The effects of age on health-related quality of life in cancer populations: a pooled analysis of randomized controlled trials using the EORTC QLQ-C30 involving 6,106 cancer patients

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The manuscript has been prepared in accordance with the style of the journal, and all authors have approved of its contents. This manuscript is not being considered for publication elsewhere and the findings of this manuscript have not been previously published. There is no conflict of interest.

Key words: increasing age, cancer burden, general population, normative data, health related quality of life

Abstract

Background

Cancer incidence increases exponentially with advancing age, cancer patients live longer than in the past, and many new treatments focus on stabilizing disease and health related quality of life (HRQOL). The objective of this study is to examine how cancer affects patients' HRQOL and whether their HRQOL is age-dependent.

Methods

Data from 25 European Organisation for Research and Treatment of Cancer (EORTC) randomized controlled trials was pooled. EORTC QLQ-C30 mean scores for the cancer cohort and five general population cohorts were compared to assess the impact of cancer on patients' HRQOL. Within the cancer cohort, multiple linear regressions were used to investigate the association between age and HRQOL, adjusted for gender, WHO performance status (PS), distant metastasis and stratified by cancer site. A difference of 10 points on the 0-100 scale was considered clinically important.

Results

Cancer patients generally have worse HRQOL compared to the general population, but the specifically impaired HRQOL domains vary by age. When comparing the cancer versus the general population cohort, role functioning is lower in all age categories. Young cancer patients have worse financial problems and social functioning, while older cancer patients have more appetite loss, constipation, and poorer emotional functioning.

Within the cancer cohort, HRQOL was worse with increasing age for physical, cognitive functioning and constipation, and better with increasing age for social, role and emotional functioning, insomnia and financial problems.

Conclusion

HRQOL is impaired in cancer patients compared to the general population, but the impact on specific HRQOL domains varies by age. Within the cancer population, some HRQOL components improve by age while others deteriorate. Optimal care for older cancer patients should target HRQOL domains most relevant to this population.

Introduction

To improve the care of cancer patients, it is essential for health care professionals to understand how the disease and its treatment affect cancer patients' health-related quality of life (HRQOL). Health care professionals can incorporate HRQOL in shared decision making to enhance patient management.[1] Several HRQOL questionnaires exist, including the 30-item Quality of Life Questionnaire Core model developed by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30).

Reference values for the EORTC QLQ-C30 are calculated within certain general populations and can be used for baseline HRQOL in cancer patients. These values are based on population studies from Sweden[2], the Netherlands[3], Germany[4,5] and Norway[6]. The data show how increasing age is associated with decreasing HRQOL for all functioning scales. However the relationship is less clear for the symptoms scales. Within cancer studies, patients' age has also been demonstrated[7,8,9] to be an important factor contributing to HRQOL impairment. However the magnitude of this relationship is not well established.[10, 11]

Knowing that cancer occurs later in life, with nearly 80% of all cancers diagnosed among individuals aged 55 and older, a clearer picture is needed regarding differential HRQOL effects of cancer by age and possible therapies tailored to older cancer patients given their HRQOL. It is well-known that elderly patients do not tolerate chemotherapy as well as their younger counterparts and express a higher symptom burden, due to the higher

prevalence of comorbid conditions and organ failure. In addition, the biology of some cancers changes with age, e.g. myeloid leukemia,[12] such that specific trials are needed for the older age group. Further concerns relate to comorbidities and physiological changes associated with aging that may influence anticancer drug metabolism and toxicity.[13,14]

Above concerns raise the need for specific trials for the older age group.[15,16,17] The availability of new molecularly targeted agents and newly improved existing agents has expanded the range of treatments options available for elderly cancer patients.[18] Some of these agents have shown better tolerability and a better safety profile[19] and may therefore provide new options for systemic therapy suitable to the elderly cancer population.

In this study, we investigated HRQOL in cancer patients compared to a population that did not have cancer; and the impact of ageing on cancer-related HRQOL. The specific objectives of this study were to examine 1) the HRQOL differences on the EORTC QLQ-C30 HRQOL domains between cancer patients and the general population and 2) how age influences the HRQOL of cancer patients, adjusted for known confounding factors.

Methods

General Population Cohorts

For the general population cohort, five population samples were pooled derived from Swedish[2], Dutch[3], German[4,5], Norwegian[6]surveys. All samples were representative to the general population with regard to age and sex. All respondents completed the EORTC QLQ-C30. The published unadjusted crude EORTC QLQ-C30 mean scores for specific age and gender categories are used. Only those general population cohorts that could be compared given their published age categories were included in the analysis.

Cancer Cohorts

For the cancer cohort, we pooled individual patient data from 25 closed phase 3 randomized controlled trials conducted by the EORTC. Our study included 10 cancer sites: colorectal (three trials), lung (five), oesophageal (one), ovarian (two), prostate (four), testicular (one), breast (three), head & neck (two), melanoma (three) and pancreas (one). HRQOL was assessed as a secondary endpoint using the EORTC QLQ-C30. Patients eligible for the study were those who had completed a valid baseline EORTC questionnaire, using established EORTC guidelines. Baseline data reflect HRQOL following diagnosis but prior to the beginning of protocol therapy. Patients may have had prior treatment or therapies before entering the trial - some never had anti-cancer treatment, others had prior surgery, and still others may have had multiple rounds of palliative chemotherapy or radiotherapy before entering these trials.

The EORTC QLQ-C30 incorporates five functioning scales (physical, role, cognitive, emotional and social functioning); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health scale.[20] The remaining single items assess additional symptoms commonly reported by cancer patients: dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea, as well as the perceived financial impact of the disease and treatment. For ease of statistical interpretation and psychometric validation, all scale and item scores were linearly transformed to a 0 to 100 scale. For the five functional scales and the global health scale, a higher score represents a better level of functioning. For the symptom-oriented scales and items, a higher score corresponds to a higher level of symptom burden.[21]

Statistical Analyses

To allow for comparison between the general population and cancer cohort, crude unadjusted mean scores were calculated for three available age categories: <50 years, 50-70 years and >70 years. Comparison of the mean scores was performed using students' t-test. The t-test has a two-sided significance level of 0.05. Differences of 10 points on the 0-100 scale are considered clinically important as suggested by Osoba.[22]

To assess the effect of age on the EORTC QLQ-C30 scores in the cancer cohort, multiple linear regression models were used adjusted for gender, World Health Organization (WHO) PS, distant metastases and stratified by cancer site. WHO PS was dichotomised (0-1 versus 2-3), representing "good" versus "bad" performance status. Distant metastasis status was classified into 'no' versus 'yes', according to the TNM classification developed by the International Union Against Cancer.[23].

The relationships were assessed via the point estimate (regression coefficient β) of the mean of each HRQOL scale, its 95% confidence intervals (CI), and the P-value of the Wald X^2 statistic. The two-sided level of significance was set at 0.05.

In addition, a second set of multiple linear regression models were assessed whereby age was treated as a continuous variable. The models were supported by histograms to investigate the relationship between age and the EORTC QLQ-C30 scores.

For those cancer sites with the highest number of observations, EORTC QLQ-C30 mean scores adjusted for gender, WHO PS and distant metastasis were calculated for each cancer site individually using multiple linear regression models.

All analyses were performed with SAS (version 9.1.3) and Stata 13.

Results

General Population Cohorts

Details for each population sample are shown in Table 1.

INSERT Table 1.

Cancer Cohorts

Valid baseline HRQOL data in the cancer cohort was available for 6,106 of the 8,201 (75%) patients who participated in the selected trials. We excluded further patients older than 89 and younger than 18 cases from analysis due to a low number of observations (n<5) for each excluded age. The distribution of socio-demographic and clinical characteristics for each age group is reported in Table 2. The age of the analyzed cancer patients ranged from 18-89 years with a mean of 54.47 years. The youngest age group (<50) accounted for 33,2% (2,001/6,024) of the cancer cohort, the middle age group for 57,7% and the oldest age group for only 9,1 %. The age distribution differed across the included cancer sites; as expected, 52.9% of the patients with melanoma were under the age of 40 and 44% of the patients with prostate cancer were above the age of 70. For 4,486 of the 6,024 patients the country of residence was reported. Patients in the included trials were selected from 34 countries. A total of 93% came from an EU country. The remaining patients came from the U.S.A, New Zealand, Canada, South Africa and Australia.

INSERT Table 2.

Comparison between cancer and population cohorts

The mean scores and standard deviations (SD) of the EORTC QLQ-C30 scores for the cancer and general population cohorts are shown in Table 3. Role functioning was statistically significant and clinically meaningfully (≥10 difference) worse in the cancer cohort, in all 3 age categories, and is not mentioned further below.

Within the youngest age category, cancer patients reported statistically significant worse HRQOL for global health status, social and physical functioning and for the symptoms nausea and vomiting, pain, insomnia, appetite loss, constipation and financial problems. Only the differences regarding social functioning (78.79 vs. 91.04) and financial problems (18.01 vs. 5.52) were clinically meaningful

Within the middle age category, cancer patients reported statistically significant worse HRQOL for global health status, social, physical functioning and for the symptoms fatigue, nausea/vomiting, appetite loss and constipation. Only appetite loss (18.71 vs 4.92) was clinically meaningful.

For the oldest age category, cancer patients reported statistically significant worse HRQOL for emotional functioning, nausea/vomiting, constipation and appetite loss. Only the differences with respect to emotional functioning (81.93-71.23), appetite loss (25.69-8.65) and constipation (23.85-12.38) were clinically meaningful.

INSERT Table 3.

Multiple Linear Regression Models

The results of the linear regression models with age as a categorical variable are reported in Table 4. The table reports the regression coefficients (β), CI and P-value for the models assessing the association between the EORTC QLQ-C30 scores and age categories adjusted for gender, WHO PS, metastatic status. Cancer patients reported a statistically significantly worse HRQOL with increasing age for physical and cognitive functioning and constipation. Cancer patients reported a statistically significant better HRQOL with increasing age for social, role and emotional functioning and the symptoms insomnia and financial problems.

Men compared to women reported statistically significant HRQOL impairment for all the functional scales and fatigue, nausea and vomiting, insomnia, appetite loss and constipation, however none were clinical meaningful (data not shown). For all the EORTC QLQ-C30 scores, cancer patients with a poor WHO PS reported a significant deterioration in HRQOL. For global health status, social, physical and role functioning and appetite loss the difference was higher than 10 points. Distant metastasis has a statistical significant negative impact on HRQOL, except for emotional functioning and financial problems, however none were clinical meaningful.

INSERT Table 4.

Within the cancer cohort, we plotted the average means scores for the EORTC QLQ-C30 scales against age as a continuous variable (see Figure 1. and 2. online only). The plots demonstrate the linear relationship between HRQOL with increasing age.

Table 5 reports the regression coefficients (β), CI and P-value for the models assessing the association between the EORTC QLQ-C30 scores and age as continuous variable adjusted for gender, WHO PS, metastatic status and stratified by cancer site. Cancer patients reported a statistically significant worse HRQOL with increasing age for physical and cognitive functioning and constipation. Cancer patients reported a statistical significant better HRQOL with increasing age for social, role and emotional functioning and financial problems.

Women and men reported statistically significant HRQOL impairment except for role functioning, pain, dyspnea and diarrhea however none were clinical meaningful. For all the EORTC QLQ-C30 scores, cancer patients with a poor WHO PS reported a significant deterioration in HRQOL. For global health status, social, physical and role functioning, pain and appetite loss the difference was higher than 10 points. Distant metastasis has a statistical significant negative impact on HRQOL, except for emotional functioning and financial problems, however none of them were clinical meaningful.

INSERT Table 5.

Our data also allows for comparison between different cancer groups, after adjusting for gender, WHO PS and distant metastasis. Table 6 shows the mean scores for the three most prevalent cancer sites in our database; melanoma (2,112 patients), colorectal (1,141 patients) and lung cancer (940 patients). HRQOL burden changed with age for each cancer site, but the magnitude and size differed between cancer sites. Statistically significant HRQOL worsening by age group was seen in the melanoma cohort for seven subscales, in the colorectal cohort for three subscales. Within the lung cancer group, only the scale financial problems was statistically and clinically (25.60 vs. 12.68) significant different between the age groups, whereby financial problems were worse in younger patients.

INSERT Table 6.

Discussion

Our study shows that cancer patients generally have worse HRQOL compared to the general population, but the specifically impaired HRQOL domains vary by age. When comparing the cancer versus the general population cohort, role functioning is lower in all age categories. Young cancer patients have worse financial problems and social functioning, while older cancer patients have more appetite loss, constipation, and poorer emotional functioning. Within the cancer cohort, after adjusting for confounding variables, HRQOL was worse with increasing age for physical and cognitive functioning, and constipation, and better with increasing age for social, role and emotional functioning, insomnia and financial problems. Overall, our modelling supports the general findings that the impact of ageing on the QLQ-C30 scale scores follows a linear relationship. Our study confirms previous studies[24,25,26] that the health status of a cancer patient is influenced by not only age, but also by disease stage, gender and WHO performance status.

Within the cancer cohort, HRQOL differences by age do not appear to be clinical relevant. Snöbohm et al.[27] mentioned that younger people experience their cancer differently than older cancer patients due to a lack of previous experience of severe illness. Previous studies[28,29] have revealed that it is easier for older people to accept physical decrements. For the younger people, any reduce in physical activity due to a chronic illness is perceived far more negatively. This might also explain why the elderly score higher on some of the functioning scales. In addition, not being able for younger

cancer patients to fulfil the social expectations causes a sense of disappointment and loss, resulting in a poorer HRQOL. A paper published by Krok et al.[30] suggests that older patients have more effective coping mechanisms to help them manage their pain. This might explain why pain scores are higher for the younger patients compared to the eldest group, however the younger age group had more patients with metastatic cancer, found to be significantly associated with HRQOL impairment in our study (models not shown).

A limitation of this study is that we did not have detailed data on general health/frailty status as measured by a geriatric assessment in the older population, and no information on comorbidity in either cohort. Frailty is a crucial aspect of older persons, with major impact on HRQOL and outcome. Several guidelines indicate the need for systematic geriatric evaluation in older cancer patients.[31,32] Increasing age is associated with comorbidity, which has a negative impact on HRQOL[33], especially in cancer patients.[34,35] However, comorbidity is frequently an exclusion factor in randomized controlled trials. It is likely that the elderly in the cancer cohort reported here have a better overall health status than their counterparts in the general population cohort. Another limitation is that our general population cohorts are based on a selected population from specific countries and therefore not necessary matching a non-cancer population or a wider population as the right reference group for our cancer cohorts. Also within the cancer cohorts, our data is limited to a selection of cancer trials with their own selection and eligibility criteria and therefore not necessarily representative for all cancer trials. Our cancer specific models demonstrate that the HRQOL outcomes can be very depending on the cancer group, but most likely this is driven by the selected trials for each group with each their own specific

in- and exclusion criteria. Although our models were stratified for cancer site to account for these between cancer differences, there is still a chance that the HRQOL differences are related to selected cancer groups and trials.

The content validity of the EORTC QLQ-C30 for an elderly population could be open to debate. The EORTC Quality of Life Elderly Task Force[36] and the EORTC Quality of Life Group developed a new HRQOL questionnaire for elderly cancer patients given that the EORTC-QLQ-C30 was developed using data from generally younger patients. A systematic literature review by Fitzsimmons et al.[37] suggests that the concerns of older patients differ from those of younger patients; a specific module may be needed to capture the needs and concerns most relevant to them.

Our results suggest that treatment decisions should also include HRQOL.[38] Currently, many elderly patients are excluded from certain treatments because of their age or by stringent physical conditions. However, judgment of fitness for treatment would ideally incorporate a patient's HRQOL[39] and coping mechanism, rather than age or performance status (PS) alone as demonstrated in this study. Available evidence suggests[40] that elderly patients can derive similar survival benefits from aggressive treatments as younger patients. A systematic assessment of HRQOL at baseline may allow physicians to select appropriate elderly patients and reduce underutilization of aggressive treatments.

By demonstrating the age-related differences in HRQOL, even among a highly selected group of elderly patients included in clinical trials (those likely to have minimal

comorbidity), this study supports the need to include the elderly in clinical trials where accurate measurement of HRQOL is a focus. Trials of lower-toxicity treatment strategies, or of low risk supportive care interventions, could be designed specifically for older patients where the focus is not efficacy, but maintaining active life expectancy; the average number of years of life remaining in an independent state –i.e., free from significant disability.[41, 42] Biologic agents with less toxic effects, focused on stabilization of disease, may be tailor-made for the elderly. Delay of disease progression should be combined with a proper HRQOL assessment to determine the overall benefit of such a drug. Another option might be to enroll older patients in smaller "sub-trials" within bigger trials or to design end points specifically for older patients, which could include HRQOL endpoints such as physical functioning which are equally important for the elderly than extending survival.[17] However more longitudinal and observational studies, with no stringent inclusion criteria, are needed to confirm these statements.

The inclusion of HRQOL endpoints can also lead to shared decision making by physicians and patients.[43] This is also acknowledged by EORTC elderly task force, the US Food and Drug Administration in its Guideline for the Study of Drugs Likely to Be Used in the Elderly[44] and in the mission statement of the Cancer and Aging Research Group in collaboration with the National Cancer Institute.[45] As expected, many sources are now showing that cancer is becoming a chronic disease and a disease something for the elderly. Our evidence shows support for the many health needs these patients have and society needs to take urgent action to assure that these growing number of patients receive their health needs.

Author's Disclosures of Potential Conflicts of Interests

The authors declared no conflicts of interest

Acknowledgement:

This work was funded by an unrestricted academic grant from the Pfizer Foundation, administered through the King Baudouin Foundation, for the EORTC PROBE group. We thank the EORTC Headquarters, EORTC Clinical Groups and all the Principal Investigators who helped us better understand the needs of cancer patients, which will ultimately lead to better patient care. And a very special thanks to all patients who participated in these trials.

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TABLES

Table 1. Distribution (N=actual numbers; %=percentage) of age and gender for the five general population cohorts.

Variables	Norwegian cohort	German cohort	German cohort	Dutch cohort	Swedish cohort
	N=1,965	N=2,208	N=4,684	N=1,731	N=4,910
Age (years)					
Mean (Min-Max)	47.4 (19-93)	49.4 (16-92)	51.8 (NA)*	52.90 (NA)	65 (40-49)
Age (categories)					
<50	1,100 (56%)	1,014 (50%)	2,112 (45%)	690 (40%)	410 (8%)
<=50 and <=70	550 (28%)	730 (36%)	1,539 (33%)	766 (44%)	2,615 (53%)
>70	315 (16%)	284 (14%)	1,033 (22%)	275 (16%)	1,903 (39%)
Men	1,022 (52%)	892 (44%)	2,050 (44%)	935 (54%)	3,224 (66%)

*NA=Not available

Table 2. Distribution (N=actual numbers; %=percentage) of socio-demographic and clinical variables in the cancer cohort for the three age categories: <50; 50-70; >70.

Variables	Category	Age <50	Age <=50 and Age <=70	Age > 70
		N=2,001	N=3,476	N=547
Performance Status				
	WHO 0-1	1,704 (85.2%)	3,130 (90.0%)	443 (80.9%)
	WHO 2-3	55 (2.7%)	242 (7.0%)	96 (17.6%)
	Unknown	242 (12.1%)	104 (3.0%)	8 (1.5%)
Distant Metastases				
	Yes	1,377 (68.8%)	1,868 (53.7%)	120 (21.9%)
	No	338 (16.9%)	1,370 (39.4%)	402 (73.5%)
	Unknown	286 (14.3%)	238 (6.9%)	25 (4.6%)
Gender				
	Female	1,118 (55.9%)	2,243 (64.5%)	426 (77.9%)
	Male	883 (44.1%)	1,231 (35.4%)	121 (22.1%)
	Unknown	0 (0.0%)	2 (0.1%)	0 (0.0%)
Cancer site				
	Colorectal	174 (8.70%)	807 (23.22%)	160 (29.25%)
	Lung	210 (10.49%)	676 (19.45%)	54 (9.87%)
	Esophageal	14 (0.70%)	44 (1.27%)	7 (1.28%)
	Ovarian	48 (2.40%)	140 (4.03%)	14 (2.56%)
	Prostate	11 (0.55%)	290 (8.34%)	224 (40.95%)
	Testicular	223 (11.14%)	10 (0.29%)	0 (0.0%)
	Breast	160 (8.00%)	145 (4.17%)	16 (2.93%)
	Head & Neck	94 (4.70%)	278 (8.0%)	21 (3.84%)
	Melanoma	1,059 (52.9%)	1,010 (29.06%)	43 (7.86%)
	Pancreas	8 (0.40%)	76 (2.19%)	8 (1.46%)

Table 3. EORTC QLQ-C30 unadjusted mean scores for the cancer and the general population cohort for the three age categories <50; 50-70; >70.

	Observed Mean Scores								
	Age < 50			Age <=50 and Age <=70			Age > 70		
	Cancer cohort	General Population cohort	P-value	Cancer cohort	General Population cohort	P-value	Cancer cohort	General Population cohort	P-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
EORTC QLQ-C30 Functioning Scales‡									
Global Health Status	66.20 (21.99)	75.41 (3.48)	0.0043	61.77 (23.19)	71.72 (5.71)	0.0176	57.41 (23.13)	66.25 (9.12)	0.0861
Social Functioning	**78.69** (25.31)	**91.04** (4.36)	0.0033	77.68 (27.83)	87.47 (5.35)	0.015	78.90 (26.11)	83.83 (7.79)	0.211
Physical Functioning	85.76 (20.60)	94.42 (1.75)	0.0004	78.72 (24.19)	87.2 (3.18)	0.004	68.53 (27.03)	74.99 (6.59)	0.08
Role Functioning	**71.35** (31.19)	**91.84** (3.99)	0.0003	**69.73** (32.42)	**85.73** (5.56)	0.0031	**65.42** (34.91)	**77.02** (8.98)	0.0415
Emotional Functioning	72.15 (22.85)	79.23 (8.58)	0.1444	70.45 (23.60)	80.14 (8.22)	0.0584	**71.31** (23.60)	**81.93** (8.11)	0.0466
Cognitive Functioning	88.91 (17.54)	90.24 (4.41)	0.5374	87.10 (18.59)	88.20 (3.33)	0.5002	83.53 (20.05)	82.87 (4.63)	0.8456
EORTC QLQ-C30 Symptom Scales†									
Fatigue	26.81 (24.27)	21.34 (9.00)	0.2539	32.03 (26.85)	22.81 (6.65)	0.0364	39.44 (27.52)	30.51 (8.98)	0.0907
Nausea/Vomiting	5.31 (13.88)	3.54 (0.96)	0.0164	6.86 (16.44)	3.10 (1.11)	0.0016	9.45 (19.27)	4.25 (1.42)	0.0016
Pain	23.76 (26.41)	14.80 (5.75)	0.0266	27.24 (29.41)	23.1 (6.03)	0.1996	32.26 (30.61)	28.62 (9.67)	0.3649

Dyspnea	11.54 (21.55)	8.34 (4.56)	0.2045	17.06 (25.44)	12.63 (4.63)	0.0991	22.30 (27.35)	22.26 (6.78)	0.9703
Insomnia	24.39 (29.25)	15.79 (6.14)	0.0368	28.95 (31.48)	23.53 (7.86)	0.1984	28.89 (30.77)	27.17 (9.43)	0.5485
Appetite loss	12.42 (23.82)	5.64 (2.65)	0.0048	**18.71** (29.68)	**4.92** (2.01)	0.0001	**25.69** (34.23)	**8.65** (4.45)	0.0011
Constipation	8.55 (20.65)	4.56 (2.43)	0.0225	14.84 (26.57)	7.32 (3.06)	0.0053	**23.85** (31.82)	**12.38** (5.72)	0.0094
Diarrhea	6.34 (15.97)	6.32 (3.11)	0.9741	6.81 (17.81)	6.33 (3.30)	0.7592	8.34 (18.99)	6.75 (3.19)	0.4557
Financial Problems	**18.06** (28.33)	**5.52** (2.7)	0.0005	12.62 (25.28)	8.74 (4.83)	0.1473	7.88 (19.53)	8.74 (6.16)	0.7202

‡Higher scores indicate better functioning and Global Health Status †Higher scores indicate more symptoms
Bold values indicate statistically significant, and clinically meaningful differences between cancer and general population for each age category
QLQ-C30=the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire

Table 4. Multiple linear regression models in the cancer cohort reporting the regression coefficients (β), CI and p-value for the fifteen models assessing the association between the EORTC QLQ-C30 scores and three age categories (<50; 50-70; >70) adjusted for gender, WHO PS, metastatic status stratified by cancer site.

Variables	Age group (<50;<=50 and <=70; >70)		Gender (men vs women)		WHO PS (good vs poor)		Distant metastasis (no vs yes)	
	β* (CI)**	P-value	β (CI)	P-value	β (CI)	P-value	β (CI)	P-value
EORTC QLQ-C30 Functioning Scales‡								
Global Health Status	-0.03 (-2.24;1.63)	0.757	-4.2 (-5.19;-2.86)	<0.001	-10.93 (-11.90;-9.96)	<0.001	-1.85 (-3.07;-0.64)	0.003
Social Functioning	6.84 (4.38-9.30)	<0.001	-2.55 (-3.98;-1.13)	<0.001	-11.4 (-12.59;-10.21)	<0.001	-3.13 (-4.62;-1.65)	<0.001
Physical Functioning	**-4.37** (-6.28;-2.46)	<0.001	-3.58 (-4.73;-2.43)	<0.001	-13.84 (-14.80;-12.88)	<0.001	-5.62 (-6.82;-4.43)	<0.001
Role Functioning	2.86 (0.075;5.65)	0.004	-2.04 (-3.71;-0.37)	0.017	-15.13 (-16.52;-13.73)	<0.001	-3.19 (-4.93;-1.44)	<0.001
Emotional Functioning	3.18 (1.03;5.33)	0.004	-5.67 (-6.92;-4.43)	<0.001	-5.64 (-6.69;-4.61)	<0.001	-0.07 (-1.37;1.22)	0.914
Cognitive Functioning	**-1.72** (-3.42;-0.02)	0.047	-3.06 (-4.05;-2.08)	<0.001	-5.997 (-6.80;-5.15)	<0.001	-1.46 (-2.49;-0.44)	0.005
EORTC QLQ-C30 Symptom Scales†								
Fatigue	0.84 (-1.30;2.99)	0.44	5.08 (3.79;6.38)	<0.001	13.61 (12.53;14.69)	<0.001	5.33 (3.99;6.67)	<0.001
Nausea/Vomiting	-0.17 (-1.54;1.19)	0.802	2.51 (1.69;3.33)	<0.001	5.49 (4.81;6.17)	<0.001	2.52 (1.66;3.37)	<0.001
Pain	-1.65 (-4.06;0.75)	0.178	0.11 (-1.33;1.55)	0.881	15.53 (14.32;16.73)	<0.001	5.31 (3.80;6.81)	<0.001
Dyspnoea	1.91	0.076	-0.08	0.894	7.65	<0.001	-2.93	<0.001

	(-0.20;4.03)		(-1.36;1.18)		(6.59;8.72)		(-4.25;-1.60)	
Insomnia	-4.15 (-6.88;-1.43)	0.003	2.73 (1.09;4.36)	0.001	8.86 (7.49;10.22)	<0.001	3.06 (1.36;4.77)	<0.001
Appetite loss	0.26 (-2.11;2.65)	0.825	3.61 (2.18;5.05)	<0.001	13.93 (12.73;15.12)	<0.001	4.48 (2.99;5.97)	<0.001
Constipation	**5.62** (3.36;-7.88)	<0.001	1.97 (0.62;3.33)	0.004	7.67 (6.54;8.80)	<0.001	6.88 (5.47;8.30)	<0.001
Diarhoea	-0.41 (-1.97;1.13)	0.601	-0.78 (-1.72;0.15)	0.098	0.81 (0.03;1.59)	0.041	1.32 (0.35;2.29)	0.008
Financial Problems	-8.64 (-11.09;6.19)	<0.001	-0.95 (-2.38;0.47)	0.188	4.22 (3.03;5.41)	<0.001	-0.24 (-1.73;1.24)	0.749

***β = Regression coefficient ** CI = Confidence Intervals**
‡Higher scores indicate better functioning and Global Health Status †Higher scores indicate more symptoms
QLQ-C30=the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire
Bold values indicate significantly worse HRQOL components with increasing age
Italic values indicate significantly better HRQOL components with increasing age

Table 5. Multiple linear regression models reporting the regression coefficients (β), CI and p-value for the fifteen models assessing the association between the EORTC QLQ-C30 scores and age adjusted for gender, WHO PS, metastatic status stratified by cancer site

Variables	Agegroup (<50;<=50 and <=70; >70)		Gender (men vs women)		WHO PS (good vs poor)		Distant metastasis (no vs yes)	
	B* (CI)**	P-value	B (CI)	P-value	B (CI)	P-value	B (CI)	P-value
EORTC QLQ-C30 Functioning Scales‡								
Global Health Status	-0.02 (-0.07;0.019)	0.238	-4.12 (-5.29;-2.95)	<0.001	-10.87 (-11.84;-9.89)	<0.001	-1.77 (-2.99;-0.56)	0.004
Social Functioning	0.019 (0.13-0.25)	<0.001	-2.25 (-3.68;-0.82)	0.002	-11.51 (-12.68;-10.32)	<0.001	-3.28 (-4.77;-1.79)	<0.001
Physical Functioning	**-0.14** (-0.19;-0.09)	<0.001	-3.85 (-5.01;-2.70)	<0.001	-13.72 (-14.68;-12.76)	<0.001	-5.46 (-6.65;-4.26)	<0.001
Role Functioning	0.18 (0.12;0.25)	<0.001	-1.47 (-3.15;0.21)	0.087	-15.51 (-16.91;-14.12)	<0.001	-3.65 (-5.39;-1.90)	<0.001
Emotional Functioning	0.04 (-0.01;0.09)	0.121	-5.72 (-6.97;-4.46)	<0.001	-5.55 (-6.60;-4.51)	<0.001	0.018 (-1.28;1.32)	0.978
Cognitive Functioning	**-0.06** (-0.10;-0.02)	0.002	-3.19 (-4.18;-2.21)	<0.001	-5.9 (-6.72;-5.07)	<0.001	-1.38 (-2.40;-0.35)	0.008
EORTC QLQ-C30 Symptom Scales†								
Fatigue	-0.01 (-0.05;0.05)	0.973	5.02 (3.72;6.32)	<0.001	13.68 (12.60;14.76)	<0.001	5.4 (4.05;6.75)	<0.001
Nausea/Vomiting	-0.01 (-0.04;0.02)	656	2.49 (1.66;3.32)	<0.001	5.5 (4.82;6.18)	<0.001	2.53 (1.68;3.39)	<0.001
Pain	-0.02 (-0.08;0.03)	0.419	0.12 (-1.33;1.58)	0.867	15.48 (14.27;16.69)	<0.001	5.27 (3.76;6.78)	<0.001

Dyspnoea	0.04 (-0.01;0.09)	0.114	-0.04 (-1.32;1.24)	0.947	7.66 (6.60;8.73)	<0.001	-2.93 (-4.26;-1.60)	<0.001
Insomnia	-0.01 (-0.06;0.06)	0.983	3.02 (1.36;4.67)	<0.001	8.55 (7.18;9.92)	<0.001	2.74 (1.03;4.45)	0.002
Appetite loss	0.03 (-0.02;0.09)	0.264	3.74 (2.29;5.18)	<0.001	13.84 (12.64;15.04)	<0.001	4.38 (2.88;5.87)	<0.001
Constipation	**0.21** (0.16;0.27)	<0.001	2.46 (1.11;3.83)	<0.001	7.39 (6.27;8.53)	<0.001	6.54 (5.13;7.96)	<0.001
Diarhoea	-0.02 (-0.06;0.01)	0.136	-0.88 (-4.82;0.06)	0.066	87 (0.09;1.65)	0.028	1.39 (0.42;2.37)	0.005
Financial Problems	-0.37 (-0.43;-0.31)	<0.001	-1.82 (-3.24;-0.41)	0.12	4.75 (3.57;5.93)	<0.001	0.39 (-1.08;1.86)	0.604

***Regression coefficient ** Confidence Intervals**
‡Higher scores indicate better functioning and Global Health Status †Higher scores indicate more symptoms
QLQ-C30=the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire

Table 6. Multiple linear regression models reporting mean scores by age categories (<50; 50-70; >70) for the EORTC QLQ-C30 scores adjusted for gender, WHO PS, metastatic status for the cancer groups melanoma, colorectal and lung.

Populations	Adjusted Mean Scores Melanoma Cancer (N=2,112)			P-Value	Adjusted Mean Scores Colorectal Cancer (N=1,141)			P-Value	Adjusted Mean Scores Lung Cancer (N=940)			P-Value
	Age <50 N= 1059	Age <=50 and Age <=70 N=1010	Age >70 N=43		Age <50 N=174	Age <=50 and Age <=70 N=807	Age >70 N=160		Age <50 N=210	Age <=50 and Age <=70 N=676	Age >70 N=54	
EORTC QLQ-C30 Functioning Scales‡												
Global Health Status	55.04	54.50	58.12	0.439	49.68	53.10	52.92	0.191	52.50	50.96	52.79	0.668
Social Functioning	72.28	74.51	80.89	0.011	61.43	67.47	72.81	0.002	62.73	65.63	70.63	0.226
Physical Functioning	76.03	73.54	73.23	0.006	64.61	66.48	63.34	0.258	63.42	62.57	57.97	0.372
Role Functioning	67.19	70.86	76.46	0.009	53.48	57.59	58.10	0.297	55.77	53.73	44.43	0.109
Emotional Functioning	73.73	73.69	78.36	0.385	60.14	63.41	63.48	0.269	62.88	61.29	63.77	0.648
Cognitive Functioning	94.61	93.95	90.44	0.176	80.75	80.65	78.94	0.594	82.99	82.63	82.39	0.973
EORTC QLQ-C30 Symptom Scales†												
Fatigue	45.76	45.75	46.40	0.567	48.05	46.76	47.06	0.854	46.68	46.17	51.20	0.457
Nausea/Vomiting	10.14	9.49	13.25	0.017	16.58	13.58	12.54	0.061	12.45	11.99	9.10	0.463
Pain	44.70	44.15	41.30	0.598	41.35	34.65	28.54	0.001	44.91	42.49	38.25	0.384
Dyspnoea	20.11	20.95	21.12	0.478	24.34	20.20	21.24	0.167	38.59	38.57	50.94	0.031
Insomnia	45.33	47.36	44.37	0.212	41.48	35.56	33.80	0.063	37.94	36.02	34.72	0.757
Appetite loss	54.12	53.71	64.19	0.001	34.61	33.83	36.55	0.597	34.39	35.86	30.58	0.539

Constipation	4.36	6.91	4.54	0.007	20.56	19.11	24.08	0.140	16.54	18.24	21.27	0.488
Diarhoea	4.12	2.86	4.27	0.077	14.01	11.75	8.23	0.085	5.53	5.18	4.39	0.904
Financial Problems	7.96	2.78	0.35	<.001	22.87	15.35	10.88	<.001	25.60	19.35	12.68	0.006

‡Higher scores indicate better functioning and Global Health Status †Higher scores indicate more symptoms
QLQ-C30=the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire

Figures

Figure 1. Mean EORTC QLQ-C30 scores across age for the functioning scales (online only)
Legend: Higher scores indicate better functioning and Global Health Status

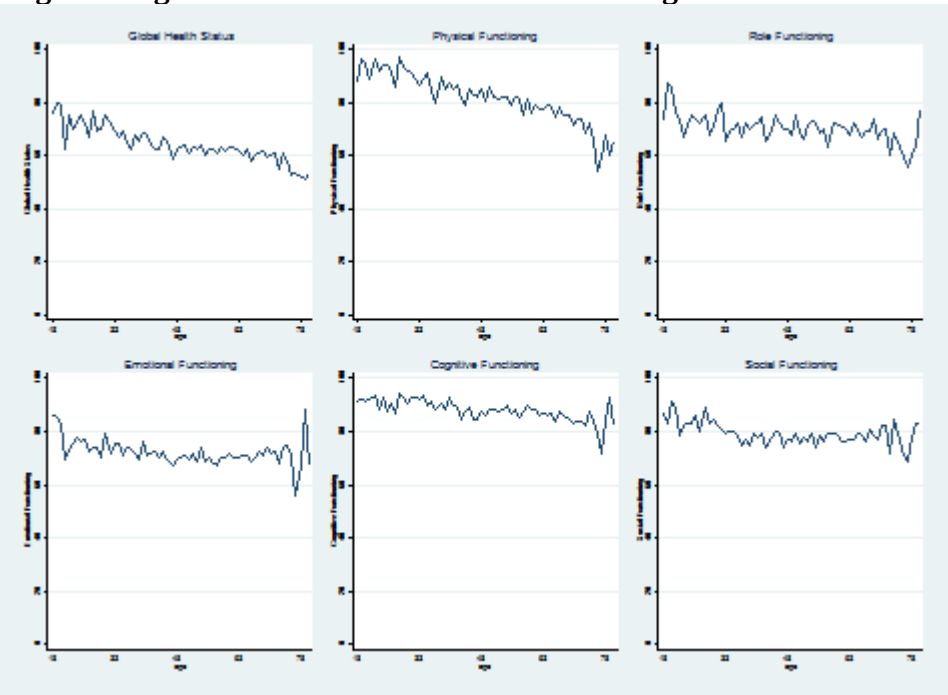

Figure 2. Mean EORTC QLQ-C30 scores across age for the symptom scales (online only)
Legend: Higher scores indicate more symptoms