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Orphan disease status of cancer cachexia in the USA and in the European Union: a systematic review

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Abstract

Background Cachexia has significant impact on the patients' quality of life and prognosis. It is frequently observed in patients with cancer, especially in advanced stages, but prevalence data for the overall population are lacking. Good quality estimates of cancer cachexia in general and for each of the major cancer types would be highly relevant for potential treatment development efforts in this field. Both the USA and European Union (EU) have implemented special clinical development rules for such rare disorders what are called 'orphan diseases'. The cut-off level for a disease to be considered an orphan disease in the USA is 200 000 people (0.06% of the population) and EU is 5 per 10 000 people (0.05% of the population).

Methods For this systematic review, we searched at PubMed (from inception to 31 January 2018) to identify clinical studies that assessed the prevalence of cachexia in cancer patients at risk. Studies reporting the prevalence of either cancer cachexia or wasting disease in the top-10 cancer types and 4 other selected cancer types known to be particularly commonly complicated by cachexia were included in this analysis (i.e. prostate cancer, breast cancer, colorectal cancer, melanoma, endometrial cancer, thyroid cancer, urinary bladder cancer, non-hodgkin lymphoma, lung cancer, kidney and renal pelvis cancer, head and neck cancer, gastric cancer, liver cancer, and pancreatic cancer). We calculated the current burden of cancer cachexia, disease by disease, in the USA and in the EU and compared them to the current guidelines for the definition of orphan disease status.

Results We estimate that in 2014 in the USA, a total of 527 100 patients (16.5 subjects per 10 000 people of the total population), and in 2013 in the EU, a total of 800 300 patients (15.8 subjects per 10 000 people of the total population) suffered from cancer cachexia (of any kind). In the 14 separately analysed cancer types, the prevalence of cancer cachexia in the USA ranged between 11 300 (0.4/10 000, gastric cancer) and 92 000 patients (2.9/10 000, lung cancer) and in the EU between 14 300 (0.3/10 000, melanoma of the skin) and 150 100 (3.0/10 000, colorectal cancer).

Conclusions The absolute number of patients affected by cancer cachexia in each cancer group is lower than the defined thresholds for orphan diseases in the USA and EU. Cancer cachexia in each subgroup separately should be considered an orphan disease.

Keywords Cachexia; Orphan disease; Prevalence; Epidemiology; European Union; USA

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Introduction

Cancer cachexia is a recognized problem in the clinical setting of patients suffering from malignant cancer. It is well known to be associated with increased mortality[1] and decreased well-being of patients.[2] Therapies to stop or even reverse the loss of body weight and muscle mass—which are the hallmarks of cancer cachexia—are lacking[3]; hence, cancer cachexia is an area of unmet medical need and is hence of great research interest.[4]

What is less known is that the prevalence of cancer cachexia is relatively low in the general population, compared to common afflictions. This is very relevant for today's research efforts because both the USA and the European Union (EU) have implemented special clinical development rules for what are called 'orphan diseases'. Thereby, both the USA and EU have promoted research into these fields and supported the development of new therapies for these relatively rare diseases. To our knowledge, published evidence has not been available examining whether cancer cachexia should be considered an orphan disease. Therefore, a significant discussion point in any such research context is the actual number of patients who might benefit from new treatment approaches. We therefore wish to address the question of whether cancer cachexia associated with various cancer types, complicating the major cancer subtypes prevalent in developed countries, could be classified as a collection of orphan diseases, based on the available evidence of the number of patients affected.

In the USA, with ca. 319 million inhabitants in 2014,[5] any illness affecting less than 200 000 people is considered to be an orphan disease (as defined by the 'rare disease act of 2002').[6] In the EU, presently consisting of 28 countries with ca. 505 million inhabitants in 2013,[7] the limit to establish the presence of an orphan disease is 5 per 10 000 people (as defined by the European Medicines Agency)[8]—amounting to a cut-off at 255 000 people for the EU as a whole.

Methods and results

The aim of this analysis was to estimate the number of patients currently suffering in the USA and EU from cachexia complicating both the common cancer types and other specific cancer types where cachexia is known to be a frequent complication. We therefore needed three variables: (i) the prevalence of each cancer type, (ii) the percentage of such patients that are at risk to develop cachexia, and (iii) the prevalence of cachexia in all patients at risk (Figure 1).

Prevalence of cancer entities

In oncologic research, most commonly the 5-year prevalence is used to show the burden of different cancer entities. This is the number of patients who have developed any type of cancer in previous 5 years and who are still alive (at the time of assessment). At the same time, this number does not reveal whether the patient is still suffering from the condition or in fact has actually already been cured. Numbers for the total prevalence of individual cancer types (the proportion of the population with cancer at any time during their lifetime, or 'lifetime prevalence') are not published in EU, in an effort not to stigmatize patients that have been cured of cancer, but these data are available for the USA. These total prevalence data from the USA should be used with some caution, because an unknown proportion of these patients may have already been cured (or be in complete remission). To present the complete picture on both total and 5-year prevalence for both regions, the latest available data for the USA from 2014 (Table 1[9]) were used to estimate the total prevalence estimates for the EU in 2013 in Table 2,[9,10] using the same ratios that were observed between 5-year prevalence and total prevalence in the USA, based on the working assumption that expected total prevalence rates between these two populations would be similar. In both tables, we analysed the top-10 cancer types with the highest prevalence overall and four additional cancer types that are known to be frequently associated with cancer cachexia, namely, head and neck cancer, gastric cancer, liver cancer, and pancreatic cancer. The resulting 14 cancer types selected for analysis represent about 85% of all cancer cases.

Of the two prevalence estimates, total and 5 years, the more relevant 5-year prevalence of each cancer type was used in the calculations described below. The 5-year prevalence represents the ongoing burden of each cancer in the USA and EU more accurately and is less influenced by patients who are often considered cured after 5 years of follow-up. In simple terms, this methodology estimates the prevalence of each cancer type after exclusion of likely long-term survivors, thereby more accurately defining the population most likely to be at risk of cachexia.

Figure 1 Formula for estimating the number of patients suffering from cancer cachexia.

$$\text{5-year prevalence of respective cancer (n)} \times \frac{\text{percentage of patients at risk to develop cachexia (\%)}}{100} \times \frac{\text{Cancer cachexia prevalence in patients at risk (\%)}}{100} = \textbf{number of patients suffering from cancer cachexia}$$

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Table 1 Prevalence of cancer cachexia in the USA (2014)

USA (2014)	Prevalence of respective cancer	5-year prevalence of respective cancer	5-year survival rate (%) of respective cancer	Patients at risk to develop cachexia (%)	Patients at risk to develop cachexia (*n*)	Cancer cachexia prevalence in patients at risk (%)	Patients suffering from cancer cachexia in USA (2014)	Prevalence in USA per 10 000 people (2014)
	(data as published)	(data as published)	(data as published)	(estimate)	(estimate)	(estimate)	(estimate)	(estimate)
All cancer patients	14 738 719	4 811 335	67	36.4	1 751 326	30.1	527 100	16.5
Prostate cancer	3 085 209	1 038 106	99	20	207 621	15.3	31 800	1.0
Breast cancer	3 346 387	992 786	91	30	297 836	23.5	70 000	2.2
Colorectal cancer	1 317 247	446 441	66	50	223 221	31.8	71 000	2.2
Melanoma of the skin	1 169 351	343 875	94	20	68 775	22.1	15 200	0.5
Endometrial cancer	710 228	219 407	83	40	87 763	32.2	28 300	0.9
Thyroid cancer	726 646	226 991	98	30	68 097	39.9	27 200	0.9
Urinary bladder cancer	696 440	258 861	78	30	77 658	25.2	19 600	0.6
Non-hodgkin lymphoma	661 996	247 549	73	30	74 265	28.4	21 100	0.7
Lung cancer	527 228	309 108	20	80	247 286	37.2	92 000	2.9
Kidney and renal pelvis cancer	483 225	197 821	75	40	79 128	31.6	25 000	0.8
Head and neck cancer	446 816	172 669	66	70	120 868	42.3	51 100	1.6
Gastric cancer	95 764	48 271	31	70	33 790	33.3	11 00	0.4
Liver cancer	66 771	47 284	19	90	42 556	50.1	21 300	0.7
Pancreatic cancer	64 668	48 921	9	90	44 029	45.6	20 100	0.6

Prevalence of cachexia

For this systematic review, we searched in PubMed to identify clinical studies that assessed the prevalence of cachexia in at least 50 cancer patients at risk, considering articles from inception to 31 January 2018 (Figure 2). Our search algorithm was defined as 'cachexia OR weight loss OR malnutrition AND (cancer OR prostate cancer OR breast cancer OR colorectal cancer OR melanoma OR endometrial cancer OR thyroid cancer OR urinary bladder cancer OR non-hodgkin lymphoma OR lung cancer OR kidney and renal pelvis cancer OR head and neck cancer OR gastric cancer OR liver cancer OR pancreatic cancer) AND (frequency OR epidemiology OR prevalence OR estimate)'. We excluded all reviews, clinical trials, case reports, animal studies, studies in children aged $<$18 years, not published in English, less than 50 patients, lacking data on cachexia, or weight loss prevalence in specific cancer entities. Studies reporting the prevalence of either *cachexia* or *wasting disease* in any of the top-10 most prevalent cancer types plus 4 other selected cancer types known to be particularly often complicated by cachexia were screened and included in this analysis. Senior colleagues were interviewed to find additional relevant papers in areas were few or no reports of interest could be identified.

Altogether, we identified 21 studies published between 1980 and 2017 and reporting on 31 047 cancer patients as shown in Table 3.[11–31] These studies provided acceptably reliable data for all of the 14 cancer entities selected for analysis. Depending on the diagnosis, results for 500 to 4900 patients were available. Only for melanoma were fewer patients reported upon, because cachexia in melanoma patients is rarely studied alone and is frequently reported only in a combined category with other less common cancer entities. The data found for melanoma patients were sufficient, however, for estimation purposes. The 21 studies each looked separately at one to nine cancer types. Studies that did not differentiate between different cancer types and their occurrence of cachexia were not considered for this analysis. It should be noted that the individual studies analysed had varying inclusion criteria for the diagnosis of cachexia ranging from weight loss of $\geq$1% to $\geq$10%. The consensus definition of cachexia by Evans *et al.*[32] defined cachexia as a complex metabolic syndrome associated with the underlying illness. In alignment with the consensus definition, a weight loss of at least $\geq$5% is considered sufficient to diagnose cachexia. A low body mass index ($<$20 or $<$18.5) has also been used to define presence of cachexia, often in combination with weight loss of 2–5% or biochemical abnormalities.[33] The data for the 31 047 patients shown in Table 3 originate in the USA, EU, Australia, Canada, and Asia and therefore represent, it is believed, a broad cross section of cancer experience appropriate to characterize the diverse populations in the USA and EU. The proportions of patients in advanced tumour stages or with metastatic disease were generally high in these studies (up to 100% metastatic disease). The frequency of cachexia ranged from 11–74%.

The average prevalence of cachexia in each cancer diagnosis was calculated by taking into account all patients with that diagnosis (Table 4). The data were not weighted based on the origin of patients (continent, country, etc.) and so, lacking a

Table 2 Prevalence of cancer cachexia in the European Union (2013)

European Union (2013)	Prevalence of respective cancer	5-year prevalence of respective cancer	5-year survival rate (%) of respective cancer	Patients at risk to develop cachexia (%)	Patients at risk to develop cachexia (*n*)	Cancer cachexia prevalence in patients at risk (%)	Patients suffering from cancer cachexia in Europe (2013)	Prevalence in Europe per 10 000 people (2013)
	(estimate)	(data as published)	(data as published)	(estimate)	(estimate)	(estimate)	(estimate)	(estimate)
All cancer patients	21 734 000	7 094 752	67	37.6	2 667 627	30.0	800 300	15.8
Breast cancer	4 831 000	1 433 147	91	30	429 944	23.5	*101 000*	2.0
Prostate cancer	3 774 000	1 269 716	99	20	253 943	15.3	*38 900*	0.8
Colorectal cancer	2 785 000	943 864	66	50	471 932	31.8	*150 100*	3.0
Urinary bladder cancer	1 103 000	409 811	78	30	122 943	25.2	*31 000*	0.6
Melanoma of the skin	1 100 000	323 467	94	20	64 693	22.1	*14 300*	0.3
Endometrial cancer	784 000	242 071	83	40	96 828	32.2	*31 200*	0.6
Head and neck cancer	749 000	289 272	66	70	202 490	42.3	*85 700*	1.7
Kidney and renal pelvis cancer	601 000	246 231	75	40	98 492	31.6	*31 100*	0.6
Lung cancer	573 000	336 143	20	80	268 914	37.2	*100 000*	2.0
Non-hodgkin lymphoma	563 000	210 508	73	30	63 152	28.4	*17 900*	0.4
Thyroid cancer	469 000	146 631	98	30	43 989	39.9	*17 600*	0.3
Gastric cancer	234 000	117 782	31	70	82 447	33.3	*27 500*	0.5
Liver cancer	66 000	46 478	19	90	41 830	50.1	*21 000*	0.4
Pancreatic cancer	57 000	43 197	9	90	38 877	45.6	*17 700*	0.4

Figure 2 Flow diagram of the study selection process.

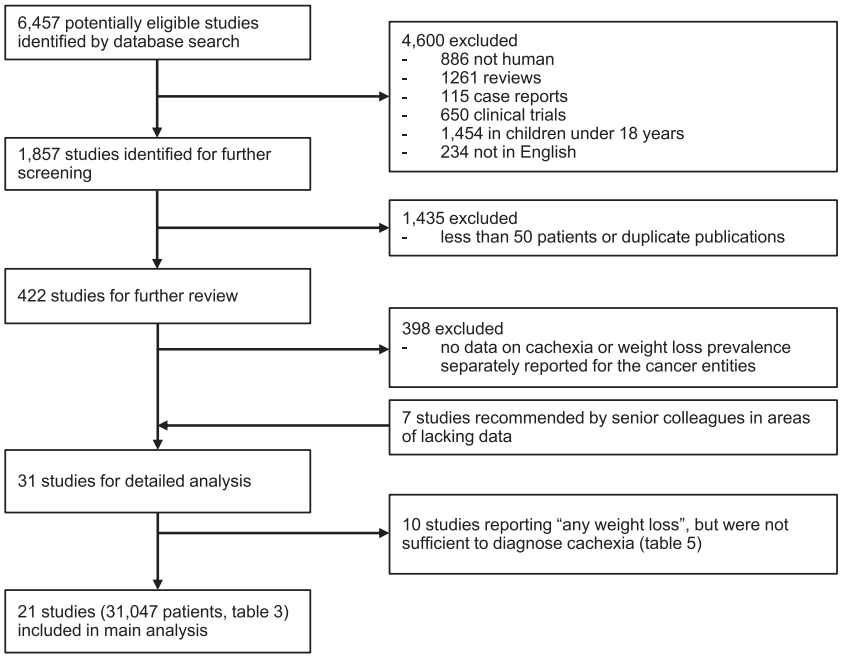

Table 3 Prevalence of cancer cachexia in all analysed studies

Cancer type	Criteria for cachexia diagnosis	Tumour stage	Patient age (years)	Study type	Date of study (years)	Number of patients	Cachexia frequency in patients (%)	Countries where data was developed	Reference
Liver cancer	WL>5% or BMI<20 and WL 2-5%	88% UICC III/IV	63±13	observational study	2012-14	25	36	Italy	Muscaritoli *et al*.[11]
Liver cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	156	24	USA	Fox *et al*.[17]
Liver cancer	BMI<18.5, S-Alb<2.8 g/dL, TLC<1200 cells/mm3	64% UICC III/IV	30-80	observational study	2004	1,497	53	South Korea	Wie *et al*.[31]
Pancreatic cancer	WL>5% or BMI<20 and WL 2-5%	86% UICC III/IV	63±13	observational study	2012-14	94	74	Italy	Muscaritoli *et al*.[11]
Pancreatic cancer	WL≥5% at time of operation	40% UICC III/IV	57-70	observational study	2004-05	227	41	Germany	Bachmann *et al*.[12]
Pancreatic cancer	diagnosis or BMI<20 and/or WL≥5%	not reported	63±12	observational study	2002-09	60	27	Germany	Barkhudaryan *et al*.[13]
Pancreatic cancer	WL≥5% in last six months	not reported	30-80	observational study	1976-80	111	54	USA	Dewys *et al*.[16]
Pancreatic cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	221	35	USA	Fox *et al*.[17]
Pancreatic cancer	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	48% metastatic	59±13	observational study	2013	42	67	France	Hébuterne *et al*.[19]
Lung cancer	WL>5% or BMI<20 and WL 2-5%	90% UICC III/IV	63±13	observational study	2012-14	312	43	Italy	Muscaritoli *et al*.[11]
Lung cancer	diagnosis or BMI<20 and/or WL≥5%	not reported	63±12	observational study	2002-09	58	34	Germany	Barkhudaryan *et al*.[13]
Lung cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	1,294	31	USA	Fox *et al*.[17]
Lung cancer	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	66% metastatic	59±13	observational study	2013	247	45	France	Hébuterne *et al*.[19]
Lung cancer	WL>10%	100% UICC III/IV	43-86	observational study	1991	100	39	USA	Krech *et al*.[24]
Lung cancer	WL≥10%	81% metastatic	59±14	observational study	2007-08	90	30	France	Pressoir *et al*.[26]
Lung cancer	BMI<18.5, S-Alb<2.8 g/dL, TLC<1200 cells/mm3	64% UICC III/IV	30-80	observational study	2004	1,802	41	South Korea	Wie *et al*.[31]
Lung cancer, non-small cell	WL≥5% in last six months	not reported	30-80	observational study	1976-80	590	36	USA	Dewys *et al*.[16]
Lung cancer, small cell	WL≥5% in last six months	not reported	30-80	observational study	1976-80	436	34	USA	Dewys *et al*.[16]
Head and neck cancer	WL>5% or BMI<20 and WL 2-5%	81% UICC III/IV	63±13	observational study	2012-14	62	39	Italy	Muscaritoli *et al*.[11]
Head and neck cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	249	37	USA	Fox *et al*.[17]
Head and neck cancer	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	11% metastatic	59±13	observational study	2013	366	49	France	Hébuterne *et al*.[19]
Head and neck cancer	WL≥10%	24% metastatic	59±14	observational study	2007-08	179	37	France	Pressoir *et al*.[26]
Gastric cancer	WL>5% or BMI<20 and WL 2-5%	80% UICC III/IV	63±13	observational study	2012-14	108	69	Italy	Muscaritoli *et al*.[11]
Gastric cancer	WL≥5% in last six months	not reported	30-80	observational study	1976-80	317	39	USA	Dewys *et al*.[16]

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Table 3 (continued)

Cancer type	Criteria for cachexia diagnosis	Tumour stage	Patient age (years)	Study type	Date of study (years)	Number of patients	Cachexia frequency in patients (%)	Countries where data was developed	Reference
Gastric cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	144	41	USA	Fox *et al*.[17]
Gastric cancer	BMI<18.5, S-Alb<2.8 g/dL, TLC<1200 cells/mm3	64% UICC III/IV	30-80	observational study	2004	2,069	30	South Korea	Wie *et al*.[31]
Colorectal cancer	WL>5% or BMI<20 and WL 2-5%	80% UICC III/IV	63±13	observational study	2012-14	318	60	Italy	Muscaritoli *et al*.[11]
Colorectal cancer	diagnosis or BMI<20 and/or WL≥5%	not reported	63±12	observational study	2002-09	59	31	Germany	Barkhudaryan *et al*.[13]
Colorectal cancer	WL≥5% in last six months	not reported	30-80	observational study	1976-80	307	28	USA	Dewys *et al*.[16]
Colorectal cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	907	25	USA	Fox *et al*.[17]
Colorectal cancer	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	69% metastatic	59±13	observational study	2013	191	39	France	Hébuterne *et al*.[19]
Colorectal cancer	WL≥10%	64% metastatic	59±14	observational study	2007-08	156	23	France	Pressoir *et al*.[26]
Colorectal cancer	BMI<18.5, S-Alb<2.8 g/dL, TLC<1200 cells/mm3	64% UICC III/IV	30-80	observational study	2004	1,778	31	South Korea	Wie *et al*.[31]
Endometrial cancer	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	57% metastatic	59±13	observational study	2013	87	41	France	Hébuterne *et al*.[19]
Endometrial cancer	BMI<18.5	45% UICC III/IV	53±12	observational study	2013	129	11	South Korea	Nho *et al*. [25]
Endometrial cancer	WL≥10%	61% metastatic	59±14	observational study	2007-08	137	28	France	Pressoir *et al*.[26]
Endometrial cancer	BMI<18.5, S-Alb<2.8 g/dL, TLC<1200 cells/mm3	64% UICC III/IV	30-80	observational study	2004	927	35	South Korea	Wie *et al*.[31]
renal cell carcinoma	WL of >2.26 kg in the last 3 months, S-Alb<3.6 g/dL, anorexia, or malaise	43% metastatic	30-80	observational study	1989-2001	1,046	35	USA	Kim *et al*.[22]
renal cell carcinoma	WL of >2.26 kg in the last 3 months, S-Alb<3.6 g/dL, anorexia, or malaise	0% UICC III/IV	63±12	observational study	1989-2001	250	15	USA	Kim *et al*.[23]
Urogenital cancer	WL>5% or BMI<20 and WL 2-5%	62% UICC III/IV	63±13	observational study	2012-14	346	30	Italy	Muscaritoli *et al*.[11]
Urogenital cancer	BMI≥28 and WL≥11% or BMI 20-27.9 + WL ≥6% or BMI<20	85% metastatic	57-74	observational study	2011-13	160	39	EU, Australia, Canada	Vagnildhaug *et al*.[30]
Urinary bladder cancer	BMI<18.5, S-Alb<3.5 g/dL, or WL>5%	44% UICC III/IV	68±10	observational study	2000-08	538	19	USA	Gregg *et al*.[18]
Urinary bladder cancer	S-Alb<3.5 g/dL, or WL>5%	not reported	66±10	observational study	1991-2002	2,538	25	USA	Hollenbeck *et al*.[20]
Unfavorable Non-Hodgkin Lymphoma	WL≥5% in last six months	not reported	30-80	observational study	1976-80	311	28	USA	Dewys *et al*.[16]
Unfavorable Non-Hodgkin Lymphoma	derived from muscle mass, albumin, neutrophils, lymphozytes	63% advanced stage	30-80	observational study	1991-2015	86	47	USA	Karmali *et al*.[21]
Favorable Non-Hodgkin Lymphoma	WL≥5% in last six months	not reported	30-80	observational study	1976-80	290	18	USA	Dewys *et al*.[16]
Leukemia, Lymphoma, Myeloma	WL≥10%	16% metastatic	59±14	observational study	2007-08	156	25	France	Pressoir *et al*.[26]

(*Continues*)

Table 3 (continued)

Cancer type	Criteria for cachexia diagnosis	Tumour stage	Patient age (years)	Study type	Date of study (years)	Number of patients	Cachexia frequency in patients (%)	Countries where data was developed	Reference
Leukemia, Lymphoma	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	37% metastatic	59±13	observational study	2013	377	34	France	Hébuterne *et al*.[19]
Thyroid cancer	WL≥5%	100% metastatic	34-77	single-arm phase II trial	2008-10	58	69	USA	Cabanillas *et al*.[15]
Thyroid cancer	WL≥5%	96% metastatic	41-81	single-arm phase II trial	2013-15	25	60	USA	Cabanillas *et al*.[14]
Thyroid cancer	WL≥5%	100% metastatic	30-80	randomized, controlled trial	2011-12	392	34	USA, EU, Asia, Australia	Schlumberger *et al*.[27]
Thyroid cancer	WL≥5%	100% metastatic	22-74	single-arm phase II trial	2008-10	59	42	USA, EU, Australia	Schlumberger *et al*.[28]
Breast cancer	WL>5% or BMI<20 and WL 2-5%	35% UICC III/IV	63±13	observational study	2012-14	431	14	Italy	Muscaritoli *et al*.[11]
Breast cancer	WL≥5% in last six months	not reported	30-80	observational study	1976-80	289	14	USA	Dewys *et al*.[16]
Breast cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	2,112	25	USA	Fox *et al*.[17]
Breast cancer	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	45% metastatic	59±13	observational study	2013	229	21	France	Hébuterne *et al*.[19]
Breast cancer	WL≥10%	44% metastatic	59±14	observational study	2007-08	375	12	France	Pressoir *et al*.[26]
Breast cancer	BMI≥28 and WL≥11% or BMI 20-27.9 + WL ≥6% or BMI<20	85% metastatic	57-74	observational study	2011-13	252	24	EU, Australia, Canada	Vagnildhaug *et al*.[30]
Breast cancer	BMI<18.5, S-Alb<2.8 g/dL, TLC<1200 cells/mm3	64% UICC III/IV	30-80	observational study	2004	877	33	South Korea	Wie *et al*.[31]
Melanoma	WL>10%	100% UICC III/IV	22-59	observational study	1982	7	14	Netherlands	Smit *et al*.[29]
Melanoma, prostate and others*	WL≥10%	51% metastatic	59±14	observational study	2007-08	349	19	France	Pressoir *et al*.[26]
melanoma, Haematologic cancer and others**	WL>5% or BMI<20 and WL 2-5%	52% UICC III/IV	63±13	observational study	2012-14	141	30	Italy	Muscaritoli *et al*.[11]
Prostate cancer	WL≥5% in last six months	not reported	30-80	observational study	1976-80	78	28	USA	Dewys *et al*.[16]
Prostate cancer	diagnosis, cachexia medication, WL≥5%	40% metastatic	64±12	observational study	1999-2004	3,351	15	USA	Fox *et al*.[17]
Prostate cancer	BMI<18.5 + <75 yrs or BMI<21 + ≥75 yrs and/or WL>10%	38% metastatic	59±13	observational study	2013	72	14	France	Hébuterne *et al*.[19]

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Table 4 Frequency of cancer cachexia and of patients at risk to develop cachexia

Cancer type (n, 5-year survival rate)	Estimated cancer cachexia prevalence in patients at risk (%)	Patients at risk to develop cachexia (%)
Very high risk group—5-year survival rate 0–30%		
Liver cancer (1 678, 19%)	50.1	90
Pancreatic cancer (755, 9%)	45.6	90
Lung cancer (4 929, 20%)	37.2	80
High risk group—5-year survival rate 31–66%		
Head and neck cancer (856, 66%)	42.3	70
Gastric cancer (2 638, 31%)	33.3	70
Colorectal cancer (3 716, 66%)	31.8	50
Middle risk group—5-year survival rate 67–90%		
Endometrial cancer (1 280, 83%)	32.2	40
Kidney and renal pelvis cancer (1 549, 75%)	31.6	40
Non-hodgkin lymphoma (1 220, 73%)	28.4	30
Urinary bladder cancer (3 329, 78%)	25.2	30
Lower risk group—5-year survival rate 91–100%		
Thyroid cancer (534, 98%)	39.9	30
Breast cancer (4 565, 91%)	23.5	30
Melanoma of the skin (<500, 94%)	22.1	20
Prostate cancer (3 501, 99%)	15.3	20

consensus standard for the diagnosis, represent a middle ground reflecting actual practice.

During the literature research, we also found 10 clinical studies in 4312 patients that asked patients whether they ever lost any weight during the course of their disease. We are showing this data in Table 5[34–43] but did not include it in our analysis, because the inclusion criteria were not sufficient to diagnose cachexia.

Patients at risk

For calculation of the patients at risk in each diagnosis, we categorized Table 4 into four groups of very high, high, middle, and lower risk of cancer cachexia by taking into account the respective 5-year survival rates of the cancer entities. Based on prior clinical experience that the intensity and progression of the cancer disease process is directly related to metabolic disorders responsible for cachexia, it has been assumed that patients with lower 5-year survival rates are more prone to develop cachexia, and therefore, they have been classified as having a higher risk for cachexia development.

Because the 5-year prevalence for each cancer takes into account the cured and sick patients alike, we had to consider this in our analysis and therefore estimated the actual patients at risk to develop cachexia with the help of these four risk groups. To the very high-risk group, we attributed that 80–90% of the patients are at risk, in the high-risk group 50–70%, in the middle-risk group 30–40%, and in the lower-risk group 20–30% (Table 4). Within the four risk groups, we considered the prevalence of cachexia in the patients at risk and again the 5-year survival rate. We were therefore able to weigh the data within these groups (Table 4). Consequently, in the very high-risk group, pancreatic cancer patients had the lowest 5-year survival rate and liver cancer the highest prevalence of cachexia in patients at risk. We therefore attributed to both diagnoses that 90% of patients are at risk. Lung cancer had a higher 5-year survival rate and lower cachexia prevalence in patients at risk within this very high-risk group, and so we attributed that 80% of the patients are at risk to develop cachexia. We did the same for the other risk groups as well (Table 4).

Number of patients with cancer cachexia

With the attained data, we were able to calculate the estimates for the numbers of cancer patients likely to be suffering from cancer cachexia in the USA (Table 1, Figure 3) and in the EU (Table 2, Figure 4). We estimate that in 2014, in the USA, 527 100 patients suffered from cancer cachexia (of any kind), equalling 16.5 subjects per 10 000 of the total population (USA inhabitants 2014: 318 622 530[5]). In 2013, in the EU, a total of 800 300 patients suffered from cancer cachexia (of any kind), equalling 15.8 subjects per 10 000 people of the general population (EU inhabitants 2013: 505 170 000[7]). For each specific cancer type, the absolute numbers of patients suffering of cachexia were lower than 200 000 patients in the USA, or less than 5 per 10 000 people in the EU, and for most types, substantially below those thresholds. Even if a high margin of error of ±30% is applied to the final results, cancer cachexia remains an orphan disease if each cancer type is considered separately, and this was true for all the specific cancer types studied. Given the wide variation in the risk of developing cachexia, we believe it is sensible to look at cancer-specific cachexia rather than considering all cancer cachexia as a single disease.

Table 5 Studies reporting weight loss ≥1% as a categorical variable
(Note: Weight loss ≥1% without further details was not considered sufficient for the diagnosis of cachexia)

Cancer type	Criteria for weight loss	Tumour stage	Patient age range (years)	Study type	Date of study (years)	Number of patients	Frequency of any weight loss in all patients (%)	Countries where data were developed	Reference
Endometrial cancer	any WL	100% UICC III/IV	30–80	observational study	1990–91	83	22	EU, USA, Australia	Vainio *et al*.[42]
Endometrial cancer	any WL	100% UICC III/IV	21–80	observational study	1981–83	74	84	USA	Wachtel *et al*.[43]
Breast cancer	any WL in last week	63% metastatic	23–86	observational study	1990–92	70	31	USA	Portenoy *et al*.[39]
Breast cancer	any WL	100% UICC III/IV	15–82	observational study	1992	44	88	India	Sebastian *et al*.[40]
Breast cancer	any WL	100% UICC III/IV	30–80	observational study	1990–91	186	22	EU, USA, Australia	Vainio *et al*.[42]
Breast cancer	any WL in last two weeks	56% metastatic	19–92	observational study	2001–02	101	28	Spain	Segura *et al*.[41]
Breast cancer	any WL	100% UICC III/IV	21–80	observational study	1981–83	127	78	USA	Wachtel *et al*.[43]
Colorectal cancer	any WL in last week	63% metastatic	23–86	observational study	1990–92	60	27	USA	Portenoy *et al*.[39]
Colorectal cancer	any WL	100% UICC III/IV	30–80	observational study	1990–91	127	53	EU, USA, Australia	Vainio *et al*.[42]
Colorectal cancer	any WL in last two weeks	56% metastatic	19–92	observational study	2001–02	103	32	Spain	Segura *et al*.[41]
Colorectal cancer	any WL	100% UICC III/IV	21–80	observational study	1981–83	148	81	USA	Wachtel *et al*.[43]
Colorectal cancer	any WL before commencing chemotherapy	100% UICC III/IV	16–84	observational study	1990–96	781	34	UK	Andreyev *et al*.[34]
Lung cancer	any WL	100% UICC III/IV	15–82	observational study	1992	10	80	India	Sebastian *et al*.[40]
Lung cancer	any WL	100% UICC III/IV	30–80	observational study	1990–91	387	49	EU, USA, Australia	Vainio *et al*.[42]
Lung cancer	any WL in last two weeks	56% metastatic	19–92	observational study	2001–02	179	36	Spain	Segura *et al*.[41]
Lung cancer	any WL	100% UICC III/IV	21–80	observational study	1981–83	288	83	USA	Wachtel *et al*.[43]
Prostate cancer	any WL in last week	63% metastatic	23–86	observational study	1990–92	63	25	USA	Portenoy *et al*.[39]
Prostate cancer	any WL	100% UICC III/IV	30–80	observational study	1990–91	78	26	EU, USA, Australia	Vainio *et al*.[42]
Prostate cancer	any WL	100% UICC III/IV	21–80	observational study	1981–83	73	86	USA	Wachtel *et al*.[43]
Lymphoma	any WL	100% advanced stage	30–80	observational study	1990–91	67	33	EU, USA, Australia	Vainio *et al*.[42]
Pancreatic cancer	any WL	64% metastatic	30–80	observational study	1990	39	51	USA	Krech *et al*.[37]
Pancreatic cancer	any WL	100% UICC III/IV	21–80	observational study	1981–83	63	89	USA	Wachtel *et al*.[43]
Pancreatic cancer	any WL before commencing chemotherapy	100% UICC III/IV	16–84	observational study	1990–96	162	72	UK	Andreyev *et al*.[34]

(*Continues*)

Table 5 (continued)

Cancer type	Criteria for weight loss	Tumour stage	Patient age range (years)	Study type	Date of study (years)	Number of patients	Frequency of any weight loss in all patients (%)	Countries where data were developed	Reference
Head and neck cancer	any WL before commencing radiotherapy	not reported	32–89	observational study	1989	100	57	UK	Lees *et al.*[38]
Head and neck cancer	any WL	100% UICC III/IV	15–82	observational study	1992	175	97	India	Sebastian *et al.*[40]
Head and neck cancer	any WL	100% UICC III/IV	30–80	observational study	1990–91	94	33	EU, USA, Australia	Vainio *et al.*[42]
Head and neck cancer	any WL	100% UICC III/IV	41–87	observational study	1990–93	38	79	UK	Forbes *et al.*[36]
Gastric cancer	any WL before commencing chemotherapy	100% UICC III/IV	16–84	observational study	1990–96	433	67	UK	Andreyev *et al.*[34]
Gastric cancer	any WL	100% UICC III/IV	30–80	observational study	1990–91	95	45	EU, USA, Australia	Vainio *et al.*[42]
Gastric cancer	any WL in last two weeks	56% metastatic	19–92	observational study	2001–02	34	50	Spain	Segura *et al.*[41]
Bladder cancer	any WL in the last 6 weeks	53% UICC III/IV	62 ± 7	observational study	1985	30	30	Denmark	Enig *et al.*[35]

WL, weight loss; UICC, Union Internationale contre le Cancer tumor stage; USA, United States of America; UK, United Kingdom.

Discussion

The estimation of the prevalence of cachexia in cancer involves both epidemiological and clinical considerations, requiring both extensive research for current relevant data on multiple cancer types and the development of an approach to integrate that data into meaningful information. Those challenges may be responsible for the lack of published reports on the disease-specific prevalence of cancer cachexia in the USA and EU populations.

Recently, Baracos *et al.*[44] provided data on the prevalence of cachexia in eight cancer diagnoses considering information provided in two original studies with a total of about 3000 patients. In the present study, however, we used data from 21 original reports with a total of over 31 000 patients and assessed 14 cancer diagnoses—the 10 most frequent cancer diagnoses and another 4 cancer types that are frequently associated with cancer cachexia. Furthermore, we calculated the prevalence of cancer cachexia in the general population, giving one the chance to evaluate, whether individual disease related cancer cachexia syndromes should be considered orphan diseases in the USA or EU. We make the case that different cachexia disease types, potentially require individually targeted therapies. Currently, the National Cancer Institute identifies more than 200 different targeted drugs approved to treat over 100 separate cancer types separately.[45]

Cancer cachexia (in different cancers) is not one and the same general disease. Underlying pathophysiology, genetics, and biochemistry, but also symptoms and prognostic importance are different[46]—both in absolute terms and in their relative impact on disease progression and the patient burden—which is relevant for the development of novel treatment and prevention strategies. Research to this end is only in its infancy. Antecedent cancers are genomically distinct and have unique characteristics associated with the primary tissue affect, thus generally requiring individualized management efforts. Hence, it is reasonable that orphan disease status for cancer cachexia is assessed on the individual cancer type level and not for all cancer cachexia types together.

In the only available original research article on this issue, it has been estimated that cachexia is the immediate or primary cause of death in approximately 30% of cancer patients.[47] Cancer cachexia is also associated with increased length of hospital stay as well as increased overall treatment costs.[48] The possible ways how cachexia can cause death have been the subject of prior publications, which have concluded that in addition to cachexia interfering in the treatment of the cancer itself, it also acts as an indirect contributor to mortality.[49] Future orphan treatments for cachexia might be divided into those that address symptoms and quality of life (palliative) and those that possibly impact mortality (directly addressing the life-limiting disease).

Figure 3 Prevalence of cancer cachexia in the USA (2014) with ±30% error bars to indicate the estimated uncertainty of the estimates.

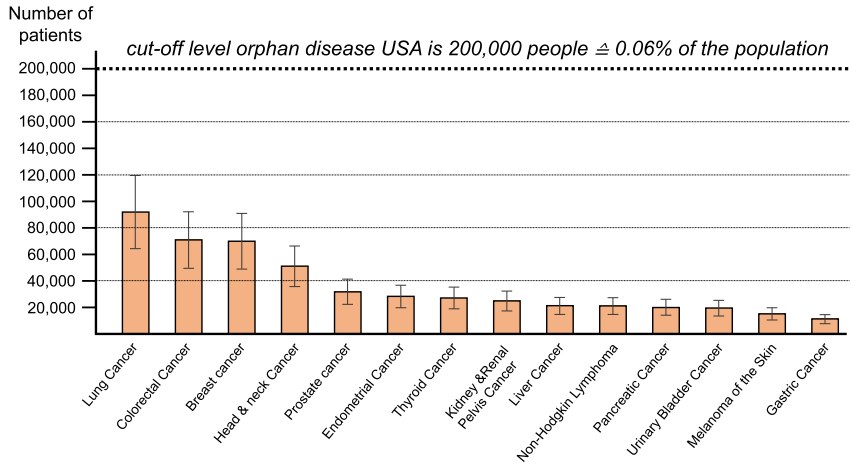
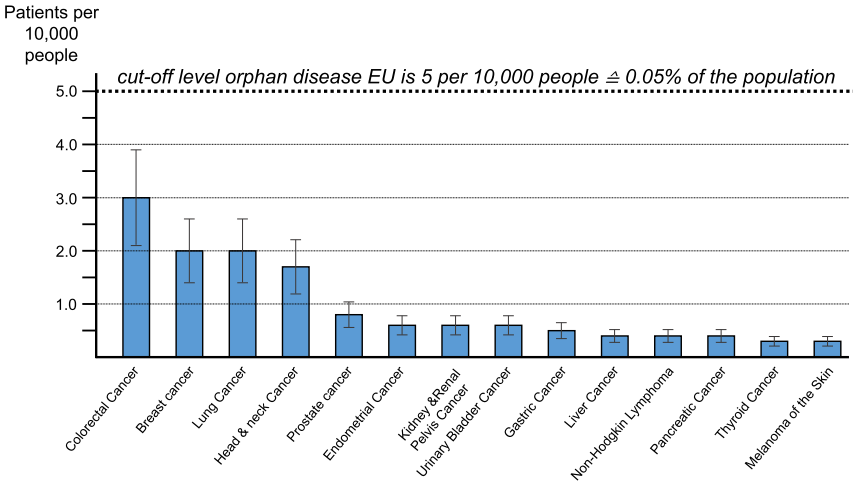


Figure 4 Prevalence of cancer cachexia in the European Union (2013) with ±30% error bars to indicate the estimated uncertainty of the estimates.



Limitations

We only have access to summaries of research based on individual patient series, and we therefore had to base our analyses on these data as published. These have somewhat varying definitions of cachexia, so that there is inherent uncertainty around our prevalence estimates. We believe that these variations are likely to be less than 20% above or below our central estimate. Even though we included >30 000 patients in this analysis, which is more than ever shown before, the analysis summarizes only 21 studies, which is due to lack of attention of medicine and frustration about not being able to treat cachexia yet.

We used the 5-year prevalence of each cancer type. This estimate is lower than the actual number of all people who ever had the cancer type and who still survive (by excluding those who have carried the diagnosis for more than 5 years). This may be thought to therefore slightly underestimate the prevalence of the respective cancer-type-specific cachexia, but the effect is likely to be small for two reasons.

1. Patients who have survived more than 5 years include those with cured cancer and those with very slowly progressing disease. These patients will have a lower rate of cachexia development than all comers for that particular cancer type.
2. The cancer patient who develops cachexia has a significantly worse survival than one who does not; therefore, the 5-year prevalence data will have 'lost' some cachexia patients who have on average died earlier. This effect will

therefore tend to overestimate the prevalence of cancer cachexia at any point in time, because we have used a constant risk of cachexia development for each cancer type whereas the 5-year prevalence data for each cancer type contains an under-representation of cachexia sufferers who have died and hence are no longer there to be counted in the 5-year prevalence data.

For these reasons, we believe our estimates may actually overestimate rather than underestimate the prevalence of cancer-type-specific cachexia in the USA and in the EU and therefore the risk of misclassifying a condition as an orphan disease when it is not is low. We also make the point that although disease prevalence is used to define orphan disease status, a high mortality condition can have a large impact, because it can affect more patients when measured as disease incidence rather than prevalence. Thus, individual cancer cachexia may be considered low prevalence orphan diseases, but higher incidence high impact disorders, a combination of features that should make them very strong candidates for new prevention and treatment development efforts.

Conclusion

We conclude from this analysis that the absolute number of patients affected by cancer cachexia in each cancer group is lower than the defined thresholds in the USA and EU. Hence, cancer cachexia in each subgroup separately should be considered an orphan disease.

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Conflict of Interest

M.M., W.H., A.J., F.S., and U.L. report no conflicts of interest. M.S.A. reports receiving personal fees from Servier. R.H. reports consultancy for bioAffinity, CranioVation, Erbe Medical, and iCAD. S.v.H. reports consultancy for Novartis, Helsinn, Bayer, Respicardia, Vifor Pharma, and Chugai. J.E.M. reports consultancy for Boehringer Ingelheim and Abbott nutrition. A.J.S.C. reports consultancy for Respicardia, Vifor, and Actimed Therapeutics. S.D.A. reports consultancy and/or speaking for Vifor International, Novartis, Servier, Helsinn, Bayer, Boehringer Ingelheim, and Actimed Therapeutics. S.D.A. reports grant support for clinical trials from Vifor International and Abbott. A.J.S.C. and S.D.A. report owning shares of Actimed Therapeutics.

Contributors

M.S.A., R.H., A.J.S.C., and S.D.A. designed the study, and all authors oversaw its implementation. M.S.A. did all review activities, including searches, study selection (including inclusion and exclusion of studies), data extraction, and data analysis. M.M. provided additional published and unpublished data. R.H. and S.D.A. supported data analysis. M.S.A. wrote the first draft, and all authors contributed to revising the manuscript. All authors reviewed the study findings and read and approved the final version before submission. The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017.[50]

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