Frailty and quality of life among older people with and without a cancer diagnosis: Findings from TOPICS-MDS

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Abstract

Background

The number of older cancer patients is rising. Especially in older people, treatment considerations should balance the impact of disease and treatment on quality of life (QOL) and survival. How a cancer diagnosis in older people interacts with concomitant frailty to impact on QOL is largely unknown. We aimed to determine the association between frailty and QOL among community-dwelling older people aged 65 years or above with and without a cancer diagnosis cross-sectionally and at 12 months follow-up.

Methods

Data were derived from the TOPICS-MDS database. Frailty was quantified by a frailty index (FI). QOL was measured with the subjective Cantril's Self Anchoring Ladder (CSAL, range: 0–10) and the health-related EuroQol-5D (EQ-5D, range:-0.33–1.00) at baseline and after 12 months. To determine associations, linear mixed models were used.

Results

7493 older people (78.6±6.4 years, 58.4% female) were included. Dealing with a cancer diagnosis (n = 751) was associated with worse QOL both at baseline (CSAL:-0.25 (95%-CI:-0.36;-0.14), EQ-5D:-0.03 (95%-CI:-0.05;-0.02)) and at follow-up (CSAL:-0.13 (95%-CI:-0.24;-0.02), EQ-5D:-0.02 (95%-CI:-0.03;-0.00)). A ten percent increase in frailty was also associated with a decrease in QOL at baseline (CSAL:-0.35 (95%-CI:-0.38;-0.32), EQ-5D:-0.12 (95%-CI:-0.12;-0.11)) and follow-up (CSAL:-0.27 (95%-CI:-0.30;-0.24), EQ-5D:-0.07 (95%-CI:-0.07;-0.06)). When mutually adjusting for frailty and a cancer diagnosis, associations between a cancer diagnosis and QOL only remained significant for CSAL at baseline (-0.14 (95%-CI:-0.25;-0.03)), whereas associations between frailty and QOL remained significant for all QOL outcomes at baseline and follow-up. No statistical interactions between cancer and frailty in their combined impact on QOL were found.

Conclusions

Cancer diagnosis and frailty were associated with worse health-related and self-perceived QOL both at baseline and at follow-up. Differences in QOL between older people with and without a cancer diagnosis were explained to a large extent by differences in frailty levels. This stresses the importance to take into account frailty in routine oncologic care.

Introduction

The number of older patients qualifying for oncologic treatment is rising. Due to concomitant multi-morbidity and frailty among these patients, physicians need to deal with complex treatment decision-making processes[1–6]. In order to evaluate treatment options, physicians in oncology care generally focus on short-term complications, morbidity and survival as primary outcomes[7–9]. Especially in older people with cancer, however, treatment considerations should be based on individual preferences regarding quality or quantity of life[10–12]. To be able to balance the impact of disease and treatment on quality of life (QOL) and survival, physicians should understand how the disease affects individual's QOL taking into account the personal context of this patient[13]. Among other factors, patients may greatly differ with respect to the type and severity of frailty and co-morbidity. A cancer diagnosis has been reported to relate to worse health-related QOL[14, 15]. Older people with cancer had more complaints and self-reported diseases compared to older people without cancer[14]. In addition, people with and without cancer had more complaints with increasing age[14] and the specific health-related QOL domains impaired also varied with age[15]. Though individual characteristics among cancer patients such as functional impairment, co-morbidity and psychosocial disabilities have predictive value for QOL[16–19], most studies on the association between cancer and QOL lack focus on older patients' frailty. Currently, the interest in frailty in geriatric oncology is mainly focused on an older person's ability to cope with the burden of cancer treatment[20]. Despite the observation that frailty is associated with worse QOL among older people in general[21–23], the interaction between frailty and a cancer diagnosis in their combined impact on QOL of older cancer patients is largely unknown (Fig 1). We aimed to study the differences in the association between frailty and self-perceived and health-related QOL between community-dwelling older people aged 65 years or above with and without a cancer diagnosis cross-sectionally and at 12 months follow-up.

Methods

Design

1.1. Data source. The data for this study were derived from The Older Persons and informal Caregivers Survey Minimum DataSet (TOPICS-MDS) repository[24]. This is a public data repository which contains information on the physical and mental health being of older persons and informal caregivers across the Netherlands[25]. In total, 60 research projects have contributed data to this initiative which may have differed in study design, sampling framework, and inclusion criteria. All data were cleaned locally using a standardized protocol. Anonymized individual-level data were then submitted to a central institution (Radboud university medical center, Nijmegen, the Netherlands) for further validation checks and creation of the pooled dataset[25]. Since TOPICS-MDS is a fully anonymized dataset available for public access, no ethical review was needed for our analyses according to Dutch law[25].
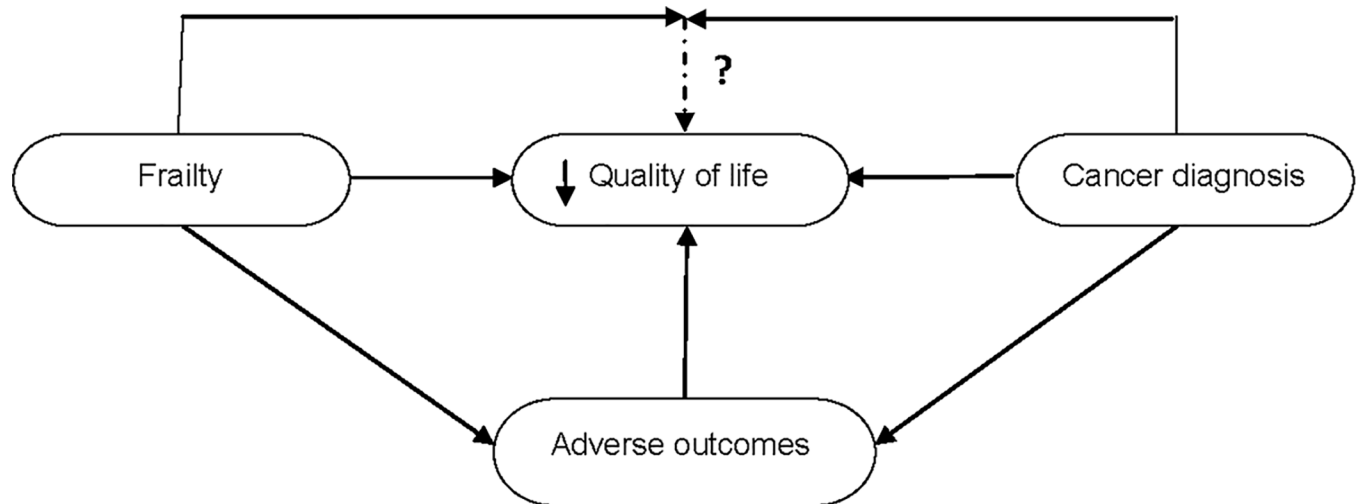
Fig 1. Interrelations between cancer, frailty, adverse outcomes and quality of life.

1.2. Inclusion criteria. The following inclusion criteria were utilized to select appropriate research projects for which TOPICS-MDS data were in the repository:

- Community-dwelling people who were 65 years or older at baseline;

- The study setting was primary care or general population;

- Longitudinal data were available in the separate research project (not necessarily for each individual within that project) at 12 months follow-up.

1.3. Measures. The primary outcomes were QOL at baseline (cross-sectional analyses) and QOL after 12 months, respectively. Independent variables of prime interest comprised frailty and cancer diagnosis. Operational definitions for these variables and measurement can be found below. Adjustment variables were age, gender and education level.

1.3.1. Quality of life. In the TOPICS-MDS baseline questionnaire for care receivers (T0), self-perceived and health-related QOL were measured by a modified Cantril's Self Anchoring Ladder and the EuroQol-5D, respectively. Both QOL outcomes were also included in the TOPICS-MDS follow-up questionnaire for care receivers which was gathered after 12 months (T12).

- Modified Cantril's Self Anchoring Ladder (CSAL)
  CSAL is a one-dimensional index ranging from 0 (completely unsatisfied with life) to 10 (completely satisfied with life) and measures self-perceived general QOL[26]. We used a modified version of CSAL where respondents were asked to rate their present life on a scale between zero and ten, without use of the image of a ladder.

- EuroQol-5D (EQ-5D)
  The EQ-5D utility score measures health-related QOL[27]. Five dimensions (mobility, self-care, daily activities, pain and discomfort, anxiety and depression) with three levels each (1 = no problems, 2 = moderate problems, and 3 = extreme problems) are combined into one utility score by means of applying the scoring values for the Dutch population[27]. The EQ-5D utility score ranges from -0.33 to 1.00 where a score below zero is indicative of a health state worse than death[27].

1.3.2. Frailty. To quantify frailty, frailty indices based on the concept of deficit accumulation were used[28]. Specifically, we used a slightly modified version of the long TOPICS-MDS frailty index which originally consists of 46 items (TOPICS-FI46) and which can be derived from the TOPICS-MDS baseline questionnaire[29]. Since the EQ-5D+C was part of the deficits counted in the TOPICS-FI46, we excluded these items to be able to determine the association between frailty and QOL as measured with the EQ-5D. In addition, as the cancer diagnosis was also used as independent variable to differentiate between older people with and without cancer, this morbidity item was also excluded from the frailty index. Since one item concerned gender-specific prostate symptoms which, moreover, may be associated with a cancer diagnosis, this morbidity item was additionally excluded. Consequently, our adjusted frailty index consisted of 38 items (TOPICS-FI38). By dividing the number of deficits endorsed with the number of total deficits included, a frailty index score was calculated that ran from 0 to 1. Whereas theoretically the FI score can be 1 (38 of 38 deficits endorsed), the maximum FI score observed is usually around 0.6 and 0.7[28]. Participants were considered to be frail when their TOPICS-FI38 score was equal to or above 0.25.

1.3.3. Cancer diagnosis. In the TOPICS-MDS baseline questionnaire, individuals were asked to tick boxes which illnesses and conditions they had at the moment or had had in the past 12 months. To differentiate between people with and without cancer, we used the self-reported presence of a type of cancer (malignant condition). Beyond this information, no information on type or severity of cancer was available.

1.3.4. Education level. Since QOL is associated with the education level of people, we adjusted for education level in our analyses. In the TOPICS-MDS baseline questionnaire, individuals were asked what the highest level of education was that they had completed as defined by Verhage[30]. We classified the lowest four levels of education (ranging from less than 6 years primary school to vocational school) as 'low', level 5 and 6 (ranging from secondary professional education to university entrance level) were classified as 'moderate' and level 7 (university or tertiary education) was classified as 'high'.

1.4. Procedure

We used the TOPICS-MDS dataset for care receivers available in January 2017 (version TOPICS_2.0). Based on our inclusion criteria, 14 projects were appropriate to answer our research question. For these studies, intervention groups were excluded since the interventions may have influenced respondents' frailty and/or QOL. Furthermore, respondents living in nursing homes and respondents with an unknown cancer diagnosis status at baseline were also excluded. If the respondents' date of follow-up assessment was outside a 6 months window (3 months before or 3 months after the intended 12 months follow-up), these respondents were excluded in the analyses. Studies in which the follow-up date was exceeded in more than 60% of the respondents were excluded as a whole. In the end, 7493 respondents in 11 projects were included in our analyses (Fig 2).

1.5. Statistical analysis

Demographic characteristics were compared between respondents with and without cancer. Student's t-test was used for continuous data and the chi-square test was used to compare categorical data. The proportions of frailty deficits endorsed among frail respondents with cancer were compared with those among frail respondents without cancer and were considered clinically relevant if the proportions differed by 5%. To determine the association between frailty and QOL, we used linear mixed models to account for clustering within individual research
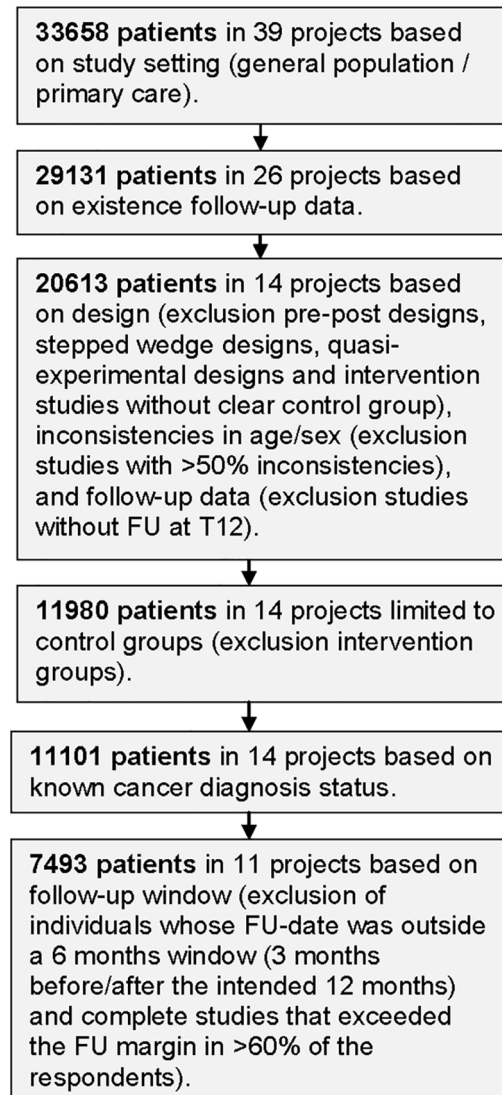
Fig 2. Flowchart included TOPICS-MDS studies. FU = Follow-up.

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projects. Independent variables included age, sex, education level, frailty, cancer diagnosis status, the interaction term frailty*cancer diagnosis and (for the longitudinal analyses) the score on the respective QOL measure at T0. Associations with the primary determinants were examined in unadjusted models as well as models adjusted for age, sex and education level. Data were analyzed using the statistical software program SPSS version 22.

Results

Sample characteristics

In total, 7493 respondents were included in this study. Significant differences in age, frailty and outcome variables existed between included respondents and excluded respondents (S1 Table). Of the included respondents, 10.0% (n = 751) reported to have cancer at the moment of the baseline measurement or to have had cancer in the 12 months prior to the baseline assessment. The majority had no missing data points for TOPICS-FI38: 99.2% (n = 7433),

Table 1. Sample characteristics of the respondents with versus without cancer.

	People without cancer		People with cancer		p-value
	n	Mean ± SD / %	n	Mean ± SD / %	
Age	6736	78.6 ± 6.4	751	79.1 ± 6.5	0.05
Sex (% female)	6742	4006 (59.4%)	751	373 (49.7%)	<0.001
Education level	6683		745		0.99
Low		3248 (48.6%)		361 (48.5%)	
Moderate		2641 (39.5%)		296 (39.7%)	
High		794 (11.9%)		89 (11.8%)	
CSAL (T0)	6628	7.2 ± 1.5	743	6.9 ± 1.4	<0.001
CSAL (T12)	5974	7.1 ± 1.5	648	6.8 ± 1.4	<0.001
EQ-5D (T0)	6639	0.77 ± 0.2	740	0.73 ± 0.2	<0.001
EQ-5D (T12)	5936	0.76 ± 0.2	648	0.71 ± 0.3	<0.001
TOPICS-FI38 (T0)	6717	0.20 ± 0.13	716	0.23 ± 0.13	<0.001

Education level: education levels as defined by Verhage[30] were classified as low (ranging from less than 6 years primary school to vocational school), moderate (ranging from secondary professional education to university entrance level) and high (university or tertiary education). CSAL: Modified Cantril's Self Anchoring Ladder, range 0 to 10, where 10 indicates the best score for present life as rated by individuals. EQ-5D: EuroQol-5D utility score, range -0.33 to 1.00 where a score below zero is indicative of a health state worse than death. TOPICS-FI38: TOPICS-MDS frailty index consisting of 38 items to quantify frailty, range 0 to 1, where participants with a score equal to or above 0.25 are considered to be frail. T0 indicates the baseline measurement, T12 indicates the measurement after 12 months.

CSAL: 98.4% (n = 7371), and EQ-5D: 98.5% (n = 7379). Among respondents without cancer, the majority was female (59.4%) contrary to respondents with cancer (49.7%, p<0.001). Age was comparable between both groups (Table 1). Respondents with cancer were significantly more frail compared to respondents without cancer (TOPICS-FI38: 0.23±0.13 and 0.20±0.13, p<0.001, respectively) and QOL was rated significantly worse both at baseline (CSAL: 6.9±1.4 and 7.2±1.5, p<0.001. EQ-5D: 0.73±0.2 and 0.77±0.2, p<0.001) and at follow-up (CSAL: 6.8± 1.4 and 7.1±1.5, p<0.001. EQ-5D: 0.71±0.3 and 0.76±0.2, p<0.001).

Analysis of the differences in deficits between frail respondents with and without cancer (Fig 3) showed that frail respondents with cancer had more benign prostate hypertrophy (13 vs. 7%, mean difference: -0.06, 95%-CI: -0.10; -0.01), more depression (24 vs. 19%, mean difference: -0.05, 95%-CI:-0.10; 0.00), more heart failure (39 vs. 30%, mean difference: -0.09, 95%-CI: -0.15; -0.03), more dizziness with falling (41 vs. 31%, mean difference: -0.10, 95%-CI: -0.16; -0.04), more hearing disorders (59 vs. 52%, mean difference: -0.07, 95%-CI: -0.13; -0.00), and they felt more unhealthy (81 vs. 72%, mean difference: -0.09, 95%-CI: -0.15; -0.04). Frail respondents without cancer had more dementia (19 vs. 14%, mean difference: -0.06, 95%-CI: -0.01; -0.10).

Outcomes

Univariable analyses showed that CSAL and EQ-5D scores at baseline and follow-up, in addition to being related to frailty and cancer diagnosis, were significantly higher in respondents who were younger, and higher educated. For the EQ-5D at baseline and at follow-up, also males scored significantly higher in univariable analyses (S2 Table). Adjusted for age, gender, education level and baseline QOL score if appropriate, a cancer diagnosis continued to be associated with worse QOL at baseline (CSAL: -0.25 (95%-CI: -0.36; -0.14, p<0.001), EQ-5D: -0.03 (95%-CI: -0.05; -0.02, p<0.001)) and at follow-up (CSAL: -0.13 (95%-CI: -0.24; -0.02, p = 0.02), EQ-5D: -0.02 (95%-CI: -0.03; -0.00, p = 0.03)). Likewise, increasing frailty continued to be associated with a decrease in QOL at baseline and follow-up when multivariably adjusted (Tables 2

People without cancer	People with cancer	
5	7	Hip fracture
5	3	Problems with eating
7	13	Benign prostatic hyperplasia
8	9	Problems with going to the toilet
10	9	Fracture other than hip
10	10	Problems with combining your hair or with shaving
11	11	Feeling down
12	14	Stroke, cerebral hemorrhage, cerebral infarction, TIA
14	14	Anxiety, panic disorder
16	12	Problems with using the telephone
19	14	Dementia
19	24	Depression
20	20	Problems with transferring
24	26	Feeling blue
26	30	Asthma, COPD, chronic bronchitis, lung emphysema
26	31	Diabetes
26	28	Problems with getting dressed
28	30	Feeling nervous/anxious
28	28	Problems with social functioning
28	25	Problems with taking medication
30	39	Heart failure
31	41	Dizziness with falling
33	36	Feeling not calm
33	35	Osteoporosis
37	33	Problems with dealing finances
40	39	Problems with bathing
43	47	Feeling unhappy
43	43	Problems with self-care
44	46	Mood problems
46	51	Urinary incontinence
48	48	Problems with vision
50	47	Problems with preparing a meal
52	59	Hearing problems
53	53	Cognitive problems
53	55	Using incontinence products
55	57	Problems with walking
58	62	Self-perceived health decline
62	61	Arthrosis, degenerative arthritis
65	64	Problems with daily activities
65	59	Problems with grocery shopping
72	70	Problems with traveling
72	81	Self-perceived unhealthy feelings
79	78	Pain
84	87	Problems with mobility
91	91	Problems with household tasks

Fig 3. Heat map presenting the proportions of frailty deficits in frail* respondents with versus without cancer. The proportions in frailty deficits per item among older frail people with and without cancer were graphically represented as colors. The higher the proportion, the higher the color intensity. In addition, percentages of participants with the deficit endorsed were also shown. * Cut-off point for frail people: TOPICS-FI38 $\geq$ 0.25.

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and 3). Per 0.1 increase on the frailty index, the CSAL score decreased with 0.35 (95%-CI: 0.32–0.38, p<0.001) and the EQ-5D score decreased with 0.12 (95%-CI: 0.11–0.12, p<0.001) at baseline. At follow-up, the CSAL score decreased with 0.27 (95%-CI: 0.24–0.30, p<0.001) per 0.1 increase on the frailty index and the EQ-5D score with 0.07 (95%-CI: 0.06–0.07, p<0.001).

When mutually adjusting for frailty and a cancer diagnosis, parameter estimates for the strength of the associations between a cancer diagnosis and types of QOL diminished

Table 2. Associations of baseline frailty, cancer and their interaction with CSAL score at baseline and follow-up.

Determinants in model[a]	CSAL at baseline (T0)			CSAL at follow-up (T12)		
	Estimates (95% CI)			Estimates (95% CI)		
	Cancer (yes vs. no)	Frailty index (per 0.10 increase)	Cancer*frailty index	Cancer (yes vs. no)	Frailty index (per 0.10 increase)	Cancer*frailty index
Cancer	**-0.25 (-0.36; -0.14)[b]**			**-0.13 (-0.24; -0.02)**		
Frailty		**-0.35 (-0.38; -0.32)[b]**			**-0.27 (-0.30; -0.24)[b]**	
Cancer, frailty	**-0.14 (-0.25; -0.03)**	**-0.35 (-0.38; -0.32)[b]**		-0.05 (-0.16; 0.06)	**-0.27 (-0.30; -0.24)[b]**	
Cancer, frailty, cancer*frailty	**-0.12 (-0.23; -0.01)**	**-0.34 (-0.37; -0.31)[b]**	-0.08 (-0.16; 0.01)	-0.05 (-0.16; 0.05)	**-0.27 (-0.30; -0.24)[b]**	0.02 (-0.06; 0.11)

[a]All models presented were adjusted for age, gender and education (cross-sectional) and for age, gender, education and baseline CSAL score (longitudinal).

[b]P-value is below 0.001.

P-values below 0.05 are in bold.

considerably and only remained significant for CSAL at baseline (-0.14 (95%-CI: -0.25; -0.03), p<0.05). Vice versa, the strength of the associations between frailty and QOL diminished much less and remained significant for all QOL outcomes at baseline (CSAL: -0.35 (95%-CI: -0.38; -0.32), EQ-5D: -0.12 (95%-CI: -0.12; -0.11)) and follow-up (CSAL: -0.27 (95%-CI: -0.30; -0.24), EQ-5D: -0.07 (95%-CI: -0.07;-0.06)). The interaction term frailty*cancer diagnosis was neither significant for QOL scores at baseline nor for QOL scores at follow-up.

Discussion

The purpose of this study was to examine the association between frailty and cancer in their combined impact on self-perceived and health-related QOL in community-dwelling older people aged 65 years or above. We showed that older people with cancer were more frail than

Table 3. Associations of baseline frailty, cancer and their interaction with EQ-5D score at baseline and follow-up.

Determinants in model[a]	EQ-5D at baseline (T0)			EQ-5D at follow-up (T12)		
	Estimates (95% CI)			Estimates (95% CI)		
	Cancer (yes vs. no)	Frailty index (per 0.10 increase)	Cancer*frailty index	Cancer (yes vs. no)	Frailty index (per 0.10 increase)	Cancer*frailty index
Cancer	**-0.03 (-0.05; -0.02)[b]**			**-0.02 (-0.03; -0.00)**		
Frailty		**-0.12 (-0.12; -0.11)[b]**			**-0.07 (-0.07; -0.06)[b]**	
Cancer, frailty	0.01 (-0.01; 0.02)	**-0.12 (-0.12; -0.11)[b]**		-0.00 (-0.02; 0.01)	**-0.07 (-0.07; -0.06)[b]**	
Cancer, frailty, cancer*frailty	0.01 (-0.00; 0.02)	**-0.12 (-0.12; -0.11)[b]**	-0.01 (-0.01; 0.00)	-0.00 (-0.02; 0.01)	**-0.07 (-0.07; -0.06)[b]**	0.01 (-0.01; 0.02)

[a]All models presented were adjusted for age, gender and education (cross-sectional) and for age, gender, education and baseline EQ-5D score (longitudinal).

[b]P-value is below 0.001. P-values below 0.05 are in bold.

people without cancer and that the type of frailty differed. Cancer negatively affected QOL of older people cross-sectionally and longitudinally, which was to a large extent associated with higher frailty levels of people with cancer. Irrespective of cancer diagnosis, frailty was independently associated with lower patient-reported QOL at baseline as well as after 12 months, both subjectively rated and concerning health-related QOL.

Comparison with existing literature

Previous research in oncology care mainly focused on health-related QOL among patients with specific cancer types[17, 31]. Few studies focused on QOL in older cancer patients[16]. Frailty in geriatric oncology reports is mainly evaluated for its relation with the ability of patients to tolerate cancer treatment in terms of morbidity and survival, not for its direct relationship with QOL outcomes of care. We identified that cancer negatively affects QOL of older people, which to a large extent may be explained by increased frailty levels. Among community-dwelling older people, frailty was already described to be associated with worse QOL cross-sectionally[21, 22] and over time[23, 32]. In addition, patients' frailty has been shown to be related with the occurrence of adverse outcomes[1–5]. Patient-reported outcomes such as QOL seem essential in order to evaluate interventions concerning patient-centered care[33] and personalized medicine on which current healthcare is increasingly focused[33, 34]. However, assessing and optimizing older patients' frailty are rarely part of (evaluations of) that kind of interventions[11]. To assess individuals' functional impairment, physicians in oncology care regularly use the Karnofsky performance score. The Karnofsky performance score has been shown to be correlated with response to chemotherapy, chemotherapy tolerability and survival[35–37] and is therefore basically used to determine the patient's fitness for cancer treatment. Though decreasing performance scores are also related with worse QOL[16, 31, 38], tools such as the Karnofsky performance score have relevant limitations[39]. Comprehensive geriatric assessments have been shown to provide more information regarding functional impairment than performance score measurement alone[40–44]. In other words, where the Karnofsky performance score seems to focus on the functional impact of the cancer diagnosis on that moment, frailty also focuses on non cancer-related vulnerability prior to or beside the cancer diagnosis. Therefore, differences in Karnofsky performance scores may be better understood if we do not only take into account the cancer severity, but also additional frailty with co-morbidity[45].

Strengths and limitations

Strength of this study is the large sample size which resulted in outcomes with high ecological validity. In addition, we used patient-reported QOL both concerning health-related QOL and on a subjective scale in general. The cancer group was based on one question in the TOPICS-MDS questionnaire. Misclassification might have happened, however, the accuracy of a self-reported cancer diagnosis compared to registry data is quite high[46, 47]. We did not have information about cancer type, stage, grade or treatment. All these factors may impact on patients' QOL and additionally may be related with patients' frailty. However, we do not pretend to argue that the cancer diagnosis including its severity is irrelevant[48]. We emphasize the need to take into account patient's frailty beside a cancer diagnosis as it may predict outcome and thus impact on patients' needs and goals for pre-habilitation in order to optimize their QOL. The impossibility to include patients with missing cancer diagnosis status could be an attrition bias, but with only a small number of missings (7%) its impact on the results is limited[49]. To finalize this section, we recognize that both the biological presence of cancer and the psychological implications of having the disease may be linked to frailty and QOL. By the

use of self-reported questionnaires, however, we cannot distinguish these effects. In this study, we did not account for ethnicity in our models though QOL will be different among ethnic minorities. In our sample size, only 8.9% of the respondents was not native Dutch whereof 1.3% was non-Western, that made these minorities quite underrepresented. Moreover, the TOPICS-MDS research projects greatly differ in study design, inclusion criteria, sample size and data collection, whereby several studies targeted vulnerable or disease-specific subpopulations. This may have downsized the representativeness of the sample size and caused some selection bias. However, representativeness is not necessarily essential when examining associations[50]. Similar to other studies, ceiling effects were found for the EQ-5D utility score reducing its discriminative ability for the most 'healthy' (or least frail) people. However, their potential effect seems limited since no ceiling effects were found for Cantril's Self-Anchoring Ladder which had similar patterns in associations between frailty and QOL.

Practice implications

Based on this study we recommend to take into account patient's frailty beside the cancer diagnosis as part of routine oncology care to be able to accurately predict natural progression of cancer not only in terms of survival but also in terms of QOL. This enables physicians to deliver tailor-made care and pre-habilitation options for cancer treatment based on patients' needs. Pro-active interventions aiming to optimize older patients' frailty may be related with positive results for these patients[51]. In addition, since frailty was independently associated with QOL, it can be assumed that assessing frailty should be part of evaluations of the effectiveness of interventions based on patient-reported outcomes such as QOL.

Conclusions

Between community-dwelling older people aged 65 years or above with and without a cancer diagnosis, differences in quality of life are explained to a large extent by differences in the frailty levels. Therefore, non cancer-related vulnerability should be taken into account as part of routine oncologic care. This may ultimately help to decrease the occurrence of negative outcomes and guide treatment plans on how to optimize patients' quality of life.

Supporting information

S1 Table. Sample characteristics of the included versus excluded respondents. CSAL: Modified Cantril's Self Anchoring Ladder, range 0 to 10, where 10 indicates the best score for present life as rated by individuals. EQ-5D: EuroQol-5D utility score, range -0.33 to 1.00 where a score below zero is indicative of a health state worse than death. TOPICS-FI38: TOPICS-MDS frailty index consisting of 38 items to quantify frailty, range 0 to 1, where participants with a score equal to or above 0.25 are considered to be frail. T0 indicates the baseline measurement, T12 indicates the measurement after 12 months.
(DOC)

S2 Table. Associations between sample characteristics and QOL outcomes. Education level: education levels as defined by Verhage[30] were classified as low (ranging from less than 6 years primary school to vocational school), moderate (ranging from secondary professional education to university entrance level) and high (university or tertiary education). CSAL: Modified Cantril's Self Anchoring Ladder, range 0 to 10, where 10 indicates the best score for present life as rated by individuals. EQ-5D: EuroQol-5D utility score, range -0.33 to 1.00 where a score below zero is indicative of a health state worse than death. TOPICS-FI38: TOPICS-MDS frailty index consisting of 38 items to quantify frailty, range 0 to 1, where

participants with a score equal to or above 0.25 are considered to be frail. T0 indicates the baseline measurement, T12 indicates the measurement after 12 months. [a]References are in bold, for example: mean CSAL female = 7.07, male = (7.07 + 0.02) = 7.09.
(DOC)

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References

1. Naeim A, Keeler EB, Reuben D. Perceived causes of disability added prognostic value beyond medical conditions and functional status. J Clin Epidemiol. 2007; 60(1):79–85. https://doi.org/10.1016/j.jclinepi. 2005.11.026 PMID: 17161758

2. Vermillion SA, Hsu FC, Dorrell RD, Shen P, Clark CJ. Modified frailty index predicts postoperative outcomes in older gastrointestinal cancer patients. J Surg Oncol. 2017; 115(8):997–1003. https://doi.org/ 10.1002/jso.24617 PMID: 28437582

3. Gani F, Cerullo M, Amini N, Buettner S, Margonis GA, Sasaki K, et al. Frailty as a Risk Predictor of Morbidity and Mortality Following Liver Surgery. J Gastrointest Surg. 2017; 21(5):822–830. https://doi.org/ 10.1007/s11605-017-3373-6 PMID: 28265844

4. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. J Geriatr Oncol. 2016; 7(6):479–491. https://doi.org/10.1016/j.jgo.2016.06. 001 PMID: 27338516

5. Choe YR, Joh JY, Kim YP. Association between frailty and readmission within one year after gastrectomy in older patients with gastric cancer. J Geriatr Oncol. 2017; 8(3):185–189. https://doi.org/10.1016/ j.jgo.2017.02.002 PMID: 28259489

6. Huisman MG, Kok M, de Bock GH, van Leeuwen BL. Delivering tailored surgery to older cancer patients: Preoperative geriatric assessment domains and screening tools—A systematic review of systematic reviews. Eur J Surg Oncol. 2017; 43(1):1–14. https://doi.org/10.1016/j.ejso.2016.06.003 PMID: 27406973

7. Verweij NM, Schiphorst AH, Maas HA, Zimmerman DD, van den Bos F, Pronk A, et al. Colorectal Cancer Resections in the Oldest Old Between 2011 and 2012 in The Netherlands. Ann Surg Oncol. 2016; 23(6):1875–1882. https://doi.org/10.1245/s10434-015-5085-z PMID: 26786093

8. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol. 2007; 197(6):676.e671-677.

9. Abt NB, Flores JM, Baltodano PA, Sarhane KA, Abreu FM, Cooney CM, et al. Neoadjuvant chemotherapy and short-term morbidity in patients undergoing mastectomy with and without breast reconstruction. JAMA Surg. 2014; 149(10):1068–1076. https://doi.org/10.1001/jamasurg.2014.1076 PMID: 25133469

10. Repetto L, Comandini D, Mammoliti S. Life expectancy, comorbidity and quality of life: the treatment equation in the older cancer patients. Crit Rev Oncol Hematol. 2001; 37(2):147–152. PMID: 11166588

11. Ghignone F, van Leeuwen BL, Montroni I, Huisman MG, Somasundar P, Cheung KL, et al. The assessment and management of older cancer patients: A SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol. 2016; 42(2):297–302. https://doi.org/10.1016/j.ejso.2015.12.004 PMID: 26718329

12. Swaminathan V, Audisio R. Cancer in older patients: an analysis of elderly oncology. Ecancermedicalscience. 2012; 6:243. https://doi.org/10.3332/ecancer.2012.243 PMID: 22423250

13. Ziegelstein RC. Personomics. JAMA Intern Med. 2015; 175(6):888–889. https://doi.org/10.1001/ jamainternmed.2015.0861 PMID: 25867929

14. Thome B, Dykes AK, Hallberg IR. Quality of life in old people with and without cancer. Qual Life Res. 2004; 13(6):1067–1080. https://doi.org/10.1023/B:QURE.0000031342.11869.2f PMID: 15287273

15. Quinten C, Coens C, Ghislain I, Zikos E, Sprangers MA, Ringash J, et al. The effects of age on health-related quality of life in cancer populations: A pooled analysis of randomized controlled trials using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 involving 6024

cancer patients. Eur J Cancer. 2015; 51(18):2808–2819. https://doi.org/10.1016/j.ejca.2015.08.027 PMID: 26602015

16. Baier P, Ihorst G, Wolff-Vorbeck G, Hull M, Hopt U, Deschler B. Independence and health related quality of life in 200 onco-geriatric surgical patients within 6 months of follow-up: Who is at risk to lose? Eur J Surg Oncol. 2016; 42(12):1890–1897. https://doi.org/10.1016/j.ejso.2016.07.013 PMID: 27519617

17. Momeni M, Ghanbari A, Jokar F, Rahimi A, Leyli EK. Predictors of quality of life in patients with colorectal cancer in Iran. Indian J Cancer. 2014; 51(4):550–556. https://doi.org/10.4103/0019-509X.175331 PMID: 26842192

18. Faller H, Brahler E, Harter M, Keller M, Schulz H, Wegscheider K, et al. Performance status and depressive symptoms as predictors of quality of life in cancer patients. A structural equation modeling analysis. Psychooncology. 2015; 24(11):1456–1462. https://doi.org/10.1002/pon.3811 PMID: 25851732

19. Pergolotti M, Deal AM, Williams GR, Bryant AL, Bensen JT, Muss HB, et al. Activities, function, and health-related quality of life (HRQOL) of older adults with cancer. J Geriatr Oncol. 2017.

20. Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin. 2010; 60(2):120–132. https://doi.org/10.3322/caac.20059 PMID: 20173172

21. Chang SF, Wen GM. Association of frail index and quality of life among community-dwelling older adults. J Clin Nurs. 2016; 25(15–16):2305–2316. https://doi.org/10.1111/jocn.13248 PMID: 27161863

22. Kojima G, Iliffe S, Jivraj S, Walters K. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. J Epidemiol Community Health. 2016; 70 (7):716–721. https://doi.org/10.1136/jech-2015-206717 PMID: 26783304

23. Gobbens RJ, van Assen MA, Luijkx KG, Schols JM. The predictive validity of the Tilburg Frailty Indicator: disability, health care utilization, and quality of life in a population at risk. Gerontologist. 2012; 52 (5):619–631. https://doi.org/10.1093/geront/gnr135 PMID: 22217462

24. The Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS) [Available from: http://topics-mds.eu/.

25. Lutomski JE, Baars MA, Schalk BW, Boter H, Buurman BM, den Elzen WP, et al. The development of the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS): a large-scale data sharing initiative. PLoS One. 2013; 8(12):e81673. https://doi.org/10.1371/journal.pone.0081673 PMID: 24324716

26. H. C. The pattern of human concerns. 1965.

27. Szende A OM, Devlin NJ. EQ-5D value sets: inventory, comparative review and user guide. 2007.

28. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008; 8:24. https://doi.org/10.1186/1471-2318-8-24 PMID: 18826625

29. Lutomski JE, Baars MA, van Kempen JA, Buurman BM, den Elzen WP, Jansen AP, et al. Validation of a frailty index from the older persons and informal caregivers survey minimum data set. J Am Geriatr Soc. 2013; 61(9):1625–1627. https://doi.org/10.1111/jgs.12430 PMID: 24028364

30. Verhage F. Intelligentie en leeftijd; onderzoek bij Nederlanders van twaalf tot zevenenzeventig jaar. Assen: Van Gorcum; 1964.

31. Lam K, Chow E, Zhang L, Wong E, Bedard G, Fairchild A, et al. Determinants of quality of life in advanced cancer patients with bone metastases undergoing palliative radiation treatment. Support Care Cancer. 2013; 21(11):3021–3030. https://doi.org/10.1007/s00520-013-1876-6 PMID: 23775156

32. Kojima G, Iliffe S, Morris RW, Taniguchi Y, Kendrick D, Skelton DA, et al. Frailty predicts trajectories of quality of life over time among British community-dwelling older people. Qual Life Res. 2016; 25 (7):1743–1750. https://doi.org/10.1007/s11136-015-1213-2 PMID: 26747318

33. Ugolini G, Ghignone F, Zattoni D, Veronese G, Montroni I. Personalized surgical management of colorectal cancer in elderly population. World J Gastroenterol. 2014; 20(14):3762–3777. https://doi.org/10.3748/wjg.v20.i14.3762 PMID: 24833841

34. Cooper Z, Koritsanszky LA, Cauley CE, Frydman JL, Bernacki RE, Mosenthal AC, et al. Recommendations for Best Communication Practices to Facilitate Goal-concordant Care for Seriously Ill Older Patients With Emergency Surgical Conditions. Ann Surg. 2016; 263(1):1–6. https://doi.org/10.1097/SLA.0000000000001491 PMID: 26649587

35. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer. 1980; 45(8):2220–2224. PMID: 7370963

36. Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46(4):M139–144. PMID: 2071835

37. Evers PD, Logan JE, Sills V, Chin AI. Karnofsky performance status predicts overall survival, cancer-specific survival, and progression-free survival following radical cystectomy for urothelial carcinoma. World J Urol. 2014; 32(2):385–391. https://doi.org/10.1007/s00345-013-1110-7 PMID: 23756991

38. Choi D, Fox Z, Albert T, Arts M, Balabaud L, Bunger C, et al. Prediction of Quality of Life and Survival After Surgery for Symptomatic Spinal Metastases: A Multicenter Cohort Study to Determine Suitability for Surgical Treatment. Neurosurgery. 2015; 77(5):698–708; discussion 708. https://doi.org/10.1227/NEU.0000000000000907 PMID: 26204361

39. Kelly CM, Shahrokni A. Moving beyond Karnofsky and ECOG Performance Status Assessments with New Technologies. J Oncol. 2016; 2016:6186543. https://doi.org/10.1155/2016/6186543 PMID: 27066075

40. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol. 2002; 20(2):494–502. https://doi.org/10.1200/JCO.2002.20.2.494 PMID: 11786579

41. Ferrucci L, Guralnik JM, Cavazzini C, Bandinelli S, Lauretani F, Bartali B, et al. The frailty syndrome: a critical issue in geriatric oncology. Crit Rev Oncol Hematol. 2003; 46(2):127–137. PMID: 12711358

42. Schulkes KJ, Souwer ET, Hamaker ME, Codrington H, van der Sar-van der Brugge S, Lammers JJ, et al. The Effect of A Geriatric Assessment on Treatment Decisions for Patients with Lung Cancer. Lung. 2017; 195(2):225–231. https://doi.org/10.1007/s00408-017-9983-7 PMID: 28280921

43. Hamaker ME, Schiphorst AH, ten Bokkel Huinink D, Schaar C, van Munster BC. The effect of a geriatric evaluation on treatment decisions for older cancer patients—a systematic review. Acta Oncol. 2014; 53 (3):289–296. https://doi.org/10.3109/0284186X.2013.840741 PMID: 24134505

44. Guerard EJ, Deal AM, Williams GR, Jolly TA, Wood WA, Muss HB. Construction of a frailty index for older adults with cancer using a geriatric assessment. Journal of Clinical Oncology. 2015; 33 (15_suppl):9535–9535.

45. Aapro MS. The frail are not always elderly. J Clin Oncol. 2005; 23(10):2121–2122. https://doi.org/10.1200/JCO.2005.10.976 PMID: 15710951

46. Loh V, Harding J, Koshkina V, Barr E, Shaw J, Magliano D. The validity of self-reported cancer in an Australian population study. Aust N Z J Public Health. 2014; 38(1):35–38. https://doi.org/10.1111/1753-6405.12164 PMID: 24494943

47. Bergmann MM, Calle EE, Mervis CA, Miracle-McMahill HL, Thun MJ, Heath CW. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. Am J Epidemiol. 1998; 147(6):556–562. PMID: 9521182

48. Ronning B, Wyller TB, Nesbakken A, Skovlund E, Jordhoy MS, Bakka A, et al. Quality of life in older and frail patients after surgery for colorectal cancer-A follow-up study. J Geriatr Oncol. 2016; 7(3):195–200. https://doi.org/10.1016/j.jgo.2016.03.002 PMID: 27067579

49. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol. 2004; 19(8):751–760. PMID: 15469032

50. Rothman KJ, Gallacher JE, Hatch EE. Why representativeness should be avoided. Int J Epidemiol. 2013; 42(4):1012–1014. https://doi.org/10.1093/ije/dys223 PMID: 24062287

51. Mazzola M, Bertoglio C, Boniardi M, Magistro C, De Martini P, Carnevali P, et al. Frailty in major oncologic surgery of upper gastrointestinal tract: How to improve postoperative outcomes. Eur J Surg Oncol. 2017; 43(8):1566–1571. https://doi.org/10.1016/j.ejso.2017.06.006 PMID: 28669651