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Diagnostic criteria for cancer cachexia: reduced food intake and inflammation predict weight loss and survival in an international, multi-cohort analysis

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Abstract

Background Cancer-associated weight loss (WL) associates with increased mortality. International consensus suggests that WL is driven by a variable combination of reduced food intake and/or altered metabolism, the latter often represented by the inflammatory biomarker C-reactive protein (CRP). We aggregated data from Canadian and European research studies to evaluate the associations of reduced food intake and CRP with cancer-associated WL (primary endpoint) and overall survival (OS, secondary endpoint).

Methods The data set included a total of 12,253 patients at risk for cancer-associated WL. Patient-reported WL history (% in 6 months) and food intake (normal, moderately, or severely reduced) were measured in all patients; CRP (mg/L) and OS were measured in $N = 4960$ and $N = 9952$ patients, respectively. All measures were from a baseline assessment. Clinical variables potentially associated with WL and overall survival (OS) including age, sex, cancer diagnosis, disease stage, and performance status were evaluated using multinomial logistic regression MLR and Cox proportional hazards models, respectively.

Results Patients had a mean weight change of −7.3% (±7.1), which was categorized as: ±2.4% (stable weight; 30.4%), 2.5–5.9% (19.7%), 6.0–10.0% (23.2%), 11.0–14.9% (12.0%), ≥15.0% (14.6%). Normal food intake, moderately, and severely reduced food intake occurred in 37.9%, 42.8%, and 19.4%, respectively. In MLR, severe WL (≥15%) (vs. stable weight) was more likely ($P < 0.0001$) if food intake was moderately [OR 6.28, 95% confidence interval (CI 5.28–7.47)] or severely reduced [OR 18.98 (95% CI 15.30–23.56)]. In subset analysis, adjusted for food intake, CRP was independently associated ($P < 0.0001$) with ≥15% WL [CRP 10–100 mg/L: OR 2.00, (95% CI 1.58–2.53)] and [CRP > 100 mg/L: OR 2.30 (95% CI 1.62–3.26)]. Diagnosis, stage, and performance status, but not age or sex, were significantly associated with WL. Median OS was 9.9 months (95% CI 9.5–10.3), with median follow-up of 39.7 months (95% CI 38.8–40.6). Moderately and severely reduced food intake and CRP independently predicted OS ($P < 0.0001$).

Conclusions Modelling WL as the dependent variable is an approach that can help to identify clinical features and biomarkers associated with WL. Here, we identify criterion values for food intake impairment and CRP that may improve the diagnosis and classification of cancer-associated cachexia.

Keywords Cancer; Cachexia; Malnutrition; Reduced food intake; Inflammation; Weight loss

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Introduction

Cancer cachexia is a multifactorial syndrome of weight loss (WL) associated with treatment complications, distress, reduced physical function, reduced quality of life, and mortality.[1–4] A formal consensus process defined cachexia as a state of progressive negative protein and energy balance *driven by a variable combination of reduced food intake and abnormal metabolism* (e.g. inflammation, hypermetabolism, excess lipolysis and proteolysis).[1] Based on this framework, development of diagnostic criteria for cancer cachexia should be based upon the mechanism(s) most likely to contribute to weight loss, including the level of food intake. Reductions in food intake are considered clinically important and could be a dominant driver of WL; alterations in metabolism are also thought to play a role; however, their exact contribution is not known. C-reactive protein (CRP) is an inflammatory biomarker and a suggested diagnostic criterion for cachexia but its association with WL has not been extensively evaluated.[5,6]

Examining candidate diagnostic criteria for cancer cachexia requires data sets of sufficient size to accommodate the numerous demographic and clinical covariables that may influence WL. Aggregation of cachexia-related data from multiple studies was recommended to better understand their relationships to clinical outcomes, given the current lack of large data sets.[1] Our international research consortium created a data repository, initially to define a grading system for cancer-associated weight loss (WL).[3] This was subsequently validated.[3–5,7,8] The current study used the data repository to evaluate how proposed diagnostic criteria, reduced food intake, and CRP associate with cancer-associated WL.

Combining existing data sets is not without challenges. The lack of agreed standards for measurement of food intake was evident.[1,9–11] Reductions in food intake were evaluated with one of three validated tools recommended for use[10] in oncology patients: the Patient-Generated Subjective Global Assessment Short Form (PG-SGA-SF),[12–14] the Ingesta Score,[15,16] and the Mini-Nutrition Assessment Short Form (MNA-SF).[17,18] All three tools measure the degree to which food intake is reduced based on patients' own estimates of their recent food intake relative to their normal intake.[19] However, they have different measurement scales and are variously recorded as numerical or descriptive and have 3, 7, or 10 different levels to describe the severity of food intake impairment, respectively, rendering the interpretation of results across studies challenging. Indices of altered metabolism in patients at risk for cachexia are relatively rarely recorded and were not measured in most of the studies combined here. Measures of CRP were, however, included in several studies.

The primary objective of this study was to test the hypothesis that reduced food intake is a key determinant of cancer-associated weight loss (WL), using multinomial logistic regression (MLR). To accomplish this objective, we first determined that three food intake measures used in oncology could be used synonymously for the detection of normal food intake, and moderately or severely reduced food intake. Secondary objectives were to evaluate the association of CRP to WL, and the relationship of reduced food intake and CRP to overall survival.

Methods

Data repository and patients

Data were aggregated from multiple studies (Supporting Information, *Table* S1) for the purpose of conducting data analysis to advance our understanding of cancer cachexia, including patients most at risk for developing cachexia [i.e. locally advanced or metastatic tumours as well as specific cancers associated with weight loss (oesophageal, head, and neck)].[1,20] Included studies were prospectively collected under the auspices of human ethics approvals from respective institutions[3,7,16,21–26] and were de-identified. A single baseline data point was included: most contributed studies included patients at the time they were referred to Medical Oncology clinics to begin a first or new line of systemic therapy, and baseline data were collected prior to the start of a treatment plan. In several data sets, the patients were already receiving systemic therapy and were referred to multidisciplinary specialist symptom control/supportive care consultation services (n = 2108), and baseline data were collected at the initial consultation, prior to start of a symptom management plan (Supporting Information, *Table* S1). Contributed data were predominantly (~73%) population based, that is, patients were consecutively referred, attending a first outpatient visit to oncology clinics at regional tertiary cancer centres, the Cross Cancer Institute (n = 5141) serving northern Alberta, Canada (*pop*. 1.9 million), and the Montpellier Cancer Institute (n = 3791) serving Languedoc-Roussillon, France (*pop*. 2.7 million). Remaining data were from prospective

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observational studies or a randomized clinical trial conducted in Medical Oncology settings.[21–24,26]

To answer our primary objective, we included patients (*N* = 12,253) that had the following common data elements: age (≥18 years), sex, cancer site [International Classification of Diseases (ICD)-10 classifications] and stage American Joint Committee on Cancer (AJCC V6.0; V7.0 from 2011 onwards); performance status [PS; Eastern Cooperative Oncology Group (ECOG)], height, body weight and WL history, and a measure of food intake: (i) PG-SGA-SF, (ii) Ingesta Score, or (iii) MNA-SF. We defined three independent patient cohorts based on the food intake measurement: a PG-SGA, an Ingesta Score, and an MNA cohort to establish whether these tools could be used synonymously (*Figure* 1). Patients on artificial (i.e. non-volitional) nutrition support were excluded (*N* = 145, 1.2%). Our primary outcome was patient-reported WL, which was recorded at a baseline assessment [e.g. over previous 6 months or from usual body weight; % weight loss = ([current weight-previous weight]/previous weight) *100%]. Short-term and long-term patient-reported weight history has been shown to be valid and reproducible when compared with clinician measured body weight.[27–30] We compared self-reported weights and heights of 100 cancer patients within our data set with measures made by health care professionals, which were shown to be reproducible.[31]

Secondary objectives were evaluated using data from contributed studies that also included: a single baseline CRP (mg/L; *N* = 4960/12,253) and overall survival (*N* = 9952/12,253; *Figure* 1, Supporting Information, *Table* S1). In studies where baseline CRP was measured, it was at the same time food intake was measured. European studies contributed most of the CRP data, measured as part of routine blood work, which is not the case in Canada. Canadian studies measuring CRP did so as part of a study protocol (%WL was not different between European and Canadian patients with CRP data, *P* = 0.110).

Measures of food intake

Food intake was measured at baseline using validated instruments designed for patient report; these are practicable for use in outpatient settings, which are completed by 97–98% of patients.[7,16,32,33] The PG-SGA-SF lists descriptive categories that best represents patients current food intake: 'I am now taking' (1) normal food in my normal amount, (2) normal food but less than normal amount, (3) little solid food, (4) only nutritional supplements (ONS), (5) only liquids, or (6) very little of anything.[12,13] The Ingesta Score is a 10-point numerical scale, allowing the patient to communicate the severity of their current food intake impairment (0 = nothing at all, 10 = eating as normal).[16] The MNA-SF inquires: 'Has food intake declined over the past three months due to loss of appetite, digestive problems, chewing or swallowing difficulties' (1) no decrease, (2) moderate decrease, or (3) severe decrease.[17,18]

Alignment of food intake measures

The MNA-SF has only three food intake categories, thereby defining the maximum number of categories that could be aligned across tools. All three tools shared a common category representing a *normal* level of food intake, as defined by the patient. Based on differences in mean %WL, we grouped the five remaining PG-SGA-SF categories and nine remaining Ingesta Scores and aligned them with the moderate or severe decrease categories of the MNA-SF. A subset of the Ingesta cohort (*N* = 2326/3186; 73%) had corresponding energy intakes (kcal/kg/day) calculated from a 24 h diet recall, completed on the same day as the Ingesta Score, by an experienced dietitian using French food composition tables.[16] A 24 h recall details information about all the food/drink consumed in the previous 24 h. We evaluated

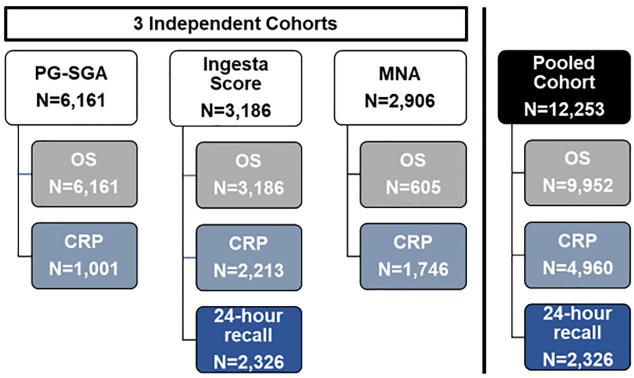

Figure 1 Summary of data elements from each cohort (PG-SGA, Ingesta score, and MNA) and for the pooled cohort. PG-SGA, patient generated-subjective global assessment; MNA, mini nutrition assessment; OS, overall survival data; CRP, C-reactive protein data.

the mean energy intakes corresponding to the food intake categories derived from the Ingesta Score: normal, moderately reduced, and severely reduced.

Statistics

Summary statistics describe the three independent patient cohorts: PG-SGA, Ingesta Score, and MNA cohorts. One-way *ANOVA* (*with Tukey post hoc test*) compared means between independent groups.

Statistical analysis included two steps

1 Multinomial logistic regression (MLR) is an extension of logistic regression and is a robust statistical approach when the dependent variable has >2 categories.[34] The dependent variable in this analysis was %WL, with five categories of increasing severity (±2.4%, 2.5–5.9%, 6.0–10.9%, 11.0–14.9%, and ≥15.0%) as previously defined.[3] The reference group for the dependent variable was *weight stable* (±2.4%). MLR models evaluated the association of food intake with %WL separately in each of the three independent cohorts (PG-SGA, Ingesta Score, and MNA), and the pooled cohort (*n* = 12,253). MLR models were adjusted for pre-specified variables including age (continuous), sex (reference = female), cancer site (ICD-10, reference = respiratory tract), cancer stage (AJCC, reference = IV), Eastern Cooperative Oncology Group (ECOG) PS (reference = ECOG 0–1).[3] MLR analysis conducted in the PG-SGA cohort was also adjusted for setting (medical oncology vs multidisciplinary specialist supportive care consultation service). In secondary analysis (*N* = 4960), MLR models were adjusted for baseline CRP (mg/L), evaluated as three categories (<10, 10–100, and >100 mg/L). All variables were evaluated at the univariable level; variables significant at the *P* value level <0.1 (two-sided) were used to construct the final multivariable MLR model. Results are reported as odds ratios (OR) and 95% confidence intervals (CI).
2 Secondary survival analysis evaluated the association between reduced food intake and OS, defined as the number of months a patient survived between their baseline assessment and date of death. OS data were available for *N* = 9952 patients (Supporting Information, *Table* S1). Patients were observed until death or were censored at their last confirmed contact with the health care system. Survival analysis included the Kaplan–Meier method (comparisons with Cox–Mantel log-rank tests) and the Cox proportional hazards model [estimated hazard ratios (HRs) and 95% CIs]. All variables were evaluated at the univariable level; variables significant at the *P* value level <0.1 (two-sided) were used to construct the final multivariable OS model. Survival analysis was also conducted in a subset (*n* = 3691) of patients who had both a baseline measure of food intake and CRP (mg/L).

Analyses were completed using IBM SPSS Statistics for Windows version 23.0 (SPSS, Chicago, IL) and were considered statistically significant at the *P* value level <0.05 (two-sided).

Results

Patient characteristics for the three independent cohorts (PG-SGA, Ingesta Score, and MNA) as well as the pooled cohort (*n* = 12,253) are presented (*Table* 1). Overall,

Table 1 Patient characteristics

	PGSGA Cohort (*N* = 6161)	Ingesta Score Cohort (*N* = 3186)	MNA Cohort (*N* = 2906)	Pooled Cohort (*N* = 12,253)
Age, years (mean, SD)	64.6 (12.1)	62.1 (12.4)	68.3 (12.6)	64.9 (12.5)
Sex, *N* (%)				
Female	2558 (41.5)	1553 (48.7)	1476 (50.8)	5587 (45.6)
Male	3603 (58.5)	1633 (51.3)	1430 (49.2)	6666 (54.4)
Setting, *N* (%)				
Medical oncology	4053 (66.8)	3186 (100)	2906 (100)	10,145 (82.8)
Multidisciplinary specialist supportive care consultation service	2108 (34.2)			2108 (17.2)
Cancer diagnosis,[a] *N* (%)				
Respiratory	1913 (31.1)	363 (11.4)	405 (13.9)	2681 (21.9)
Other	454 (7.4)	514 (16.1)	268 (9.2)	1236 (10.1)
Genitourinary organs	386 (6.3)	478 (15.0)	535 (18.4)	1399 (11.4)
Upper gastrointestinal	950 (15.4)	433 (13.6)	526 (18.1)	1995 (16.3)
Lower gastrointestinal	1009 (16.4)	519 (16.3)	538 (18.5)	1980 (16.2)
Head and neck	1191 (19.3)	346 (10.9)	99 (3.4)	1636 (13.4)
Breast	258 (4.2)	533 (16.7)	535 (18.4)	1326 (10.8)

(*Continues*)

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Table 1 (continued)

	PGSGA Cohort (*N* = 6161)	Ingesta Score Cohort (*N* = 3186)	MNA Cohort (*N* = 2906)	Pooled Cohort (*N* = 12,253)
AJCC cancer stage, *N* (%)				
1	280 (4.5)	85 (2.7)	285 (9.8)	650 (5.3)
2	442 (7.2)	166 (5.2)	349 (12.0)	957 (7.8)
3	859 (13.9)	299 (9.4)	538 (18.5)	1696 (14.8)
4	4580 (74.3)	2636 (82.7)	1734 (59.7)	8950 (73.0)
ECOG PS, *N* (%)				
0–1	3497 (56.8)	1609 (50.5)	2148 (73.9)	7254 (59.2)
2	1181 (19.2)	994 (31.2)	511 (17.6)	2686 (21.9)
3–4	1483 (24.1)	583 (18.3)	247 (8.5)	2313 (18.9)
% WL[b] (mean, SD)	−8.0 (7.5)	−7.2 (6.7)	−6.2 (6.4)	−7.3 (7.1)
WL categories,[c] *N* (%)				
±2.4% (weight stable)	1777 (28.8)	928 (29.1)	1025 (35.3)	3730 (30.4)
2.5–5.9%	1139 (18.5)	655 (20.6)	625 (21.5)	2419 (19.7)
6.0–10.9%	1347 (21.9)	818 (25.7)	673 (23.2)	2838 (23.2)
11.0–14.9%	816 (13.2)	376 (11.8)	280 (9.6)	1472 (12.0)
≥15.0%	1082 (17.6)	409 (12.8)	303 (10.4)	1794 (14.6)
BMI, kg/m^2 (mean, SD)	25.0 (5.3)	23.5 (4.6)	24.5 (4.3)	24.5 (4.9)
BMI categories,[c] *N* (%)				
<20.0	935 (15.2)	707 (22.2)	359 (12.4)	2001 (16.3)
20.0–21.9	863 (14.0)	551 (17.3)	426 (14.7)	1840 (15.0)
22.0–24.9	1540 (25.0)	890 (27.9)	970 (33.4)	3400 (27.7)
25.0–27.9	1289 (20.9)	571 (17.9)	641 (22.1)	2501 (20.4)
≥28.0	1534 (24.9)	467 (14.7)	510 (17.5)	2511 (20.5)
WL grade,[c] *N* (%)				
Grade 0	1066 (17.3)	417 (13.1)	522 (18.0)	2005 (16.4)
Grade 1	900 (14.6)	510 (16.0)	555 (19.1)	1965 (16.0)
Grade 2	992 (16.1)	538 (16.9)	466 (16.0)	1996 (16.3)
Grade 3	1766 (28.7)	973 (30.5)	883 (30.4)	3622 (29.6)
Grade 4	1437 (23.3)	748 (23.5)	480 (16.5)	2665 (21.7)
PGSGA: food intake, *N* (%)				
Normal food	2112 (34.3)	—	—	—
Normal food, less amount	2765 (44.9)	—	—	—
Little solid food	588 (9.5)	—	—	—
Only oral nutritional supplements	125 (2.0)	—	—	—
Only liquids	134 (2.7)	—	—	—
Very little anything	407 (6.6)	—	—	—
Ingesta score: food intake, *N* (%)				
10 (as usual)	—	1193 (37.4)	—	—
9	—	53 (1.7)	—	—
8	—	229 (7.2)	—	—
7	—	281 (8.8)	—	—
6	—	212 (6.7)	—	—
5	—	481 (15.1)	—	—
4	—	220 (6.9)	—	—
3	—	233 (7.3)	—	—
2	—	171 (5.4)	—	—
1 (almost nothing)	—	113 (3.5)	—	—
MNA: food intake, *N* (%)				
Severely decreased	—	—	350 (12.0)	—
Moderately decreased	—	—	1220 (42.0)	—
Not deceased	—	—	1336 (46.0)	—
Pooled food intake categories, *N* (%)	—	—	—	
Normal intake	—	—	—	4641 (37.9)
Moderately reduced intake	—	—	—	5241 (42.8)
Severely reduced intake	—	—	—	2371 (19.4)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; MNA, Mini-Nutrition Assessment; *N*, number; PG-SGA, Patient-Generated Subjective Global Assessment; SD, standard deviation; WL, weight loss.

[a]Upper gastrointestinal (oesophageal, stomach, pancreas, liver, biliary tract, and small bowel); lower gastrointestinal (colon, rectum, and anus); genitourinary (kidney, bladder, adrenal, prostate, testes, and penis); other (gynaecological, haematological, peritoneum, unknown, and thyroid).

[b]% weight loss calculated as: [(current weight − previous weight)/previous weight in kg]*100.

[c]WL categories, BMI categories, and WL grades calculated based on Martin *et al*.[3]

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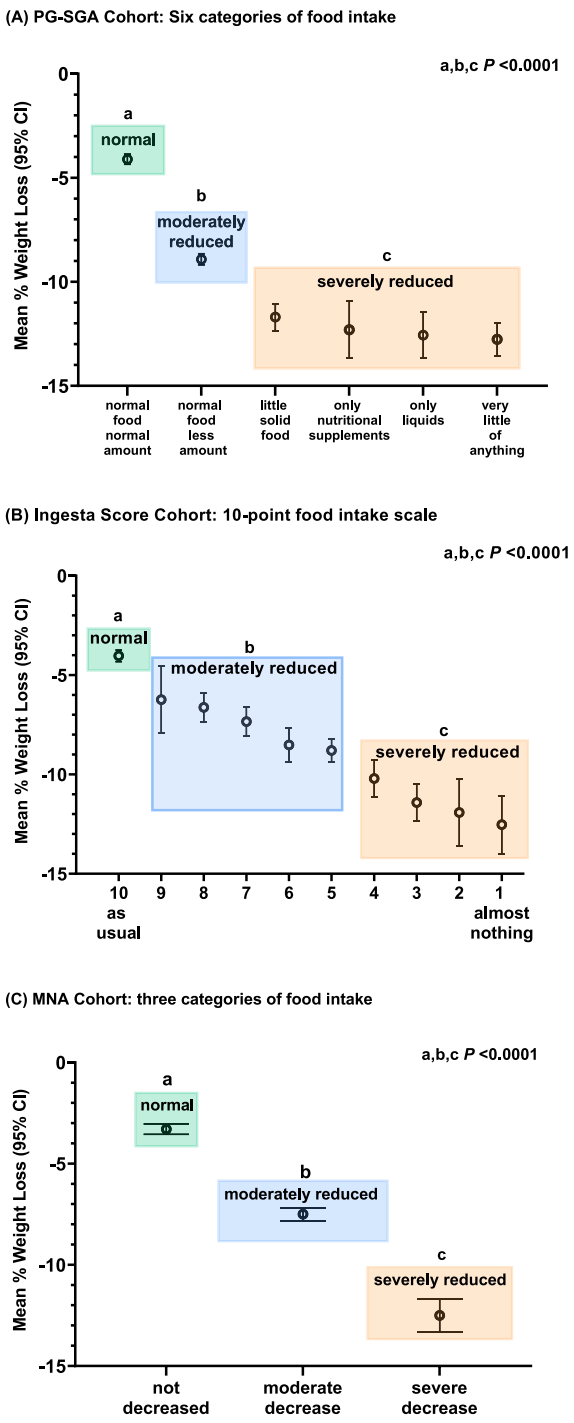

Figure 2 Alignment of food intake measures (PG-SGA-SF, Ingesta score, and MNA SF) according to percent (%) weight loss. These figures represent the mean percent (%) weight loss (WL; with 95% confidence intervals) according to three different food intake measurements. (A) The PG-SGA has 6 categories of food intake; when there was no significant difference for mean % WL between food intake categories, they were combined to represent normal (normal food, normal amount; mean (95% CI) WL −4.1 (−4.4 to −3.9)%, moderately (normal food, less amount; WL −8.9 (−9.2 to −8.6%) or severely reduced (little solid food; only nutritional supplements; only liquids and very little of anything; WL −12.2 (−12.6 to −11.8)% (B) The Ingesta Score is a 10 point numeric scale; when there was no significant difference for mean % WL across the scale, these points were combined to represent normal[10/10; WL −4.0 (−4.3 to −3.7)%], moderately [5/10 to 9/10; WL −7.9 (−8.3 to −7.6)%], or severely reduced [1/10–4/10; WL −10.9 (−11.4 to −10.4)%] (C) the MNA is the food intake measurement with the least number of categories (n = 3) and was the tool to which (A) the PG-SGA and (B) the Ingesta Score were aligned.

86.9% of the sample had locally advanced and metastatic cancers. Patients with early stage (I + II; 13.1%) cancers can also experience WL, particularly within specific tumour sites such as oral cavity, laryngeal, pharyngeal, and oesophageal.[1,20]

Association between food intake and weight loss

Alignment of food intake measures

Assignment of a three-item categorical scale for food intake (normal, moderately reduced, and severely reduced; *Figure* 2)

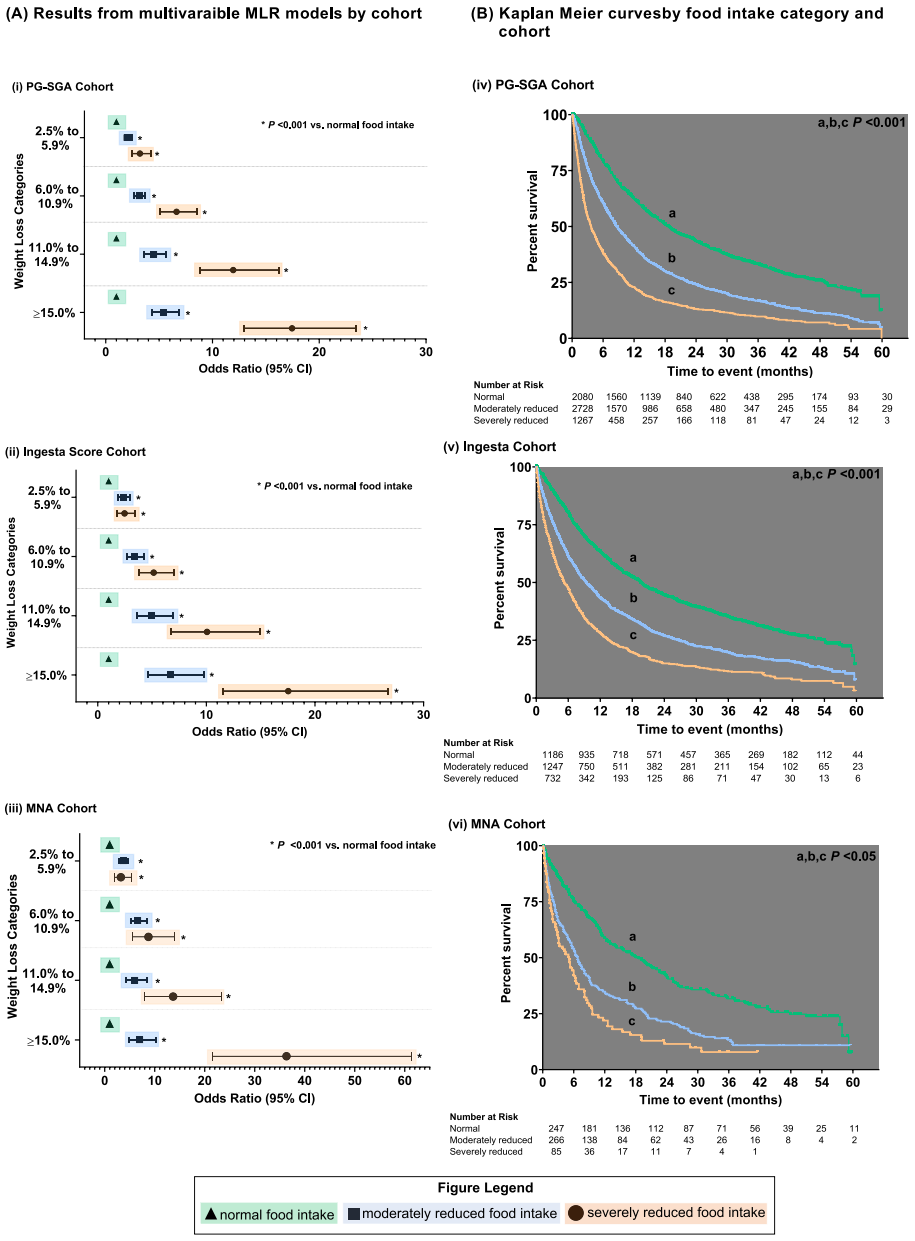

Figure 3 Categories of food intake are associated with weight loss (WL) and overall survival (OS) independent of patient cohort: PG-SGA, Ingesta score, and MNA. Figure 2(A) Represents the odds ratios (with 95% confidence intervals) for categories of food intake (normal, moderately or severely reduced) from multivariable multinomial logistic regression (MLR) models for three patient cohorts, (i) PG-SGA, (ii) Ingesta Score, and (i) MNA. Analysis for each cohort was adjusted for age, sex, cancer site, AJCC cancer stage and ECOG PS. The PG-SGA-cohort was also adjusted for care setting. Within each WL category (2.5 to 5.9%; 6.0 to 10.9%; 11 to 14.9%; and ≥15%) moderately and severely reduced food intake were compared to the reference category normal food intake (OR 1.0); and within each weight loss category for (i) PG-SGA, (ii) Ingesta Score, and (iii) MNA moderately or severely reduced food intake were consistently ($P < 0.001$) associated with WL. Figure 2(B) represents the overall median survival curves according to food intake categories for each cohort (i) (ii) PG-SGA (n = 6,161), (ii) Ingesta Score (n = 3,186), and MNA (n = 605) using Kaplan Meier curves (with Mantel-Cox log-rank tests). Median OS was different ($P < 0.05$) between the categories of food intake within each cohort.

was carried out across all tools according to mean %WL associated with each item in their respective measurement scales. Four of the PG-SGA-SF descriptors (little solid food, only oral nutritional supplements, only liquids, and very little of anything) associated with high weight loss and were combined to reflect severely reduced food intake. Ingesta Scores associated linearly with WL and were divided into moderate (VAS 5–9) and severely (VAS 1–4) reduced food intake.

The planned analyses including both MLR (*Figure* 3A, Supporting Information, *Tables* S2–S8) and OS (Kaplan–Meier curves; *Figure* 3B) were conducted in each cohort separately with food intake defined by the three-item categorical scale. Results from the multivariable MLR models were similar for each cohort (*Figure* 3A; Supporting Information, *Tables* S6–S7); for example, patients were more likely to have experienced WL 11.0–14.9% if their food intake was severely reduced (vs. normal) $P < 0.001$: (i) PGSGA [OR 11.94 (95% CI 8.81–16.20)], (ii) Ingesta Score [OR 10.06 (95% CI 6.77–14.95)], (iii) MNA [OR 13.69 (95% CI 8.04–23.30)]. Likewise, median OS differed between food intake categories ($P < 0.001$; *Figure* 3B) and was similar across cohorts: (iv) PGSGA cohort: 3.7 months (95% CI 3.2–4.1) vs. 18.5 months (95% CI 16.9–20.1), (v) Ingesta Score cohort: 5.3 months (95% CI 4.5–6.1) vs. 19.6 months (95% CI 17.5–21.7), (vi) MNA cohort severely reduced vs. normal food intake 5.1 months (95% CI 2.7–7.5) vs. 18.0 months (95% CI 13.1–22.9).

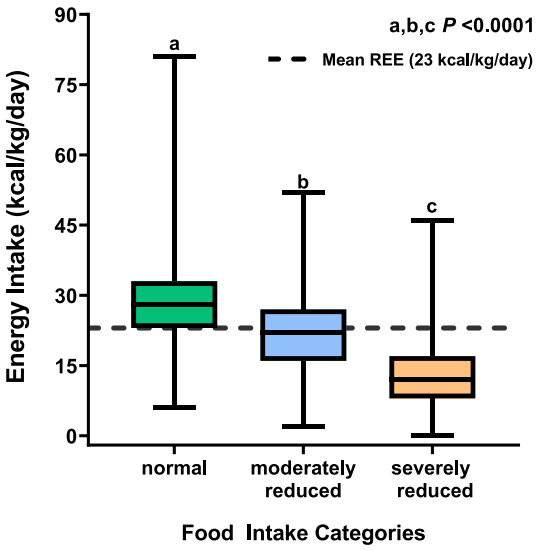

Figure 4 A boxplot of energy intakes (kcal/kg/day) corresponding to 3 categories of food intake derived from the Ingesta Cohort for a subset of patients who completed a 24-hour dietary recall (n = 2,326). There was a significant difference ($P<0.0001$) in the mean (SD) energy intakes between categories of food intake. The dashed line represents the mean measured resting energy expenditure (REE) from subsets of our patient population.[35–37]

Patient factors associated with weight loss

Food intake

Figure 4 depicts the mean (SD) energy intake (kcal/kg/day) corresponding to three-item categorical scale derived from the Ingesta Score (N = 2326) for normal food intake, moderately reduced, and severely reduced food intake were 28.6 (8.8), 22.2 (7.7), and 13.3 (7.7) kcal/kg/day, respectively ($P < 0.0001$).

Based on the similarity across cohorts for WL and OS, further analyses are presented for the pooled cohort (*Figure* 1). The pooled univariable (Supporting Information, *Table* S5) and multivariable MLR analyses (*Table* 2) are presented. In the pooled multivariable MLR analysis, reduced food intake was the variable with largest overall contribution to WL [e.g. patients were more likely to have experienced severe WL (≥15.0%) compared with being weight stable if food intake was moderately, OR 6.28 (95% CI 5.28–7.47); $P < 0.001$, or severely reduced, OR 18.98 (95% CI 15.30–23.56); $P < 0.001$]. Cancer stage I/II was associated with a lesser risk of WL compared with stage IV, [OR 0.53 (95% CI 0.41–0.67); $P < 0.001$]; however, stages III and IV did not differ from each other. Performance status was related to WL, with a maximum risk for severe WL (≥15.0%) in patients with PS 3/4 [OR 2.81 (95% CI 2.33–3.38); $P < 0.001$]. Patients with upper or lower gastrointestinal tumours showed the highest risk and patients with breast cancer the lowest risk of WL ($P < 0.001$). Not surprisingly, patients seen in a multidisciplinary specialist supportive care consultation service were more likely to experience WL, than patients referred to medical oncology clinics. There were trends for patients of male sex to have a higher risk of WL, and for older patients to have a reduced risk of WL.

Systemic inflammation

We evaluated the association of systemic inflammation with WL in patients with a baseline CRP value [n = 4960/12,253 (40.5%); mean (SD) 40.23 (60.05) mg/L]. In multivariable MLR (*Table* 2), CRP had a modest association with ≥15% WL [CRP 10–100 mg/L: OR 2.00 (95% CI 1.58–2.53); $P < 0.001$] and [CRP > 100 mg/L: OR 2.30 (95% CI 1.62–3.26); $P < 0.001$], whereas moderately or severely reduced food intake had a strong association with an OR = 5.67 (95% CI = 4.35–7.39; $P < 0.001$) and OR = 17.37 (95% CI 2.49–24.17; $P < 0.001$), respectively.

Survival analysis

Overall survival was available for 81.2% of the patients in the pooled cohort (n = 9952/12,253), death occurred in 7097 cases. Median OS was 9.9 months (95% CI 9.5–10.3), and median follow-up was 39.70 months (95% CI 38.8–40.6). Food intake categories and variables known to impact OS including

Table 2 Multivariable multinomial logistic regression analysis for the pooled cohort (N = 12,253) and for a subset of the pooled cohort with C-reactive protein (CRP; mg/L; N = 4960) values

	Weight loss[c] 2.5–5.9%			Weight loss 6.0–10.9%		
	N (%)	OR (95% CI)	*P*-value	*N* (%)	OR (95% CI)	*P*-value
Pooled cohort (*N* = 12,253)	2419 (19.7%)			2838 (23.2%)		
Cancer diagnosis[a]						
Respiratory	572 (24)	1 [reference]		611 (21)	1 [reference]	
Other	227 (9)	0.70 (0.56–0.86)	0.001	279 (10)	0.76 (0.62–0.93)	0.009
Genitourinary	301 (12)	0.87 (0.71–1.07)	0.187	337 (12)	0.88 (0.72–1.08)	0.219
Upper GI	333 (14)	1.38 (1.13–1.68)	0.002	504 (18)	1.85 (1.53–2.25)	<0.001
Lower GI	413 (17)	1.29 (1.08–1.54)	0.005	533 (19)	1.78 (1.49–2.11)	<0.001
Head & neck	320 (13)	0.72 (0.60–0.86)	<0.001	307 (11)	0.70 (0.58–0.84)	<0.001
Breast	253 (11)	0.57 (0.46–0.71)	<0.001	267 (9)	0.54 (0.44–0.67)	<0.001
ECOG PS						
0–1	1580 (65)	1 [reference]		1553 (55)	1 [reference]	
2	485 (20)	1.21 (1.04–1.40)	0.013	742 (26)	1.60 (1.39–1.84)	<0.001
3–4	354 (15)	1.21 (1.04–1.4)	0.191	543 (19)	1.40 (1.18–1.65)	<0.001
AJCC cancer stage						
4	1702 (70)	1 [reference]		2212 (78)	1 [reference]	
3	400 (17)	1.14 (0.98–1.33)	0.086	366 (13)	0.88 (0.75–1.03)	0.108
1 & 2	317 (13)	0.73 (0.63–0.86)	<0.001	260 (9)	0.54 (0.46–0.64)	<0.001
Sex						
Female	1917 (51)	1 [reference]		1305 (46)	1 [reference]	
Male	1813 (49)	1.13 (1.00–1.27)	0.043	1533 (54)	1.09 (0.97–1.22)	0.151
Age (years)	2419 (100)	1.00 (0.99–1.00)	0.151	2838 (100)	0.99 (0.99–1.00)	0.003
Setting						
Medical oncology	2081 (86)	1 [reference]		2363 (83)	1 [reference]	
Supportive care consultation	338 (14)	1.18 (0.97–1.43)	0.102	475 (17)	1.25 (1.04–1.51)	0.018
Cohort						
PG-SGA	1139 (47)	1 [reference]		1347 (47)	1 [reference]	
Ingesta score	655 (27)	1.26 (1.07–1.47)	0.005	818 (29)	1.27 (1.09–1.49)	0.002
MNA	625 (26)	1.22 (1.04–1.43)	0.015	673 (24)	1.25 (1.07–1.47)	0.005
Food intake						
Normal	318 (13)	1 [reference]		745 (26)	1 [reference]	
Moderately reduced intake	1128 (47)	2.50 (2.22–2.81)	<0.001	1486 (52)	3.93 (3.48–4.43)	<0.001
Severely reduced intake	973 (40)	2.99 (2.46–3.63)	<0.001	607 (21)	6.41 (5.34–7.68)	<0.001
Pooled cohort with CRP values[b] **(*N* = 4960)**	1070 (22)			1155 (23)		
Food intake						
Normal	452 (42)	1 [reference]		336 (29)	1 [reference]	
Moderately reduced intake	496 (46)	2.67 (2.24–3.20)	<0.001	605 (52)	3.95 (3.28–4.74)	<0.001
Severely reduced intake	122 (11)	2.53 (1.87–3.42)	<0.001	214 (19)	4.74 (3.58–6.30)	<0.001
CRP (mg/L)						
<10	464 (43)	1 [reference]		415 (36)	1 [reference]	
10–100	515 (48)	1.37 (1.15–1.63)	<0.001	567 (49)	1.49 (1.25–1.78)	<0.001
>100	91 (9)	1.12 (0.82–1.54)	0.480	173 (15)	1.84 (1.37–2.46)	<0.001

ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; MNA, Mini-Nutrition Assessment; MLR, multinomial logistic regression; *N*, number; OR, odds ratio; PGSGA, Patient-Generated Subjective Global Assessment; Supportive care consultation, multidisciplinary supportive care consultation service.

[a]Upper GI, gastrointestinal (oesophageal, stomach, pancreas, liver, biliary tract, and small bowel); lower GI, gastrointestinal (colon, rectum, and anus); genitourinary (kidney, bladder, adrenal, prostate, testes, and penis); other (gynaecological, haematological, peritoneum, unknown, and thyroid).

[11]Pooled MLR Model–Reference weight stable (±2.4%) N = 3730 (30%).

[2b]CRP subset of pooled cohort–reference weight stable (±2.4%), N = 1568 (32%); adjusted for cancer diagnosis, AJCC cancer stage, ECOG PS, age, sex, care setting, and cohort.

[3c]% weight loss calculated as: [(current weight − previous weight)/previous weight in kg]*100; weight loss categories calculated based on Martin *et al*.[3]

Table 2 (continued)

	Weight loss 11.0–14.9%			Weight loss ≥15.0%		
	N (%)	OR (95% CI)	*P*-value	*N* (%)	OR (95% CI)	*P*-Value
Pooled cohort (*N* = 12,253)	1472 (12.0%)			1794 (14.6%)		
Cancer diagnosis[a]						
Respiratory	338 (23)	1 [reference]		369 (21)	1 [reference]	
Other	141 (10)	0.72 (0.56–0.93)	0.011	165 (9)	0.74 (0.58–0.95)	0.020
Genitourinary	141 (10)	0.70 (0.54–0.90)	0.006	189 (10)	0.84 (0.66–1.08)	0.174
Upper GI	344 (23)	2.43 (1.95–3.02)	<0.001	533 (30)	3.50 (2.82–4.33)	<0.001
Lower GI	285 (19)	2.01 (1.62–2.48)	<0.001	276 (15)	2.08 (1.68–2.58)	<0.001
Head & neck	133 (9)	0.58 (0.46–0.74)	<0.001	171 (10)	0.73 (0.58–0.93)	0.010
Breast	90 (6)	0.37 (0.28–0.50)	<0.001	91 (5)	0.34 (0.26–0.46)	<0.001
ECOG PS						
0–1	669 (45)	1 [reference]		663 (37)	1 [reference]	
2	401 (27)	1.88 (1.58–2.23)	<0.001	507 (28)	2.20 (1.86–2.61)	<0.001
3–4	402 (27)	2.10 (1.73–2.54)	<0.001	624 (35)	2.81 (2.33–3.38)	<0.001
AJCC cancer stage						
4	1168 (79)	1 [reference]		1486 (83)	1 [reference]	
3	192 (13)	0.98 (0.8–1.19)	0.815	201 (11)	0.98 (0.80–1.20)	0.848
1 & 2	112 (8)	0.55 (0.44–0.70)	<0.001	107 (6)	0.53 (0.41–0.67)	<0.001
Sex						
Female	641 (43)	1 [reference]		750 (42)	1 [reference]	
Male	831 (57)	1.15 (1–1.33)	0.045	1044 (58)	1.22 (1.06–1.40)	0.005
Age (years)	1472 (100)	1.00 (0.99–1.00)	0.106	1794 (100)	0.99 (0.98–0.99)	<0.001
Setting						
Medical oncology	1150 (78)	1 [reference]		1263 (70)	1 [reference]	
Supportive care consultation	322 (22)	1.41 (1.14–1.75)	0.002	531 (30)	1.87 (1.52–2.29)	<0.001
Cohort						
PG-SGA	816 (55)	1 [reference]		1082 (60)	1 [reference]	
Ingesta score	376 (26)	1.07 (0.88–1.30)	0.481	409 (23)	0.97 (0.80–1.17)	0.756
MNA	280 (19)	1.00 (0.82–1.22)	0.994	303 (17)	1.06 (0.87–1.29)	0.580
Food intake						
Normal	265 (18)	1 [reference]		217 (12)	1 [reference]	
Moderately reduced intake	751 (51)	5.01 (4.25–5.91)	<0.001	830 (46)	6.28 (5.28–7.47)	<0.001
Severely reduced intake	456 (31)	11.25 (9.06–13.97)	<0.001	747 (42)	18.98 (15.3–23.56)	<0.001
Pooled cohort with CRP values[b] **(*N* = 4960)**	518 (10)			649 (13)		
Food intake						
Normal	118 (23)	1 [reference]		105 (16)	1 [reference]	
Moderately reduced intake	246 (47)	4.34 (3.36–5.63)	<0.001	279 (43)	5.67 (4.35–7.39)	<0.001
Severely reduced intake	154 (30)	8.76 (6.25–12.29)	<0.001	265 (41)	17.37 (12.49–24.17)	<0.001
CRP (mg/L)						
<10	158 (31)	1 [reference]		179 (28)	1 [reference]	
10–100	273 (53)	1.75 (1.38–2.23)	<0.001	350 (54)	2.00 (1.58–2.53)	<0.001
>100	87 (17)	2.03 (1.41–2.91)	<0.001	120 (18)	2.30 (1.62–3.26)	<0.001

ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; MNA, Mini-Nutrition Assessment; MLR, multinomial logistic regression; *N*, number; OR, odds ratio; PGSGA, Patient-Generated Subjective Global Assessment; Supportive care consultation, multidisciplinary supportive care consultation service.

[a]Upper GI, gastrointestinal (oesophageal, stomach, pancreas, liver, biliary tract, and small bowel); lower GI, gastrointestinal (colon, rectum, and anus); genitourinary (kidney, bladder, adrenal, prostate, testes, and penis); other (gynaecological, haematological, peritoneum, unknown, and thyroid).

Pooled MLR Model–Reference weight stable (±2.4%) *N* = 3730 (30%).

[b]CRP subset of pooled cohort–reference weight stable (±2.4%), *N* = 1568 (32%); adjusted for cancer diagnosis, AJCC cancer stage, ECOG PS, age, sex, care setting, and cohort.

[c]% weight loss calculated as: [(current weight − previous weight)/previous weight in kg]*100; weight loss categories calculated based on Martin *et al*.[3]

Table 3 Adjusted cox proportional hazard models for overall survival for the pooled cohort (*N* = 9952) and for a subset with C-reactive protein (*N* = 3691)

	# deaths/# patients	Median OS months (95% CI)	HR (95% CI)	*P*-value
Pooled cohort with OS (*N* = 9952)				
Food intake				
Normal	2301/3556	18.9 (17.7–20.2)	1 [reference]	
Moderately reduced	3433/4289	8.7 (8.2–9.1)	1.26 (1.19-1.33)	<0.001
Severely reduced	1833/2107	4.3 (3.9–4.7)	1.65 (1.54-1.77)	<0.001
WL grade[a]				
Grade 0	971/1566	21.1 (19.2–23.2)	1 [reference]	
Grade 1	1029/1499	15.6 (14.5–16.7)	1.13 (1.03-1.23)	0.008
Grade 2	1185/1629	11.9 (10.8–13.0)	1.15 (1.05-1.25)	0.002
Grade 3	2348/2949	8.6 (8.0–9.2)	1.26 (1.17-1.37)	<0.001
Grade 4	2034/2309	5.2 (4.8–5.6)	1.57 (1.45-1.71)	<0.001
Pooled cohort with OS and CRP values (*N* = 3691)				
Food intake				
Normal	1068/1478	14.1 (12.8–15.4)	1 [reference]	
Moderately reduced	1204/1504	7.9 (7.2–8.6)	1.13 (1.03–1.23)	0.008
Severely reduced	600/709	5.2 (4.5–5.9)	1.24 (1.11–1.39)	<0.001
WL grade[a]				
Grade 0	366/531	16.5 (13.8–19.2)	1 [reference]	
Grade 1	426/582	12.4 (10.4–14.4)	1.11 (0.97–1.28)	0.142
Grade 2	472/633	10.7 (9.3–12.1)	1.09 (0.95–1.26)	0.210
Grade 3	894/1110	8.5 (7.5–9.5)	1.21 (1.06–1.38)	0.003
Grade 4	714/835	5.7 (5.0–6.3)	1.49 (1.30–1.70)	<0.001
CRP (mg/L)				
<10	454/498	19.7 (17.7–21.7)	1 [reference]	
10–100	1522/1795	6.8 (6.3–7.3)	1.70 (1.56–1.85)	<0.001
>100	896/1398	3.6 (3.1–4.1)	2.09 (1.85–2.36)	<0.001

CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; OS, overall survival; WL, weight loss.
Cox proportional hazards models adjusted for age, sex, cancer diagnosis, AJCC cancer stage, ECOG PS, setting, and cohort (PG-SGA, Ingesta, and MNA).
[a]Weight loss grades calculated based on Martin *et al*.[3]

age, sex, cancer site, AJCC stage, PS, cancer care setting, WL grades, and patient cohort were first evaluated at the univariable level (Supporting Information, *Table* S9). *Table* 3 presents the median overall survival and adjusted hazard ratios (HR) from a Cox proportional hazard model for the pooled cohort with OS: moderately [HR 1.26 (95% CI 1.19–1.33); $P < 0.001$] and severely [HR 1.65 (95% CI 1.54–1.77) - The values from the univariable analysis were inadvertently placed in the text and in table 3, which have been corrected; all other values have been checked and are correct and they are also correct in the supplementary tables); $P < 0.001$] reduced food intake, and WL Grades ($P < 0.001$) were independent predictors of reduced OS. Survival was also assessed in the subset of patients with baseline measure for both food intake and CRP (*n* = 3691/12,253, 30.1%); median OS = 9.2 months (95% CI 8.7–9.8; Supporting Information, *Table* S4). *Table* 3 presents the median overall survival and adjusted hazard ratios (HR) from a Cox proportional hazard model: moderately [HR 1.13 (95% CI 1.03–1.23); $P = 0.008$] and severely [HR 1.24 (95% CI 1.11–1.39); $P < 0.001$] reduced food intake were independent predictors of reduced OS as were WL grades ($P < 0.001$) and CRP ($P < 0.001$).

Discussion

This is the first international multicentre study of the association of reduced food intake with cancer-associated weight loss and overall survival. The results of multinomial logistic regression analyses, controlled for patient demographics, tumour site, stage, centre, performance status, and CRP, demonstrate that reduced food intake predicts a high likelihood of severe weight loss. This is not surprising, given the mean (SD) daily energy intakes for patients with severely reduced intake [13.34 (7.66) kcal/kg/day] only meet ~50% of the measured resting energy expenditure of 23 kcal/kg/day in subsets of our population.[10,35–37] This level of intake is typically classified as a very low calorie diet (10–13 kcal/kg/day; <800 kcal/day), which is only used in limited circumstances for the purpose of intentional weight loss in obese patients.[38]

Our data included recommended screening tools for use in oncology nutrition clinical practice.[10,39] Despite their diversity of concept and scales, the three food intake categories derived from these tools demonstrated similar independent associations to WL (and OS). Importantly, this analysis demonstrates the robustness of using patient report as a means

for patients to communicate the impact cancer has on their ability to eat and how this relates to both weight loss and survival.[19] A common way to assess food intake may facilitate cross-study comparisons and as a means to stratify patients for inclusion to randomized clinical trials; selecting patients with similar levels of food intake.

There are strengths and limitations to this analysis. For strengths, we leveraged our international collaborative to aggregate a large data base. As noted in the 2011 consensus,[1] there was and is still a dearth of data sets on cancer cachexia. Two research-intensive institutions, the Montpellier Cancer Institute and the Cross Cancer Institute, both provided population-based data, and the uniformity of the findings across the data attests that generalizability is likely to be high. Results were validated in three international cohorts and seen to be robust across a wide range of cancers, stages, and treatment contexts. For limitations, in the process of aggregating data, it was evident there was agreement between studies for the domains of assessment for cancer cachexia (i.e. weight loss and food intake), but there was limited agreement for the use of specific measurements within a given domain (i.e. three measures of food intake), which is a known issue in cachexia research. Our results show how different measures of food intake can be aligned relative to one another. Overall, the type of data available for aggregation highlights that our understanding pertaining to different concepts of cancer cachexia are in various stages of progress. Most studies include a measure of weight loss, whereas few included measurements of metabolic alteration (i.e. CRP or other biomarker), or skeletal muscle. The lack of biomarker data is unfortunate given the large number of putative catabolic effector molecules possibly involved in cachexia.[20] This issue can only be corrected by new prospective studies with biobanking efforts and will enhance our ability to examine many areas of interest including changes in muscle and adipose tissue with different treatment regimens and according to sex and racial differences, the inclusion of patient-reported outcomes including quality of life, and functional measures. Lastly, food intake was recorded at baseline, and we do not have information regarding the actual onset of food intake problems or about fluctuations in intake that may have occurred up until the baseline assessment. In addition, we do not have data concerning the causes of reduced food intake; however, the similarity of our findings across tools is quite striking, despite these variations.

The respective contributions of food intake and altered metabolism to cachexia are painted as a spectrum; most patients experience both to some degree, and in others reduced food intake or alterations in metabolism may predominate.[20] Ultimately, our understanding of the factors contributing to cancer-associated WL will only be fully described when both food intake and alterations in metabolism are fully accounted for. These metabolic alterations are suggested to include inflammation, increased energy expenditure, excess proteolysis/lipolysis, and other abnormalities. C-reactive protein is the most cited inflammatory biomarker associated with cancer cachexia and a suggested diagnostic criterion.[40] While we were able to verify CRP as an independent prognostic factor, its association with WL was modest compared with reductions in food intake. At present, we have an incomplete understanding about how to clinically identify or evaluate alterations in metabolism, but we anticipate that this may soon change as this is an active area of research. Candidate predictors of cachexia including proteolysis —and lipolysis inducing molecules are legion[20] and have, to date, only been tested in univariable association with cancer-associated weight loss.

Our findings may serve to sharpen the focus on food intake and anorexia. Simple tools are available to identify patients whose food intake is failing. Early (or even pre-emptive) attention to causes of reduced food intake may forestall large scale losses of weight. This is important as some symptoms associated with impairments of food intake are potentially preventable or reversible[1] with appropriate clinical management (e.g. constipation, nausea, vomiting, pain, depression, and anxiety). For example, Navari *et al.*[41] demonstrated that treatment with olanzapine significantly reduced in non-chemotherapy related nausea and vomiting in advanced cancer patients, with corresponding improvements in appetite. Appetite is a compelling therapeutic target; improving appetite may improve food intake thereby closing the gap between nutrient intake and nutrient requirements for weight maintenance/gain. While there are no approved therapies for anorexia in North America and Europe, there is encouraging investigational activity. Anamorelin hydrochloride, a small molecular weight agonist of the ghrelin receptor, showed promising results in initial Phase III clinical trials[42] and is currently in new Phase III studies[43] and has regulatory approval for treatment of cachexia in Japan.[44] Various forms of nutrition therapy have been investigated including diet counselling, oral nutritional supplements, use of specific nutrients (e.g. n-3 fatty acids and branched chain amino acids), enteral or parenteral nutrition all of which have proven to be only partially effective.[45] Patients with cancer cachexia contend with many additional issues such as pain, nutrition impact symptoms, fatigue, and depression, which can contribute to reduced food intake. It has been advocated that this multifactorial syndrome requires individualized multimodal treatment approaches inclusive of symptom management, nutrition interventions, physical therapy, psychosocial support, and when available use of target therapeutic agents.

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The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle: update 2019*.[46]

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Online supplementary material

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

Table S1. Description of data sources contributed to the PG-SGA, Ingesta, and MNA cohorts.
Table S2. Univariable MLR analysis for the PG-SGA cohort..
Table S3. Univariable MLR analysis for the Ingesta cohort.
Table S4. Univariable MLR analysis for the MNA cohort.
Table S5. Univariable MLR analysis for the Pooled cohort.
Table S6. Multivariable multinomial logistic regression analysis for PG-SGA cohort.
Table S7. Multivariable multinomial logistic regression analysis for Ingesta cohort.
Table S8. Multivariable multinomial logistic regression analysis for MNA cohort.
Table S9. Hazard ratios (HRs) for Cox proportional hazards model assessing the effect of variables associated with overall survival.

Conflict of interest

Dr. Martin reports grants from ASPEN Rhoads Research Foundation, grants from Canadian Institute of Health Research, grants from Izaak Walton Killam Memorial Scholarship, grants from Alberta Innovates Graduate Studentship, during the conduct of the study; Dr. Muscaritoli has nothing to disclose; Dr. Bourdel-Marchasson has nothing to disclose; Dr. Kubrak reports grants from Baxter-Sponsored Academic Fellowship, outside the submitted work; Dr. Laird reports personal fees from XBiotech, grants and personal fees from Artelo, personal fees from Helsinn, outside the submitted work; Dr. Gagnon has nothing to disclose; Dr. Chasen has nothing to disclose; Dr. Gioulbasanis has nothing to disclose; Dr. Wallengren reports personal fees from Nutricia Nordica AB, Sweden, personal fees from Fresenius Kabi AB, Sweden, during the conduct of the study; Dr. Voss has nothing to disclose; Dr. Goldwasser reports grants and personal fees from Baxter, personal fees from Fresenius Kabi, personal fees from Nutricia, outside the submitted work; Dr. Jagoe reports grants from Immunotec Inc, Vaudreuil QC, personal fees from Artelo Biosciences, outside the submitted work; Dr. Deans has nothing to disclose; Dr. Bozzetti has nothing to disclose; Dr. Strasser reports other financial contributions paid to the institution not to him as person from Fresenius, and from Kaiku Health, outside the submitted work; Dr. Thoresen has nothing to disclose; Dr. Kazemi has nothing to disclose; Dr. Baracos reports grants from Canadian Institutes of Health Research, during the conduct of the study; and is a consultant for Pfizer Inc.; Dr. Senesse reports personal fees from Baxter, personal fees from Fresenius Kabi, personal fees from Nutricia, personal fees and grants from Nestle Health Science outside the submitted work.

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