The prevalence and outcomes of frailty in older cancer patients: a systematic review

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Background: Frailty is a state of vulnerability to poor resolution of homeostasis following a stressor event, such as chemotherapy or cancer surgery. Better knowledge of the epidemiology of frailty could help drive a global cancer care strategy for older people. The aim of this review was to establish the prevalence and outcomes of frailty and pre-frailty in older cancer patients.

Methods: Observational studies that reported data on the prevalence and/or outcomes of frailty in older cancer patients with any stage of solid or haematological malignancy were considered. We searched Medline, CINAHL, Cochrane Library, EMBASE, Web of Science, Allied and Complementary medicine, Psychinfo and ProQuest (1 January 1996 to 30 June 2013). The primary outcomes were prevalence of frailty, treatment-related side-effects, unplanned hospitalization and mortality. Risk of bias was assessed using the Newcastle-Ottawa checklist.

Results: Data from 20 studies evaluating 2916 participants are included. The median reported prevalence of frailty and pre-frailty was 42% (range 6%–86%) and 43% (range 13%–79%), respectively. A median of 32% (range 11%–78%) of patients were classified as fit. Frailty was independently associated with increased all-cause mortality [adjusted 5-year hazard ratio (HR) 1.87, 95% confidence interval (CI) 1.36–2.57]. There was evidence of increased risk of postoperative mortality for both frailty (adjusted 30-day HR 2.67, 95% CI 1.08–6.62) and pre-frailty (adjusted HR 2.33, 95% CI 1.20–4.52). Treatment complications were more frequent in those with frailty, including intolerance to cancer treatment (adjusted odds ratio 4.86, 95% CI 2.19–10.78) and postoperative complications (adjusted 30-day HR 3.19, 95% CI 1.68–6.04).

Conclusions: More than half of older cancer patients have pre-frailty or frailty and these patients are at increased risk of chemotherapy intolerance, postoperative complications and mortality. The findings of this review support routine assessment of frailty in older cancer patients to guide treatment decisions, and the development of multidisciplinary geriatric oncology services.

Key words: frailty, geriatric oncology, geriatric assessment

introduction

The ageing global population presents considerable challenges for the planning and delivery of healthcare services internationally. Cancer disproportionately affects older people, with more than one-third of cancers diagnosed in those over the age of 70 [1]. Current UK projections indicate that by 2030, 76% of men with cancer and 70% of women with cancer will be aged over 65 years [2]. An international strategy is required to address the implications of population ageing for cancer care services [3].

Older cancer patients are often under-treated, are under-represented in clinical trials, and have poorer outcomes than younger individuals [4–7]. Chronological age alone is a poor predictor of cancer treatment tolerance [8] and the heterogeneity of the older cancer patient population requires a carefully tailored approach to care that considers individual frailty.

Frailty is a state of vulnerability to poor resolution of homeostasis following a stressor event. It develops as a consequence of cumulative decline across multiple physiological systems and increases the risk of adverse outcomes [9]. In the general population, ~10% of people aged 65 and over have frailty, rising to between 25% and 50% of those aged 85 and over [10]. Both cancer and the systemic treatments offered by oncologists are significant stressors that have the potential to challenge physiological reserve. Better knowledge of the epidemiology of frailty in older cancer patients is essential to drive a global strategy of...
cancer care for older people. It will guide shared treatment decisions based on an individualized balance of risk and benefit.

The phenotype model, cumulative deficit model and comprehensive geriatric assessment (CGA) are the three most evidence-based approaches to the identification of frailty. The phenotype model identifies frailty on the basis of three or more physical characteristics (unintentional weight loss, exhaustion, low energy expenditure, slow gait speed and weak grip strength) [11]. Those with one or two characteristics are categorized as pre-frail. The cumulative deficit model defines frailty as the cumulative effect of individual deficits, which are clinical signs, symptoms, disease states, disabilities and abnormal laboratory test results [12]. CGA is a multidimensional, multi-disciplinary assessment process that relates directly to individualized treatment plans [13]. It is recognized as the best clinical practice standard test for the identification of frailty and has been widely adopted in routine care [14]. It has also been applied more recently in the geriatric oncology setting [15].

**Objective**

The objective for this review was to evaluate the available evidence on the prevalence and outcomes of frailty in older cancer patients.

**Methods**

The methodology and reporting of this review followed published international guidance [16].

**Protocol and registration**

The review protocol is registered on the PROSPERO database (registration number CRD42014006990) and is available at [http://www.crd.york.ac.uk/PROSPERO/printPDF.php?RecordID=6990&UserID=5296](http://www.crd.york.ac.uk/PROSPERO/printPDF.php?RecordID=6990&UserID=5296).

**Eligibility criteria**

Observational studies that reported data on the prevalence and/or outcomes of frailty in older cancer patients with any stage of solid or haematological malignancy were considered potentially eligible. Data from clinical trials were only considered if the trial eligibility criteria identified participants that were representative of the general older cancer patient population. Review articles, retrospective casenote studies, case reports and case series were excluded.

Studies that identified frailty using one or more of the established frailty models (phenotype model, cumulative deficit model, CGA) as the diagnostic criteria were included. For this review, CGA was defined as a multi-disciplinary assessment that used validated tools, and included assessment of at least three of the following domains: function; mobility or falls; cognition; mood; co-morbidity; polypharmacy; presence of geriatric syndromes; nutrition; and social support. Studies that used CGA without reference to frailty were included where sufficient data were provided regarding which domains were assessed and the number of participants with each number of deficits.

Studies in which the mean age of participants was <70 years, or where CGA had not been carried out in all patients were excluded. Studies that used chronological age to define frailty were also excluded, unless separate data were reported for the number of deficits on CGA.

**Information sources**

A Medline search strategy was developed by a research librarian at the University of Leeds and was adapted for CINAHL, Cochrane Library, EMBASE, Web of Science, Allied and Complementary medicine, Psychinfo and ProQuest. All databases were searched between 1 January 1996 and 30 June 2013. The search was restricted to English language publications.

**Study selection**

Two independent reviewers screened all titles and abstracts to identify potentially eligible studies. Two independent reviewers assessed the full texts of potentially eligible studies for inclusion in the review on the basis of the stated eligibility criteria. Any disagreements were settled by consensus.

**Data extraction**

Two independent reviewers extracted data using a piloted data extraction form, with any disagreements settled by consensus.

**Outcomes**

The primary outcomes for this review were prevalence of frailty, treatment-related side-effects, unplanned hospitalization and mortality. Secondary outcomes included progression of frailty, health-related quality of life, performance status and treatment termination due to intolerable side-effects.

**Clinical heterogeneity**

We anticipated the possibility of different cut-points for frailty using the phenotype model and frailty index. We also anticipated that the domains included and cut-points for frailty using CGA might not have been standardized across included studies. We therefore extracted data on the cut-points for all the reference standards and the domains included for CGA, as reported by the study authors. When information for CGA was missing or unclear, we defined frailty as the presence of two or more impairments.

**Risk of bias in individual studies**

Two independent reviewers assessed risk of bias at the study level using the Newcastle–Ottawa checklist [17]. Studies were assessed on the domains of selection, comparability, exposure and outcome. For each domain, a judgement of low, unclear or high risk of bias was made. Studies were assessed as at overall low risk of bias if all individual domains were judged at low risk; studies were judged as at overall high risk of bias if any individual domain was judged at high risk; studies were judged as at overall unclear risk of bias in all other cases. The assessment of risk of bias was to inform a sensitivity analysis that included only data from studies judged at low overall risk of bias.

**Summary measures**

Adjusted outcome data control for important confounding variables using multivariate analyses so are considered more reliable estimates. We extracted adjusted risk ratios (RRs) and odds ratios...
(ORs) with associated 95% confidence intervals (CIs) for dichotomous outcomes. We extracted adjusted hazard ratios (HRs) with associated 95% CIs for time to event data. For all these outcomes, evidence of adjustment for at least two of the important confounding variables of age, co-morbidity and cancer stage was sought. Where these summary measures were not presented, primary data were extracted to calculate unadjusted risk ratios by random effects modelling using RevMan 5.2 software.

For adjusted outcomes, we calculated natural logarithms of RRs, ORs and HR and their associated standard errors to create summary forest plots by generic inverse variance random effects modelling using RevMan 5.2 software.

sensitivity analyses
To investigate the effects of clinical heterogeneity and methodological bias on prevalence estimates, we ran a sensitivity analysis that only included data from studies at low risk of methodological bias as the most reliable estimates.

results
study selection
A PRISMA diagram summarizing flow of studies through the review is presented (Figure 1). The search identified 4102 articles, of which 180 were considered potentially eligible for inclusion. Following review of full-text articles, a total of 22 studies from 20 cohorts evaluating 2912 participants are included.

study characteristics
Characteristics of included studies are presented in Table 1 [18–39]. The median sample size was 113 (range 37–650). The majority (n = 15) of studies were located in hospital outpatient departments. Ten studies [18, 24, 27, 28, 31–33, 36–38] included patients with a variety of cancer types, 10 [19–22, 25, 26, 29, 30, 34, 35] included patients with just one cancer type and 2 studies did not specify the type of cancer [23, 39] (Table 1). Sixteen studies used CGA as the reference standard for frailty diagnosis (Table 2), five used the phenotype model (Table 3) and one study used both CGA and the phenotype model. All studies reported data on frailty prevalence, and seven publications from five studies reported data on outcomes.

risk of bias within studies
The risk of bias was low in eight studies [19, 25, 26, 31–33, 37, 38] and high in five studies [18, 24, 29, 34, 36]. The remaining studies had an unclear risk of bias [20, 21, 27, 28, 30, 35, 39]. For patient selection, the risk of bias was generally considered to be low. Studies were considered at high or unclear risk of bias.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year published</th>
<th>Country/countries</th>
<th>Number of patients</th>
<th>Setting</th>
<th>Cancer type(s)</th>
<th>Sex (% male)</th>
<th>Age [mean (SD)]</th>
<th>Prevalence data</th>
<th>Outcome data</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baitar et al. [18]</td>
<td>2013</td>
<td>Belgium</td>
<td>170</td>
<td>Outpatient</td>
<td>Urological, digestive, head and neck, breast, lung, other</td>
<td>54%</td>
<td>77 (67–97)⁺</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Bylow et al. [19]</td>
<td>2011</td>
<td>USA</td>
<td>63</td>
<td>Outpatient</td>
<td>Prostate</td>
<td>100%</td>
<td>72.1 (±7.0)</td>
<td>Yes</td>
<td>No</td>
<td>Phenotype</td>
</tr>
<tr>
<td>Clough-Gorr et al. [20]</td>
<td>2012</td>
<td>USA</td>
<td>650</td>
<td>Community/ outpatient</td>
<td>Breast</td>
<td>0%</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>CGA</td>
</tr>
<tr>
<td>Clough-Gorr et al. [21]</td>
<td>2010</td>
<td>USA</td>
<td>650</td>
<td>Community/ outpatient</td>
<td>Breast</td>
<td>0%</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>CGA</td>
</tr>
<tr>
<td>Courtney-Brooks et al. [22]</td>
<td>2012</td>
<td>USA</td>
<td>37</td>
<td>Inpatient</td>
<td>Gynaecological</td>
<td>0%</td>
<td>73 (65–95)ᵇ</td>
<td>Yes</td>
<td>Yes</td>
<td>Phenotype</td>
</tr>
<tr>
<td>Degesys et al. [23]</td>
<td>2011</td>
<td>USA, Belgium, The Netherlands</td>
<td>77</td>
<td>Outpatient</td>
<td>Not reported</td>
<td>40%</td>
<td>79.5 (±7.1)</td>
<td>Yes</td>
<td>No</td>
<td>Phenotype</td>
</tr>
<tr>
<td>Kellen et al. [24]</td>
<td>2010</td>
<td>USA, Belgium, The Netherlands</td>
<td>113</td>
<td>Outpatient/ general practice</td>
<td>Not reported</td>
<td>60%</td>
<td>77 (±4)</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Kristjansson et al. [25]</td>
<td>2012</td>
<td>Norway</td>
<td>176</td>
<td>Inpatient</td>
<td>Colorectal</td>
<td>43%</td>
<td>80 (70–94)ᵇ</td>
<td>Yes</td>
<td>Yes</td>
<td>CGA and phenotype</td>
</tr>
<tr>
<td>Kristjansson et al. [26]</td>
<td>2010</td>
<td>Norway</td>
<td>176</td>
<td>Inpatient</td>
<td>Colorectal</td>
<td>43%</td>
<td>As above</td>
<td>Yes</td>
<td>Yes</td>
<td>CGA and phenotype</td>
</tr>
<tr>
<td>Luciani et al. [27]</td>
<td>2013</td>
<td>Italy</td>
<td>400</td>
<td>Unclear</td>
<td>Lung, colon, stomach, prostate, breast, rectum, other</td>
<td>62%</td>
<td>77.2 (70–97)⁺</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Mangia et al. [28]</td>
<td>2005</td>
<td>Italy</td>
<td>95</td>
<td>Outpatient</td>
<td>Lung, gastrointestinal, breast, other</td>
<td>60%</td>
<td>76 mean</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Mohile et al. [29]</td>
<td>2007</td>
<td>USA</td>
<td>50</td>
<td>Outpatient</td>
<td>Prostate</td>
<td>100%</td>
<td>78 (70–92)⁺</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Molina-Garrido et al. [30]</td>
<td>2011</td>
<td>Spain</td>
<td>41</td>
<td>Outpatient</td>
<td>Breast</td>
<td>0%</td>
<td>74.5 (66.5–87.5)ᵇ</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Owusu et al. [31]</td>
<td>2011</td>
<td>USA</td>
<td>117</td>
<td>Outpatient</td>
<td>Breast, colon, lung, pancreatic, other gastrointestinal, head and neck, other</td>
<td>18%</td>
<td>73 (69–80)⁺</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Puts et al. [32]</td>
<td>2011</td>
<td>Canada</td>
<td>112</td>
<td>Outpatient</td>
<td>Breast, lung, colorectal, haematological</td>
<td>30%</td>
<td>74.1 (65–92)⁺</td>
<td>Yes</td>
<td>Yes</td>
<td>CGA</td>
</tr>
<tr>
<td>Retornaz et al. [33]</td>
<td>2008</td>
<td>Canada</td>
<td>50</td>
<td>Outpatient</td>
<td>Breast, lung, colorectal, prostate, haematological, other</td>
<td>44%</td>
<td>76.8 (±5.2)</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Singhal and Cheng [34]</td>
<td>2011</td>
<td>Australia</td>
<td>122</td>
<td>Outpatient</td>
<td>Lung</td>
<td>64%</td>
<td>74.6%ᵇ</td>
<td>Yes</td>
<td>No</td>
<td>CGA</td>
</tr>
<tr>
<td>Tan et al. [35]</td>
<td>2012</td>
<td>Singapore, Japan</td>
<td>83</td>
<td>Surgery</td>
<td>Colorectal</td>
<td>Not reported</td>
<td>81 (75–93)ᵇ</td>
<td>Yes</td>
<td>Yes</td>
<td>Phenotype</td>
</tr>
</tbody>
</table>
due to the use of patient-reported outcome measures [29, 34, 36] or no description of patients lost to follow-up [20–22, 35].

CGA domains included and methods used

The 16 studies that used CGA for diagnosis of frailty assessed a variety of domains (Table 2). The median number of domains assessed across all studies was seven (range 3–9), and all studies evaluated cognition and function using a range of validated assessment tools. Other domains included in CGA were mobility, nutrition, mood, polypharmacy, social support and comorbidity. Fatigue, polypharmacy and social support were least often included, being assessed in less than half of studies.

Nine studies described which member of the multi-disciplinary team completed CGA. In five studies [25–27, 30, 37], CGA was completed by a physician (geriatrician or oncologist), another four studies [18, 24, 31, 38] employed a trained researcher. In one study, all participants were assessed by a multidisciplinary team comprising an oncologist, geriatrician, occupational therapist and dietician [36].

The processes involved in CGA varied between studies. Nine studies included a review of medical records [20, 21, 24–26, 30–32, 36], seven carried out face-to-face interviews [18, 24, 30–32, 37, 38], two carried out telephone consultations with patients at home [20, 21] and five studies used self-reported questionnaires [18, 30, 34, 36, 38].

thresholds used to define frailty

Eight studies [18, 20, 21, 24, 27–31] dichotomized patients as either frail or fit (Table 2). Four of these [18, 29–31] used the presence of impairments in two or more CGA domains to define frailty; two [20, 21] used three or more as the cut-off; one study [24] defined frailty as two or more CGA impairments or cognitive impairment only and one reported that two independent physicians defined frailty on the basis of CGA [27]. Two studies that applied CGA did not provide a detailed description of the method used to define frailty, but they assessed at least six individual domains [34, 39].

Eight studies [25, 26, 28, 32, 36–38] categorized patients as frail, pre-frail or ‘vulnerable’, or fit. There was variation in the cut-off values used to define frailty and pre-frailty following CGA (Table 2).

Six studies used the phenotype model to define frailty [19, 22, 23, 25, 26, 35]. Three studies used the original criteria proposed by Fried to define frailty or pre-frailty [19, 25, 26]. One study defined frailty as the presence of three or more of the five phenotype characteristics, but classified all other participants as fit [35]. The remaining studies differed in their definition of frailty, using thresholds of one and four variables to define frailty (Table 3).

prevalence of frailty

Prevalence data for those categorized as frail, pre-frail and fit are summarized in Table 4. The median prevalence of frailty across all studies was 42% (range 6%–86%) and the median prevalence of pre-frailty was 43% (range 13%–79%). A median of 32% (range 11%–78%) of patients were classified as fit.

The median prevalence of frailty across studies that identified frailty using CGA was 43% (range 7–68), compared with a median frailty prevalence of 13% (range 6–86) for studies that applied the...
<table>
<thead>
<tr>
<th>Studies that used CGA</th>
<th>Geriatric domains assessed</th>
<th>Thresholds used to define frailty/pre-frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Function ADL/IADL</td>
<td>Mobility/falls</td>
</tr>
<tr>
<td>Baitar et al. [18]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clough Gorr et al. [20, 21]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kellen et al. [24]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kristjansson et al. [25, 26]*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Luciani et al. [27]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mangia et al. [28]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mohile et al. [29]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Molina-Garrido et al. [30]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Owusu et al. [31]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Puts et al. [32]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Retornaz et al. [33]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Singhal and Cheng [34]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>To [36]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Valero [37]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wedding [38]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weltermann and Koller [39]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*The prevalence of frailty was determined using both CGA and the phenotype model.

bBased on reported CGA deficits and standard CGA cut-offs.

ADL, activities of daily living; CGA, comprehensive geriatric assessment; IADL, instrumental activities of daily living.
phenotype model. Studies that used CGA classified a median of 32% of patients as fit (range 11–78), compared with a median of 49% (range 14–72) for studies using the phenotype model.

The prevalence of frailty in studies that used CGA was compared with the different cut-points used to define frailty (Table 5). The median prevalence for studies using two or more deficits to define frailty was 62% (range 43%–68%). The prevalence of frailty was lower in studies that used the presence of three or four deficits on CGA to identify frailty.

### outcomes of frailty

Seven studies involving 1221 patients reported data regarding frailty outcomes [20, 21, 25, 26, 32, 35, 36]. Five studies reported multivariate analyses on outcomes of mortality and treatment-related complications, adjusting for the effects of at least two of the key confounders of age, cancer stage and sex. These studies are presented in summary forest plots (Figures 2 and 3).

**mortality.** Three studies reported the effects of frailty on mortality [20, 25, 32] (Figure 2). All three reported data that were appropriately adjusted. There was a statistically significant association between frailty and all-cause mortality at 5, 7 and 10 years follow-up (adjusted 5-year HR 1.87, 95% CI 1.36–2.57; adjusted 7-year HR 2.31, 95% CI 1.40–2.94; adjusted 10-year HR 1.74, 95% CI 1.39–2.18) [20, 21]. Five- and 10-year HRs for mortality were marginally higher for older breast cancer patients with frailty (adjusted 5-year HR 1.95, 95% CI 1.18–3.20; adjusted 10-year HR 1.99, 95% CI 1.21–3.28) [20]. There was considerable uncertainty regarding the association between frailty and 6-month mortality (adjusted HR 4.51, 95% CI 0.49–41.38) and pre-frailty and 6-month mortality (adjusted HR 3.86, 95% CI 0.41–36.18) [32] with notably wide confidence limits. Postoperative 30-day mortality was higher in frail patients defined using both the phenotype model (adjusted HR 2.67, 95% CI 1.08–6.62) and CGA (adjusted HR 3.39, 95% CI 1.82–6.69), and was also greater in patients identified as pre-frail using the phenotype model (adjusted HR 2.33, 95% CI 1.20–4.52) [25].

**treatment-related complications**

**unadjusted data:** One study reported an increased risk of serious 30-day postoperative complications (identified using the Clavien system) [40] in those with frailty (HR 4.08, 95% CI 1.43–11.64) [35]. A second study reported no significant differences in postoperative complications [defined using the American college of surgeons national surgical quality improvement programme (NSQIP) definition] of postoperative complications [41] for those with frailty (OR 6.4, 95% CI 0.89–45.99) or pre-frailty (OR 0.36, 95% CI 0.04–3.54) [22].

One study identified an increased risk of 30-day re-operation for those with frailty (OR 2.8, 95% CI 1.06–7.41) [26]. One study reported an increased risk of readmission in surgical oncology patients with frailty (OR 2.8, 95% CI 1.06–7.41) [26], but a second identified no significant difference (OR 4.00, 95% CI 0.21–75.66) [22].

**adjusted data:** Three studies reported adjusted data for the treatment-related complications of frailty (Figure 3). One study reported an increased risk of treatment intolerance in those with frailty (OR 4.84, 95% CI 2.19–10.78) [21]. One study reported an increased risk of severe 30-day postoperative complications (grade II–IV using the Clavien system [41]) in those with frailty (adjusted HR 3.19, 95% CI 1.68–6.04) [26]. One study reported no significant increase in risk of grade 3–5 chemotherapy toxicity in those with pre-frailty or frailty (pre-frail OR 1.36, 95% CI 0.36–5.15, frail OR 1.32, 95% CI 0.36–4.84) [32], although wide confidence limits indicate considerable uncertainty.

### sensitivity analyses

The median prevalence estimates for frailty and pre-frailty in the eight studies at low risk of methodological bias were 43% (range 6%–56%) and 45% (range 24%–79%), respectively [19, 25, 26, 31–33, 37, 38].

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**Table 3.** Cut-offs used to define frailty in studies using the phenotype model

<table>
<thead>
<tr>
<th>Study</th>
<th>Thresholds used to define frailty/pre-frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bylow et al. [19]</td>
<td>Frail: 3 domains impaired</td>
</tr>
<tr>
<td></td>
<td>Pre-frail: 1–2 domains impaired</td>
</tr>
<tr>
<td>Courtney-Brooks et al. [22]</td>
<td>Frail: ≥4 domains impaired</td>
</tr>
<tr>
<td></td>
<td>Pre-frail: 2 or 3 domains impaired</td>
</tr>
<tr>
<td>Degesys et al. [23]</td>
<td>Frail: ≥1 domain impaired</td>
</tr>
<tr>
<td></td>
<td>Pre-frail: 1–2 domains impaired</td>
</tr>
<tr>
<td>Kristjansson et al. [25, 26]</td>
<td>Frail: 3 domains impaired</td>
</tr>
<tr>
<td></td>
<td>Pre-frail: 1–2 domains impaired</td>
</tr>
<tr>
<td>Tan et al. [35]</td>
<td>Frail: ≥3 domains impaired</td>
</tr>
</tbody>
</table>

*The prevalence of frailty was determined using both CGA and the phenotype.

---

**Table 4.** Frailty prevalence

<table>
<thead>
<tr>
<th>Reference standard</th>
<th>Study</th>
<th>Frail (%)</th>
<th>Pre-frail (%)</th>
<th>Fit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGA</td>
<td>Baitar et al. [18]</td>
<td>64</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clough-Gorr et al. [20, 21]</td>
<td>22</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kellen et al. [24]</td>
<td>68</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kristjansson et al. [25, 26]</td>
<td>43</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Luciani et al. [27]</td>
<td>68</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mangia et al. [28]</td>
<td>7</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mohile et al. [29]</td>
<td>60</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Molina-Garrido et al. [30]</td>
<td>68</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Owusu et al. [31]</td>
<td>43</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Puts et al. [32]</td>
<td>42</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Retornaz et al. [33]</td>
<td>56</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Singhal and Cheng [34]</td>
<td>13</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To et al. [36]</td>
<td>13</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valero et al. [37]</td>
<td>10</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wedding et al. [38]</td>
<td>50</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weltermann and Koller [39]</td>
<td>34</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bylow et al. [19]</td>
<td>6</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Courtney-Brooks et al. [22]</td>
<td>16</td>
<td>27</td>
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</tr>
<tr>
<td></td>
<td>Degesys et al. [23]</td>
<td>86</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kristjansson et al. [25, 26]</td>
<td>13</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tan et al. [35]</td>
<td>28</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

Phenotype model

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discussion

prevalence of frailty

This systematic review has identified that prevalence of frailty and pre-frailty in older cancer patients is high, with the median estimates of 42% and 43%, respectively. The majority of studies used CGA to categorize patients as frail or fit, but there was considerable variation in content and approach to assessment resulting in notable variation in estimates between studies. The median prevalence estimates from studies using CGA as the reference standard were generally higher than studies that applied the phenotype model. The median prevalence estimates of 43% and 45% for frailty and pre-frailty were obtained when results were restricted to studies at low risk of methodological bias. Importantly, our findings indicate that, on the basis of either a CGA or phenotype model, less than half of older cancer patients are likely to be fit.

outcomes of frailty

Adjusted data from a small number of studies at low risk of methodological bias indicate that older people with frailty and pre-frailty are at considerably increased risk of all-cause mortality, postoperative mortality, chemotherapy intolerance and postoperative complications. These patients may also be at increased risk of chemotherapy-related side-effects, but there is considerable uncertainty regarding this outcome.

strengths of review

This systematic review has followed rigorous methodology to identify and summarize the available evidence on prevalence and outcomes of frailty in older cancer patients. Studies were only included if an internationally recognized reference standard for frailty diagnosis was applied. All studies were assessed for risk of methodological bias using a recognized tool to inform interpretation of data. For prevalence data, results from studies that used different models of frailty assessment were compared and the most robust estimates were identified through a sensitivity analysis. For outcome data, the most reliable estimates were identified by summarizing data from studies at low risk of methodological bias that adjusted for important confounding variables.

limitations of review

The main limitation of this review was the range of cut-points used for frail, pre-frail and fit patients. Half of all studies categorized patients as frail, pre-frail or fit, while the remaining studies dichotomized patients as either frail or fit. Studies using CGA as the reference standard defined frailty using a range of

### Table 5. Frailty prevalence for each of the frailty definitions used

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Frailty prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangia et al. [28]</td>
<td>7</td>
</tr>
<tr>
<td>Kristjansson et al. [25, 26]</td>
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<tr>
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</tr>
<tr>
<td>Molina-Garrido et al. [30]</td>
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<tr>
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<td>50</td>
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<tr>
<td>Clough-Gorr et al. [20, 21]</td>
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<td>Valero et al. [37]</td>
<td>10</td>
</tr>
<tr>
<td>Welterman</td>
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</tr>
<tr>
<td>Luciani et al. [27]</td>
<td>68</td>
</tr>
</tbody>
</table>

Figure 2. Forest plot showing the association between frailty, pre-frailty and mortality (adjusted data).
outcomes. but none have investigated the identi-
city analysis should be considered as the most robust estimates
reliable estimates. However, despite this complexity, our esti-
mates of frailty and pre-frailty prevalence obtained in the sensi-
tivity analysis should be considered as the most robust estimates
available.

An additional limitation was the relatively small number of
published studies investigating the association between frailty and
outcomes. Many of these studies were underpowered, in-
cluding only small numbers of patients. Three studies focused
on the surgical complications of frailty, and only one study
reported information about the effect of frailty on cancer treat-
ment toxicity. However, adjusted estimates of associations
between frailty and mortality, chemotherapy intolerance and
postoperative complications were obtained from larger studies
at low risk of methodological bias, which indicates that these
results can be considered reliable.

Another limitation of this review is that the majority of the
adjusted outcome data are from studies of patients with colorec-
tal and breast malignancies. However, although a degree of
caution should be applied, these estimates are adjusted for im-
portant confounders including age, co-morbidity and cancer
stage, indicating that frailty is the independent risk factor, which
adds confidence regarding generalizability of results across other
cancer types.

Prevalence estimates were mainly obtained from studies con-
ducted in hospital outpatient settings. Some patients with
frailty, particularly those with more advanced frailty, might not
have been referred by the diagnosing clinician to secondary care
for outpatient evaluation, which means that true prevalence of
frailty in cancer patients may have been underestimated.

conclusions and recommendations
Our findings indicate that over half of older cancer patients have
frailty or pre-frailty, and these patients are at considerably
increased risk of mortality, postoperative complications and
chemotherapy intolerance. Current treatment decisions are
often based on clinical judgement, which varies between clini-
cians and may also be subject to bias. The findings of this review
support routine assessment of individual frailty and fitness in
older cancer patients to guide treatment decisions. Failure to
detect frailty potentially exposes older cancer patients to treat-
ments from which they might not benefit, and indeed may be
harmed. Conversely, failure to consider cancer treatment options
for fitter older people on the basis of age alone is unacceptable.

International standardization of cut-points for frailty in the
geriatric oncology setting would help make study findings more
comparable, and assist in pooling of data for meta-analysis. There
was a notable absence of the use of the cumulative deficit model
of frailty in the geriatric oncology setting. This model has been
demonstrated to correlate well with other frailty models but
define risk of adverse outcomes more precisely. A study to
compare convergent and criterion validity between the phenotype
model, cumulative deficit model and CGA would help standard-
ize cut-points for frailty in the geriatric oncology setting.

other evidence
To our knowledge, this is the first review of the prevalence and
outcomes of frailty in older cancer patients. Three recent reviews
[42–44] have investigated the use of geriatric assessment in
older cancer patients, mainly focusing on diagnostic accuracy,
but none have investigated the identification of frailty to predict
outcomes.

A recent review investigated the wider prevalence of frailty in
a non-cancer population. In 21 studies of 61,500 patients, the
weighted mean prevalence of frailty was 9.9% (range 4%–59%),
which is notably lower than the median prevalence estimate
obtained in our review [45]. There is considerable overlap
between the pathophysiology of cancer and ageing, with potential common
mechanisms including genomic instability, which is a hallmark of
the biology of both cancer and ageing [46]. Our findings of a
notably high prevalence of frailty in cancer patients may lend
support to the possible presence of these common mechanisms.

The International Society of Geriatric Oncology (SIOG) has
recently published updated guidance on the use of geriatric as-
essment in older cancer patients [47]. The guidelines do not
specifically recommend frailty assessment, but do recognize the
importance of geriatric assessment in an older cancer patient
population, and acknowledge the lack of a robust screening tool
that is able to predict the outcome of a CGA.

Figure 3. Forest plot demonstrating the association between frailty, pre-frailty and treatment complications (adjusted data).
Future clinical trials of cancer treatments in older patients should include methods to select and stratify participants on the basis of frailty, and correlate these methods with cancer outcomes. Improved cancer services for older people should consider geriatrician involvement to help guide the care of those with frailty, including pre-treatment optimization and shared decision-making based on an individual balance of risk and benefit.

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**disclosure**

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**references**


Visceral adiposity and colorectal adenomas: dose-response meta-analysis of observational studies

N. Keum1*, D. H. Lee1, R. Kim2, D. C. Greenwood3 & E. L. Giovannucci1,4

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Background: Obesity-related hormonal and metabolic perturbations implicated in colorectal carcinogenesis are mainly driven by visceral adipose tissue (VAT) rather than subcutaneous adipose tissue (SAT). Yet, most epidemiologic studies have examined the relationship between excess adiposity and colorectal neoplasia using body mass index (BMI) and waist circumference (WC). Due to the inability of BMI and WC to distinguish VAT from SAT, they are likely to have underestimated the true association.

Patients and methods: We conducted a dose-response meta-analysis to summarize the relationships between VAT and colorectal adenomas and to examine the value of VAT as an independent risk factor beyond BMI, WC, and SAT. PubMed and Embase were searched through September 2014 to identify relevant observational studies. The summary odds ratio (OR) 95% confidence interval (CI) were estimated using a random-effects model.

Results: In linear dose-response meta-analysis, the summary OR for each 25 cm² increase in VAT area was 1.13 (95% CI 1.05–1.21; I² = 62%); 6 studies; 2776 cases; range of VAT area = 30–228 cm²). The dose-response curve suggested no evidence of nonlinearity (Pnon-linearity = 0.37). In meta-analysis comparing the highest versus lowest category of VAT based on 12 studies, a positive association between VAT and adenomas remained statistically significant even after adjustment for BMI, WC, and SAT. In contrast, adjustment for VAT substantially attenuated associations of BMI, WC, and SAT with adenomas. Across the studies, VAT was more strongly associated with advanced adenomas than nonadvanced adenomas.

Conclusions: VAT may be the underlying mediator of the observed associations of BMI and WC with adenomas, increasing adenoma risk continuously over a wide range of VAT area. Considering that the joint use of BMI and WC better captures VAT than the use of either one, clinicians are recommended to use both BMI and WC to identify those at high risk for colorectal neoplasia.

Key words: visceral adiposity, visceral adipose tissue, colorectal adenomas, dose-response meta-analysis, observational studies

Introduction

Adipose tissue, once regarded as a simple reservoir of excess calories, is now recognized as an active endocrine and metabolic organ. Excess adiposity results in an elevation in circulating concentrations of insulin and bioavailable IGF-I [1], which promotes colorectal carcinogenesis by enhancing proliferation and inhibiting apoptosis of colonocytes [2]. Epidemiologic studies have shown that the amount (i.e. overall adiposity) and distribution (i.e. abdominal obesity) of excess adiposity as assessed by body mass index (BMI) and waist circumference (WC), respectively, are independent risk factors of colorectal neoplasia [3].