Type:* biofeedback plus assisted behavioural training<br>Home based exercise | Usual Care | 125 men undergoing surgery<br><br>Mean age 60.9 +/- 6.9yrs.<br><br>Prostate cancer<br><br>Comorbidity reported | 6 months' post-surgery | 10% | At 6 months:<br>Difference between the groups in the proportion of men remaining incontinent was 20.03% (higher in the intervention group)<br>(95% CI 6.02% to 34.63%) ($p<0.04$).<br><br>Severe/continual leakage was still present in 19.6% of controls compared to 5.9% of those in intervention group ($p <0.04$).<br><br>Intervention group had a<br>- higher proportion of dry days ($p < 0.04$),<br>- lower proportion using pads ($p <0.05$).<br>No group differences were found in life-style variables,<br>- incontinence impact ($p = 0.36$,<br>- psychological distress ($p = 0.69$)<br>- quality of life ($p = 0.31$ to 0.89).<br>Unclear how long provided and the intensity of the exercises |
| Carli, 2010 | *Frequency*: average 52 days prior to surgery<br>*Intensity*: High intensity exercise<br>*Timing* 3 times per week<br>*Type*: Prescribed stationary cycling (daily) with strengthening prescribed | Walk/breathing group: recommendations to walk daily and perform foot and ankle exercises to enhance lower-extremity circulation as well as breathing exercises | 112 patients undergoing colorectal surgery.<br><br>Mean age 60 (SD 16)<br><br>Participants with comorbidities grade IV or V were excluded from study or if unable to complete testing procedure | 10 weeks' post-surgery | 16% | Improvement in walking capacity in walk/breathing (47%) vs. bike/strengthening pre-surgery (22%). But not sustained over time<br><br>Mean peak $VO_2$ improved in both groups: Bike/ strengthening 134 ml/min ($P = 0.003$) versus walk breathing 112 ml/min ($P = 0.007$) but not over time.<br><br>Anxiety considerably reduced after surgery but did not change in either group over the prehabilitation period.<br><br>Depression improved for the bike/strengthening group over the prehabilitation period.<br><br>Exercise participation bike/strengthening group > walk/breathing group ($P = 0.075$).<br><br>Lower exercise had better outcomes because of less dropouts, poor compliance in the higher intensity group may have been too hard for such patients |

| | | | | | | |
|---|---|---|---|---|---|---|
| Centemero, 2010 | *Frequency:* started 30 days before surgery 2x per week<br>*Intensity:* Physiotherapist encouragement<br>*Timing:* 30 min<br>*Type*: pelvic floor muscle exercises at hospital and at home | Postoperative pelvic floor muscle exercises 48hrs after catheter removal | 118 males undergoing surgery.<br><br>46-68yrs old.<br><br>Prostate cancer<br><br>Comorbidity not reported | 3 months | 17% didn't start study but were eligible | Continence in preoperative group was 59.3% vs. postoperative group 37.3% (p<0.028)<br><br>ICS male SF mean score in preoperative group 8.1 vs. postoperative group 12.2.<br><br>Study found that preoperative PFME improved quality of life (The ICFS is a symptom based tool)<br><br>No detail re adherence to exercises. The question whether the preoperative or post-operative had most effect is unclear. Differences persisted for up to 6 months at 1 year there was no difference. |
| Cheville, 2015 | *Frequency:* 2-3X per week<br>*Intensity:*<br>*Timing:(*6-8 sessions)<br>*Type*: led by psychiatrist included social, cognitive, emotional care via exercise, education and relaxation. | Usual care | 61 study sample<br><br>Women, mean age 61.2<br><br>Comorbidity not reported | 30-day readmission | Not reported | More patients in the intervention completed Chemotherapy (p=0.003) than control<br><br>Intervention group had significantly fewer treatment hospitalisations (p=0.001)<br><br>No difference in other measures<br><br>There is no data capture on medications or functional health status. No PROM outcomes or psychological measures all data capture was through EMR retrospective records. |
| Garssen, 2013 | *Frequency:* 4 sessions 5 and 1 day prior to surgery with session 2 and 30 days post-surgery<br>*Intensity*:<br>*Timing:* 40-60 minutes<br>*Type:* Stress management training delivered by clinical psychologist - relaxation, guided imagery techniques, and counselling | Usual care | 70 women undergoing surgery for breast cancer<br><br>Intervention mean age 52yrs control group mean age 54 years<br><br>Comorbidity partially reported (BMI, alcohol use) | 30- 90 days post-surgery | 18%<br><br>Only 57% of eligible patients finished study | At 3 months' post-surgery compared to baseline, the intervention group had:<br>- Significant difference at 1 month in depression<br>- no significant difference in quality of life<br>- no significant difference in wellbeing<br>- pain not measured at 3 months<br>- control group more complaints than intervention group (0.001<p<0.01).<br>At 3-month post-op measures will be affected by start of adjuvant treatment (and no information reported on this). Experience of control measured by author designed 4 item questionnaires (un validated measures). Unable to differentiate effect of intervention content or psychologist intervention.<br>The study power is not clear against its primary outcome. Targeted intervention. The differences between groups at 3 months are not significant. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Gillis, 2014 | *Frequency:* 24 days 3 days per week<br>*Intensity:* moderate aerobic and resistance exercises,<br>*Timing:* 50 minutes<br>*Type* Home-based unsupervised initially personalised to the individual. Nutrition counselling with protein supplementation<br>Coping strategies to reduce anxiety and promote adherence with exercises provided on a CD | Rehabilitation group or 8 weeks post operatively (same as intervention but after surgery) | 89 patients undergoing surgery for colorectal cancer<br><br>prehab mean age = 65.7 (13.6); rehab mean = 66.0 (9.1)<br><br>Comorbidity fully reported | 8 weeks' post-op | 13% | Difference between baseline and follow-up in prehabilitation group. Mean different 45.4m (95% CI, 13.9 to 77.0)<br><br>Baseline: Prehab 421m (SD, 120.0) Rehab 425m (SD, 83.8)<br>Pre-treatment: Prehab +25.2 (50.2) Rehab -16.4 (46.0) P=0.001<br>50% of patients in both groups remained more than 20 m below baseline<br><br>At 8 weeks, prehab +23.4 (54.8) rehab -21.8 (80.7). P = 0.020<br>Complication rates and length of hospital stay were similar in prehabilitation and rehabilitation groups.<br><br>A change of 20 m is considered clinically meaningful as this is the estimated measurement of community dwelling elderly<br><br>Limitation of the study is missing data and unclear which modality of prehabilitation responsible for outcomes.<br>. |
| Gillis, 2015 | *Frequency:* 4 weeks prior to surgery:<br>Intensity: daily intervention<br>*Timing:* 90 min per day<br>*Type:* individualised nutrition counselling with daily whey protein supplementation | Individualised nutrition counselling with a non-nutritive placebo | 43 patients undergoing surgical treatment.<br><br>Mean age 67.6yrs (sd 11.5). Mean age in placebo group (69.1yrs (sd 9.4)<br><br>Comorbidities partially reported | 4-8 weeks post-op | 10% | Before surgery improvement in whey group 20.8m (sd 42.6m) and in placebo group (1.2m (sd 65.5m) (p=0.27).<br><br>Recovery rates were similar between groups in the 4-weeks post-surgery (p=0.81).<br>Comment: intervention focused on building strength. Focus on upper body strength and not lower body. Post intervention lack of nutrition may impact on similar group trajectories.<br>Pre-surgery results are significant but not sustained at 4 weeks<br><br>6MWT data missing pre-op for 4 patients (2 placebo, 2 whey) and 12 post-op (4 placebo, 8 whey), analysis based on 32 participants. If protein required to improve muscle functional capacity, presumably protein supplementation should be continued post-op for functional capacity to be maintained? This study indicates that effects may only be short-term (i.e. 4 weeks to day of surgery, and associated with duration of intervention) |

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| Jensen, 2014 | *Frequency:* 2 weeks prior to surgery:<br>*Intensity:* 15-minute step training<br>Timing*: 2x per day*<br>Type: Written information and motivation<br>home based<br>Pt tailored exercises for 6 muscle strength and endurance<br><br>Standardised postoperative mobilisation | Standardised nutritional screening and counselling.<br><br>Standardised postoperative mobilisation was encouraged at least 2x at 30 min day | 129 patients undergoing radical cystectomy<br><br>(analysis based on 100 (intervention 47, standard 53)<br><br>Bladder cancer<br><br>Comorbidity fully reported | 4 months' post-surgery | 41% | There was no significant difference in LOS and number of adverse events.<br>Physical capacity was significantly improved (p0.02) and mean walking distance at 7 days' post op.<br><br>At follow up both groups had regained physical capacity and no difference was seen.<br><br>Patient tailored intervention but unclear as to how this was personalised Abstract has little information re intervention<br><br>Just over half (55%) completed the prehab programme at 100%, 59% fulfilled 75%. It would have been useful to compare groups on 6MWT rather than LOS as primary outcome measure. |
| Jensen, 2015 | *Frequency*: 2 x daily<br>*Intensity*: progressive strength and endurance exercises<br>*Timing* daily<br>*Type:* Preoperative home-based supervised exercise programme and postoperative and progressive postoperative mobilization | Fast track Patient education counselling on choice of urinary intervention, pre-op preparation, pain control and nutrition | 107 patients undergoing surgical treatment for bladder cancer. Mean age intervention group 66yrs, mean age control group 71yrs.<br><br>Bladder cancer<br><br>Comorbidities fully reported | 4 months' post-surgery | 7% attrition<br><br>55% adherence | Severity of complications: no significant difference was found in the incidence ($p = 0.47$) or severity ($p = 0.64$) of complications between the treatment groups at 90 days postoperatively, or in readmission within 30 days ($p = 0.49$).<br><br>Ability to perform ADL: the median time was 3 days in the intervention group, compared with 4 days in the standard group ($p < 0.05$).<br><br>Post-op mobilization: significantly higher in the intervention group, reporting 4806m walked (95% CI 4075 to 5536 m), compared to the standard group with 2906 m walked (95% CI 2408 to 3404 m) ($p < 0.001$) at 7 days<br><br>Significance in 4 month outcomes between groups not seen. |

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| Moriya 2015, | *Intervention 1*<br>*Frequency:* 5 days pre-operatively<br>*Intensity:* High dose 750ml/ day<br>*Timing:* Daily<br>*Type:* Immune-enhancing diet (IED) (enriched with arginine, omega-3 fatty acids and RNA) and normal food<br><br>*Intervention 2.*<br>*Intensity:* Low-dose 250ml/day Immune enhancing diet | Control group – normal food | 88 patients undergoing surgery for colorectal cancer<br><br>Mean age intervention 64.7 (2.3) control 63.8 (2)<br><br>Comorbidity not reported | 9-133 months after surgery | Not reported | Incisional SSI rates in the IED groups were significantly lower in the intervention group than in the Control group. (0%*, 0%* and 17%) (*P<0.01 vs. Control).<br><br>The incidences of the infections not involving the surgical site (non-SSI) and the lengths of hospital stay were similar among the three groups. No significant differences were observed in RFS or DSS. |

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| Parker, 2009 | *Frequency:* 1-2 weeks pre-op<br>*Intensity:*<br>*Timing* 2x 60-90 minute sessions plus 2 booster sessions on morning of surgery and 48 hours post-surgery)<br>*Type:*<br>*Intervention 1*. Stress management (SM) including diaphragmatic breathing and guided imagery individual sessions with clinical psychologist,<br><br>*Intervention 2* Supportive attention (SA) group discussed their concerns about the upcoming surgery and had a semi-structured medical interview. | Standard care (no meetings with clinical psychologist) | 159 men undergoing surgery for prostate cancer.<br><br>Mean age 60.9 (5.9)<br><br>Comorbidities not reported | 6-12 months post-surgery | 34% | Post treatment improvements of intervention on mood disturbance (p0.02) with the stress management group with no significant differences between groups in any of the assessment times between groups over time.<br><br>The mixed model analysis targeted therapies. Differences in mood were small and although significant are not clinically significant. At 1 year patients had better physical function (SF36) but this was self-reported. A targeted intervention on those individuals with higher stress may be more beneficial in terms of effect size.<br><br>Men in SM group had significantly higher physical component summary score on SF35 than men is SC group at one year (p=0.0009), but no difference in mental component summary score or prostate specific Qol in PCI. The study excluded emotionally distressed men who may benefit from such an intervention. |

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| Schmidt, 2015 | *Frequency*: 1 day pre-operatively<br>*Intensity*:<br>*Timing:* 7 days<br>*Type* Information booklet lifestyle advice, mobilisation, nutrition and diary keeping | Standard care - information regarding surgical and anaesthesiology risks and procedures | 652 patient's undergoing elective surgery for gastro-intestinal, genitourinary, and thoracic cancer<br><br>65 years of age<br><br>Comorbidities reported | 3 -12 months after surgery | 15% | Complications: Occurrence and severity of complications were comparable in both groups, although severe haemorrhage occurred significantly more often in the intervention group (6.7% vs. 2.5%; p = 0.01).<br><br>LOS: no significant difference between both groups (p = 0.99).<br><br>HRQoL: no significant difference between the global HRQoL 12 months after surgery in the intervention and in the control group.<br><br>Postoperative stress: (mobilization, PONV and postoperative pain). Patients in the intervention group reported less pain on the first postoperative day (75.2% vs. 82.3%, p = 0.03). There were no differences regarding mobilization within the first 24 hours (69.2% vs. 70.4%, p = 0.73), or PONV within the first five days (52.8% vs. 56.4%, p = 0.39).<br><br>Depression: There was no difference in the geriatric depression scale between intervention and control groups at discharge (p = 0.86).<br><br>Readmission: The readmission rate within 90 days was slightly higher for patients in the intervention group (p = 0.70). In-hospital length of stay at readmission was shorter than in the standard care group without reaching statistical significance (p = 0.22).<br><br>Mortality: The overall mortality did not differ significantly between the two groups (Log-Rank-test p = 0.197).<br><br>Patient empowerment failed to shorted LOS or HRQOL. This type of intervention could enhance quality of care in regards to pain, and since over-treatment of pain is particularly harmful for elderly patients, patient safely can thus be improved. Pre-operative information was received well by patients who were cognitively and physically fit. |

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| Stefanelli 2013 | *Frequency:* 3 weeks preoperatively<br>*Intensity:* high-intensity training<br>*Timing:* 15x3-hour sessions weekdays<br>*Type:* outpatient intensive pulmonary rehabilitation (PRP) based on of both upper- and lower-limb muscles | Control surgery according to the normal standard preoperative protocol | 40 NSCL and COPD undergoing lobectomy<br><br>Age >75<br><br>Excluded patients with comorbidity | 60 days after surgery | Not reported | A significant difference was observed both at T1 and T2.<br>In prehabilitation group, peak VO2 improves significantly from T0 to T1, P < 0.001 and deteriorates from T1 to T2, P < 0.001 in control reverting to a similar value to that at T0.<br>Control group peak VO2 did not change from T0 to T1 and significantly deteriorates from T1 to T2: P < 0.00001.<br>FEV1 NS T0, T1, T2<br><br>Currently, other studies are needed to demonstrate that the patients who undergo preoperative PRP could have also a better quality of life, less postoperative complications and a longer survival after surgery.<br>Good for CPT VS 6MWT comparison |
| Van Bokhorst, 2000 | *Frequency:* 7-10 days pre-operatively plus 14 days post op<br>*Intensity:* 150% of basal energy expenditure<br>*Timing*: Daily<br>*Type:*<br>1.Standard pre-and post-op enteral feeding<br><br>2.Arginine supplemented pre-op and post-op enteral feeding | No pre-op and standard post-op enteral feeding | 49 malnourished head and neck cancer patients<br><br>Mean age 56.6-61.6<br><br>Comorbidity fully reported | 6 months post-surgery. | 37% | Between baseline and the day before surgery, both preoperatively fed groups revealed a positive change for physical and emotional functioning and dyspnoea with significance in arginine group. This was not sustained long term at 6 months.<br><br>Supplemented group showed a negative change in appetite (P=0.049). Between baseline and 6 months after surgery,<br><br>There were no differences between control and both pre-fed groups.<br><br>There were no differences in favour of Arginine supplement compared to other feed group. |

*Table 3 Observational and Quasi Experimental Prehabilitation Studies with critical analysis*

| **Author, date and research design** | **Intervention and comparator** | **Population and Sample** | **Follow-up after intervention** | **Attrition** | **Critical analysis** |
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| Baima, 2015<br><br>Feasibility study with two randomised (by appointment time), non-blinded groups | Timing: 1 month prior to surgery.<br>Type: In-person teaching of exercises plus info sheet, plus link to online video provided<br><br>Comparator<br>Video-only teaching arm | 60 cancer patients undergoing surgery for breast cancer<br>1 male, 59 females<br>Age 35-81.<br><br>(I=36-C24)<br>Breast cancer | 3-mths after surgery<br><br>2 weeks to 6 months | 25% | Exercise compliance:<br>- 76% chose to exercise.<br>- No difference in exercise compliance between in-person teaching versus video teaching (OR=1.03).<br>In person 75% (24/32) compared to Video teaching 77% (10/13)<br>Pain<br>- 29% of patients (9/31) had worse shoulder pain than baseline at 1 month post-surgery (24 %, 6/25 exercisers, and 50 %, 3/6 non-exercisers).<br>- 15% percent of patients (4/27) had worse shoulder pain than baseline at 3 months' post-surgery (8 %, 2/23 exercisers, and 100 %, 2/2 non-exercisers).<br>Shoulder Abduction<br>- 66% of patients (20/30) lost greater than 10% shoulder abduction ROM at 1 month post-surgery.<br><br>Prehabilitation exercise program inferred no additional risk of seroma formation (Exercisers 21 %, 7/33 vs. non-exercisers 22 %, 2/9, OR=0.94).<br><br>No strong evidence of difference<br><br>Single site; Change in intervention based on patient preference, so not random; No control group: every participant received some sort of intervention; Stated feasibility study, but unclear re: efficacy of these home exercises; No explanation given for why study staff did not pursue missing data; Possible social desirability bias with "in-person" arm and thus improved compliance; Compliance with exercises self-reported, possibly participants overestimated; Unclear description regarding seroma formation/evaluation ; Time to follow-up variability (2 weeks – 6 months); Lumpectomy and mastectomy included, possibly allowing for very different outcomes |
| Jones, 2007<br>Single group design feasibility study | Frequency: 5 endurance sessions per week on consecutive days until surgical resection. .<br>Intensity: Highly individualised and progressive from 60-100% $VO_{2\ peak}$, Threshold sessions | 25 patients 70% F undergoing surgery for suspected lung cancer.<br>Mean age 65+/-10years<br><br>Lung cancer | Preoperative assessment<br>30 days post-surgery | Attrition 52%<br><br>Adherence 70% | For patients who achieved >/=80% adherence (n = 12), VO2 peak increased 3.3 mL/kg/min (P=0.006).<br>Six-minute walk test: Significant improvement in >80% adherence group (p=0.14) compared to <80% adherence (p=1.01).<br>The overall adherence rate was 72% (range, 0%–100%) with patients completing a mean of 30 - 27 sessions (range, 0 - 75).<br>No significant difference. (p>0.1) for all measures of pulmonary function<br>The average duration of hospital stay was 10 _ 8 days with 8 - 5 days in general |

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| | and HIIT sessions.<br>Timing: Carried out for 4-6 weeks.<br>Type: Cycle ergometry<br><br>Comparator: Individually tailored intervention and hospital based over 4-6 weeks | | | | hospital and 2 - 5 days in the intensive care unit.<br>No difference in complications or length of stay than in routine patient care.<br>The length of intervention may be problematic in a 1-2-week normal wait time for surgery, the authors comment on this re the ability to make significant change in such a short time. There is no recording of how many patients didn't meet the eligibility parameters to reflect the normal practice. |
| Li, 2013<br>Pre post intervention study<br><br>Historical control group<br><br>single centre, cohort | Frequency: Individualized aerobic exercise (30 mins x3 times a week,<br>Intensity: at 50% of max heart rate) and resistance training<br>Timing: 3 times per week, no more detail<br>Type, one or two modifiable dietary behaviours identified and discussed, use of whey protein isolate within 1 hour of exercise at 1.2g/kg body weight per day , 90 minute visit with trained psychologist with a focus on anxiety reduction. Length of prehabilitation determined by wait time for surgery | 87 patients undergoing surgery for colorectal cancer<br>(Control =45 intervention= 42)<br><br>Colorectal cancer | Assessed 1 week pre op, 4 weeks and 8 weeks post-surgery<br><br>Primary outcome measure 6MWT @ 8 weeks | 0% | The patients in the prehabilitation program had better postoperative walking capacity at 8 weeks (mean difference, 84.5 ± 83 m; p<0.01). At 8 weeks, 81 % of the prehabilitated patients were recovered compared with 40 % of the control group (p<0.01).<br>The prehabilitation group also reported higher levels of physical activity before and after surgery.<br>The postoperative complication rates and the hospital length of stay were similar.<br>There were significant emotional & social differences between control and intervention. These are not controlled for in the modelling or analysis of difference.<br>Lack of detail re nutritional component. The question of what's a clinically relevant change<br>NO data on the length of time of wait for surgery and this would determine the amount of time spent on prehabilitation intervention (see column 3). Historical control do not appear to have had baseline assessment, just pre op and 4 and 8 week. Could account for difference between groups on HRQoL measures, because pre-op measures taken at different times (control taken immediately before surgery; intervention after meeting with surgeon). No tool used to capture functional symptoms specific to colorectal cancer e.g. FACT-C, SF35 is too generic.<br>Compliance to prehabilitation intervention reported in discussion section (70% exercising at least 2 days per week, 45% fully compliant). Increase in self-reported physical activity persisted after surgery. |
| Peddle, 2009<br>Sub analysis of Jones 2007 | Frequency: 5 sessions per week on consecutive days until surgical resection<br>Intensity: Highly individualised and progressive from 60-100% $VO_2$ peak, Threshold sessions and HIIT sessions.<br>Timing: 4-6 weeks prior to surgery.<br>Type: endurance cycle ergometry | 19 patients undergoing lung resection for suspected malignancy were planned to complete baseline to pre-surgery intervention.<br><br>9 patients will full data set<br><br>Lung cancer | QoL<br>2 month post-surgery | 0% Subset analysis | Pre-surgical exercise training improved cardiorespiratory fitness, it did not seem to improve QOL from baseline to pre-surgery or mitigate the decline in QOL after surgery.<br>QoL might be influenced by several other factors for exercise to have a meaningful effect. $VO_2$ Peak did improve. |

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| | Comparator Individually tailored intervention and hospital based over 4-6 weeks | | | | |
| Sekine, 2005<br>Prospective study with usual care control | Frequency: 5x per day<br>Intensity: moderate<br>Timing: 2 weeks prior to surgery<br>Type:<br>1. Incentive spirometry<br>2. Abdominal breathing and breathing exercises<br>3. Bronchodilators 5x per day<br>4. Huffing and coughing exercises<br>5. 5000 steps per day<br><br>Comparator historical control group of 60 patients **without** COPD | N=82 (control=60)<br>Rehab (n=22)<br><br>(rehab group had more airflow obstruction FEV1/FVC)<br><br>22 patients with COPD.<br><br>Lung cancer | 30 days' post operation<br><br>1 month post-op | 0%<br>Not reported | The change in lung function as less diminished in the intervention group (p=0.023)<br><br>Post-operative pulmonary complications there were no differences<br><br>Postoperative hospital stays were significantly longer in the control group (p=0.003) equivalent to -6.8 days<br><br>Study does not mathematically control for the differences between groups re baseline health. Study is underpowered<br><br>Less decrease in pulmonary function (FEV1 and predicted decrease post-op) in Rehab group but overall pulmonary function was lower in this group. Note: This is probably because this group had COPD whereas the controls didn't.<br><br>Post-op stay was longer in the control group |
| Sueppel, 2001<br>Descriptive quasi-experimental | Frequency: Daily<br>Intensity: Low<br>Timing: Several weeks prior and night before surgery<br><br>Type: Pelvic floor exercises. Pelvic floor muscle strengthening exercises pre-op with biofeedback confirmation of correct performance, then continue PMEs<br><br>Comparator: PMEs via video, then first biofeedback at 6 weeks video for pelvic floor muscle exercises, written instructions, nurse verbal support | 16 men pre pre-radical prostatectomy<br>8 men per group<br><br>Prostate cancer | Assessment at 3,6,9,12 months | Not reported | Analysis descriptive no statistical evidence, study underpowered and not controlled. Poorly reported study.<br><br>Strengths: consistency of biofeedback instruction by same nurse<br>Limitations: missing data, small sample size; don't know prior voiding patterns of patients<br><br>Overall some pre-op information while all other studies have been done post-op |

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Table 4. Prehabilitation RCT studies with statistically significant outcomes at 30 Days post treatment

| **Prehabilitation RCT studies with statistically significant outcomes at 30 Days post treatment** | | | | | | | | | | | | | | | | | | | | | | |
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| **Ref** | | Physical functioning | | | | | | | | | | | | | | | | | | | | |
| | **Tumour type** | Objective | | | | | Perceived | | | Nutrition | | Patient reported outcome | | | | | | | Service benefit | | | |
| | | Gait: 6MWT | V02 Peak | Grip Strength | FEV1* | Pad usage* | CHAMPS | SF36 Physical function | SF36 Role scales and social function | BMI | Self report diet | SF36 mental component | Pain scores* | HADs | STA | POMs | FACT-L | ICS male SF* | LOS | Less hospitalisation | Pt satisfaction | Fewer complications |
| Bales 2000 | Prostate cancer | | | | | NS | | | | | | | | | | | | | | | | |
| Barlesi 2008 | NSCLC | | | | | | | | | | | | | | | | | | | | NS | |
| Burgio 2006 | Prostate cancer | | | | | +ve | | | | | | | | | | | | | | | | |
| Carli 2010 | Colorectal cancer | NS | NS | | | | | | | | | | | | | | | | | | | |
| Centemero 2010 | Prostate cancer | | | | | +ve | | | | | | | | | | | | +ve | | | | |
| Cheville 2015 | GI and gall bladder | | | | | | | | | | | | | | | | | | | +ve | | |
| Garssen 2013 | Breast cancer | | | | | | | | | | | | | | NS | +ve | | | | | NS | |
| Gillis 2014 | Colorectal cancer | +ve | | NS | | | | | | | | | | | | | | | NS | NS | | NS |
| Gillis 2015 | Colorectal cancer | NS | | NS | | | NS | NS | | | | NS | | | | | | | | | | |
| Jensen 2014 | Bladder cancer | | | | | | | | | | | | | | | | | | | | NS | |
| Jensen 2015 | Bladder cancer | | | | | | | | | | | | | | | | | | NS | | | NS |
| Moriya 2015 | Colorectal cancer | | | | | | | | | | | | | | | | | | NS | | | +ve |
| Parker 2009 | Prostate cancer | | | | | | | +ve | | | | NS | | | | | | | | | | |
| Schmidt 2015 | GI , GU and thoracic cancers | | | | | | | | | | | | +ve | | | | | | NS | | | NS |
| Stefanelli 2013 | NSCLC *with COPD* | | +ve | | NS | | | | | | | | | | | | | | NS | | | NS |
| VanBokhorst 2000 | Head and Neck | | | | | | | | | | | | | | | | | | | | | |
| * Measures targeted to specific diseases or health problems | | | | | outcomes (+ve )significance >p0.005 | | | | | | | | (NS)not significant | | | | | | | | | |