# The EORTC QLQ-C30 summary score as prognostic factor for survival of cancer patients in the "real-world": Results from the population-based PROFILES registry

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**Abstract**

*Background:* Health-related quality of life (HRQoL) has been shown to be a prognostic factor for cancer survival in randomized clinical trials and observational "real-world" cohort studies, however it remains unclear which HRQoL domains are the best prognosticators. The primary aims of this population-based, observational study were to: (1) investigate the association between the novel European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (QLQ-C30) summary score and all-cause mortality, adjusting for the more traditional sociodemographic and clinical prognostic factors; and (2) compare the prognostic value of the QLQ-C30 summary score with the global quality of life (QoL) and physical functioning scales of the QLQ-C30.

*Materials and methods:* Between 2008 and 2015, cancer patients (12 tumor types) were invited to participate in PROFILES disease-specific registry studies (response 69%). In this secondary analysis of 6.895 patients, multivariate Cox proportional hazard regression models were used to investigate the association between the QLQ-C30 scores and all-cause mortality.

*Results:* In the overall Cox regression model including sociodemographic and clinical variables, the QLQ-C30 summary score was associated significantly with all-cause mortality (HR=0.77; 99%CI=0.71-0.82). In stratified analyses, significant associations between the summary score and all-cause mortality were observed for colon, rectal, prostate cancer, non-Hodgkin lymphoma, chronic lymphocytic leukemia and multiple myeloma. The QLQ-C30

summary score had a stronger association with all-cause mortality than the global QoL scale (HR=0.82; 99%CI=0.77-0.86) or the physical functioning scale (HR=0.81; 95%CI=0.77-0.85).

*Conclusion:* In a "real-world" setting, the QLQ-C30 summary score has a strong prognostic value for overall survival for a number of cancer patient populations above and beyond that provided by clinical and sociodemographic variables. The QLQ-C30 summary score appears to have more prognostic value than the global QoL, physical functioning, or any other scale within the QLQ-C30.

*Implications for Practice:* The finding that HRQoL provides distinct prognostic information beyond known sociodemographic and clinical measures, not only at cancer diagnosis (baseline) but also at follow-up, has implications for clinical practice. Implementation of cancer survivorship monitoring systems for ongoing surveillance of HRQoL may improve post-treatment rehabilitation that, in turn, may lead to better outcomes.

## Introduction

Over the course of the last decades there has been a paradigm shift in the measurement of clinical outcomes, with an increasing focus placed on the patient perspective to complement and augment health care professional reports, and laboratory and imaging data[1]. Patient-reported outcomes (PROs) are defined as "any report coming directly from the patient about how they feel and function, without interpretation of the patient's response by a health care professional"[2]. Cancer patients can provide a unique perspective on their own symptom burden, functioning and health-related quality of life (HRQoL)[3]. In oncological clinical trials and health care, PRO assessment has focused primarily on the multidimensional concept of HRQoL[4]; patients' perception of the effect of their disease and treatment on their physical, psychological and social functioning[5].

PROs may provide health care professionals with additional data on patients' prognosis[6]. The prognostic value of PROs, and particularly HRQoL, for cancer survival has been studied extensively with clinical trial data[7-9]. For example, Quinten et al. examined data of 11 different cancer types (10,108 patients) pooled from 30 clinical trials and found that, for each cancer site, at least one HRQoL domain (e.g. physical functioning in lung cancer) provided prognostic information beyond that provided by clinical (e.g. World Health Organization performance status, distant metastases) and sociodemographic characteristics (e.g. age, sex)[6]. However, although clinical trial data are valuable in developing treatment guidelines and can influence clinical practice, less than 3% of the cancer population is represented in these studies, and thus these data do not necessarily reflect the prognostic value of HRQoL data in daily clinical practice[10]. "Real-world" data from large population-

based cohort studies among patients with a specific cancer diagnosis as well as heterogeneous cancer diagnoses have shown a consistent, independent association of patients' ratings of their HRQoL with survival duration, with the relative prognostic strength of different HRQoL scales varying across cancer sites[24].

In clinical research it is often difficult to define the most important prognostic HRQoL domain. Some researchers enter all HRQoL domains simultaneously in survival analyses, without exploring relationships among closely related domains. This strategy increases the risk of multicollinearity and spurious findings due to chance[8,11]. Recently, the United States Food and Drug Administration (FDA) recommended the use of three well-defined concepts proximal to a treatments' effect on the patient: symptomatic adverse events, physical functioning and, where appropriate, a measure of the key symptoms of the disease[4]. However, it remains unclear why physical functioning is being recommended as the sole functional outcome to be assessed, because this ignores the potential importance of other functional domains such as emotional and social functioning[13]. As it may be difficult to pre-specify which HRQoL domains are of most interest, some researchers rely on a one- or two-item scale assessing overall or global quality of life (QoL)[12,14].

Recently, an overall HRQoL summary score for the core HRQoL questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) has been developed[12]. This summary score encompasses all symptom (e.g. fatigue, pain) and function domains (e.g. emotional and social functioning) assessed by the QLQ-C30. A single, higher-order HRQoL score is hypothesized to be a more

meaningful and reliable measure for oncological research[12,14]. However, data on its prognostic value is lacking.

The primary aims of the present population-based, observational study were to: (1) investigate the association of the novel QLQ-C30 summary score with all-cause mortality for several cancer diagnoses; (2) determine the added prognostic value of the summary score above and beyond that of more traditional sociodemographic and clinical prognostic factors[15]; (3) compare the prognostic value of the QLQ-C30 summary score, with the frequently used global QoL scale and the recently advocated physical functioning scale. A secondary aim was to compare the prognostic value of the QLQ-C30 summary score with all other scales of the QLQ-C30.

## Materials and methods

*Design/setting*

Since 2008, the PROFILES ('Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship') registry has collected PRO data from both short- and long-term cancer survivors in the Netherlands. The PROFILES registry is a large, dynamic population-based cohort used to study the physical and psychosocial impact of cancer and its treatment[16]. To date, over 20,000 individuals with 16 different cancer diagnoses have been recruited, and data collection is still ongoing. Complete and comprehensive supplemental data on sociodemographics, clinical characteristics (e.g. tumor and treatment characteristics) and survival are available for the PROFILES cohort via the Netherlands Cancer

Registry (NCR) and via linkage with the Dutch municipal records database. Data from the PROFILES registry were used for the current secondary analysis.

*Data collection*

A detailed description of the data collection method has been reported previously[16]. In brief, all participants in PROFILES were informed about the study via a letter by their (ex-)attending medical specialist. This letter contained either an informed consent form and a paper questionnaire, or a secure link to a web-based informed consent form and online questionnaire.

*Study sample*

The current analysis comprises 12 patient samples (colon, rectal, melanoma, basal/squamous cell, endometrial, ovarian, prostate, thyroid, Hodgkin, non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma) included in the PROFILES registry between May 2009 and April 2015. Although sample size and inclusion criteria varied across samples (related to study aim), in all study samples the same questionnaires were collected (www.profilesregistry.nl) and participants were excluded if they were not able to complete a Dutch language questionnaire due to a language barrier, cognitive impairment or advanced illness. Individuals who had died or had emigrated prior to the start of the study were excluded from the analysis. Ethical approval was obtained for all study samples separately from a local, certified medical ethics committee.

*Measures*

<u>Sociodemographic and clinical data</u>

Sociodemographic variables obtained from the NCR included date of birth and sex. Study-specific questions on educational level (high/intermediate/low), partnership (yes/no) and work status (yes/no) were added to all questionnaire packages.

Clinical data obtained from the NCR included date of cancer diagnosis, tumor type and stage and primary treatments received. Time since diagnosis at time of questionnaire invitation was categorized into 4 quartiles: 0-2 years, 2-3 years 3-5 years and >5 years. Tumor type was classified according to the International Classification of Diseases for Oncology (ICDO-3)[17] and disease stage was classified according to TNM[18] or Ann Arbor Code (Hodgkin lymphoma and Non-Hodgkin lymphoma). TNM5 was used for patients diagnosed between 2002 and 2003, TNM6 for patients diagnosed between 2003 and 2010, and TNM7 for patients diagnosed from 2010 onwards. For Chronic Lymphocytic Leukemia and Multiple Myeloma, stage was either not applicable or not registered. Primary treatments received (first six months after diagnosis) were classified into surgery, systemic therapy (chemotherapy, targeted therapy, immunotherapy), radiation therapy (including brachytherapy), hormonal therapy, no treatment/active surveillance or unknown. Comorbidity was classified using a modified version of the Charlson Index[19] and categorized into no, one or more than one comorbid conditions. Patients' vital status at time of analysis, and date of death where relevant were obtained from the Dutch municipal personal records database and were last verified on February 1st 2017.

Health-related quality of life

The 30-item EORTC QLQ-C30 (version 3.0) was used to assess HRQoL[20]. This questionnaire contains five functional scales (physical, role, cognitive, emotional and social functioning), a

global QoL scale, three symptom scales (fatigue, nausea and vomiting, and pain), and six single items (appetite loss, diarrhea, dyspnea, constipation, insomnia, financial impact). The questionnaire has a 1-week time frame and uses a four-point response format (''not at all,'' ''a little,'' ''quite a bit,'' and ''very much''), with the exception of the global QoL scale, which has a seven-point response format. The scores were linearly transformed to a score between 0 and 100[21]. For the functioning and the global QoL scales, a higher score indicates better health. For the symptoms scales, a higher score indicates more symptom burden. The QLQ-C30 summary score is calculated as the mean of the combined 13 QLQ-C30 scale and item scores (excluding global QoL and financial impact), with a higher score indicating a better HRQoL[12,22]. The summary score was only calculated when all of the required 13 scale and item scores were available.

*Statistical analyses*

Statistical analyses were conducted using SAS version 9.4. (SAS Institute, Cary, NC, 1999). Independent sample t-tests were used to assess differences in the QLQ-C30 summary scores, global QoL and physical functioning between patients alive and deceased at censoring date (February 1, 2017). This was done for the total study sample and per cancer type.

For the total sample and for each cancer type separately we used Cox proportional hazard regression models to model the prognostic value of the QLQ-C30 summary score, global QoL scale, and the physical functioning scale on survival. For all cox proportional hazard regression models, date of invitation to participate in a PROFILES study was set as entry time and survival duration was specified as time from invitation until either death or censoring date (follow-up time). The Hazard Ratios (HRs) were calculated for every 10-point difference on the HRQoL scales, which range between 0 and 100. Time between diagnosis

and invitation to participate in a study was highly variable. Thus patients with a shorter time since diagnosis might have had a higher mortality risk compared to patients with a longer time since diagnosis. To adjust for this potential survivorship bias, a variable with the left-truncation time (time between diagnosis and invitation to participate in the study) was added as a variable and time of diagnosis was set as entry time, for all cox hazard regression models.

The Cox proportional hazard model assumptions for both unadjusted and adjusted analyses (known sociodemographic and clinical prognostic factors: age, sex, time from diagnosis, stage, number of comorbidities, primary treatments received, partner status, employment, educational level[15]) were assessed using a graphic method. Analyses included multiple studies/cohorts and were therefore cluster-adjusted for study. The proportional hazard requirement, assuming that the HR was constant over time, was visually checked using log-log plots, and violation of the requirement was assumed when the lines were not parallel. Likelihood ratio tests to compare the models (with predictors) against the Null model (model without predictors) are presented as a measure of robustness of our findings. The p-value for HRs was set at 0.01, lowering the risk of type I errors due to multiple testing.

Cox proportional hazard regression models were also used to estimate the HRs of the other functioning and symptom scales of the QLQ-C30 to support our decision to focus on three scales only (presented as Supplementary material only).

**Results**

*Sociodemographic and clinical characteristics*

In total, 13,993 cancer survivors were invited to participate in one of the cohort studies of the PROFILES registry. Overall, 69% (N=9,590) of those invited completed the questionnaire, with participation rates for individual tumor type samples varying between 60 and 76%. Figure 1 presents the flow-chart.

Compared to non-participants, participants were more likely to be in the 60-70 year age bracket, were more often male, were more likely to have received active treatment, had fewer comorbidities, and were more likely to have been invited to complete a questionnaire in the period 2-3 years after diagnosis[23]. In total, 2,686 (28%) participants were excluded from analyses because of incomplete EORTC-C30 scale and item scores which made it impossible to calculate the QLQ-C30 summary score. Sociodemographic and clinical characteristics of study participants are presented in Table 1.

*QLQ-C30 summary score, global QoL and physical functioning: overall and per cancer type*

Participants with colon, rectum, basal/squamous cell, ovarian, prostate, thyroid cancer and non-Hodgkin lymphoma who had died had significantly lower QLQ-C30 summary scores compared to those who were alive during follow-up (Table 2). The same pattern was found for global QoL (except for Hodgkin lymphoma where those alive had significantly higher scores compared to deceased patients) and physical functioning (except for chronic lymphocytic leukemia, multiple myeloma where those alive had significantly higher scores compared to deceased patients). Figure 2 shows the proportions of deaths at censuring date by the score distribution of the summary score, global QoL and physical functioning scale.

*Survival analyses*

In Cox proportional hazard regression models, the QLQ-C30 summary score was significantly associated with all-cause mortality, and this remained statistically significant after adjusting for covariates: every 10-point increase in HRQoL score was associated with a 23% lower risk of death.

In cancer type stratified, multivariate Cox regression models, significant associations between the QLQ-C30 summary score and all-cause mortality were observed for colon, rectal, prostate cancer, non-Hodgkin lymphoma, chronic lymphocytic leukemia and multiple myeloma (Table 3). The same pattern was found for global QoL and physical functioning, although global QoL was also significantly associated with all-cause mortality for patients with Hodgkin lymphoma. The Likelihood ratio tests of all models were statistically significant (robust) for the total group, however in stratified analyses the Likelihood tests of the global QoL (melanoma), QLQ-C30 summary score (melanoma, Hodgkin lymphoma, endometrial cancer, thyroid cancer, chronic lymphocytic leukemia, multiple myeloma) and physical functioning scale (melanoma, Hodgkin, endometrial cancer) were not significant (Table 4).

In adjusted multivariate Cox regression models, the overall QLQ-C30 summary score was the strongest predictor of all-cause mortality (HR=0.77;$p<0.01$) when compared with the global QoL scale (HR=0.82;$p<0.01$) or the physical functioning scale (HR=0.81;$p<0.01$; Table 3). The Likelihood test of all models was statistically significant (robust) for the total group and all cancer specific models except for melanoma (Table 4).

Secondary analysis of the other QLQ-C30 scales indicated that all of the functioning scales were significantly associated with all-cause mortality, with adjusted HRs ranging from 0.86

(p<0.01) for role functioning to 0.93 (p<0.01) for cognitive functioning (Online appendix 1). However, these associations were only consistently found for colon, rectal (except cognitive functioning), prostate cancer (except emotional functioning), non-Hodgkin lymphoma, chronic lymphocytic leukemia and multiple myeloma (except social functioning). Fatigue was the only symptom scale significantly associated with all-cause mortality (adjusted HR=1; p<0.01) for the total group, although pain (colon and rectal cancer) and nausea and vomiting (colon, rectal, ovarian, prostate cancer, melanoma, Hodgkin lymphoma, chronic lymphocytic leukemia) were significantly associated with all-cause mortality in certain cancer types. The Likelihood test of all adjusted models was statistically significant (robust) for the total group and all cancer specific models except for melanoma (Online appendix 2).

## Discussion

Secondary analysis of data from population-based PROFILES registry studies indicated that HRQoL was associated with all-cause mortality in the "real-world" of daily clinical practice, independent of established sociodemographic and clinical prognostic factors. However, the prognostic value of HRQoL was only observed in certain tumor types. All three EORTC HRQoL measures had prognostic value, although the summary score was most strongly associated with all-cause mortality.

Our results are in line with previous studies that have reported that HRQoL is a prognostic factor in patients with solid advanced cancers with a high symptom burden, but not always in those with non-solid tumors and early-stage cancers[24]. The three EORTC QLQ-C30 scales assessed in this study were not significantly associated with survival among melanoma and endometrial cancer patients (both predominantly including patients with early-stage disease), thyroid cancer patients with a well-differentiated tumor, and basal cell carcinoma

patients. These patients often receive less aggressive curative treatments and have high overall survival rates. For Hodgkin lymphoma patients, the QLQ-C30 summary score was not prognostic, only the global QoL scale remained significant. This suggests that, for this specific patient group, self-reported global QoL is a unique indicator of survival[25]. In general, these relatively young patients had high functioning levels and low levels of symptoms, and it might therefore be that patient satisfaction or overall enjoyment of life is a more important prognostic factor. Furthermore, we did not observe a significant association between any of the three EORTC QLQ-C30 scales and all-cause mortality for ovarian cancer patients. For these patients other factors, including age and disease stage, but also emotional and social functioning specifically, were more important prognostic indicators.

Several explanations are described in the literature for the consistent link of HRQoL and survival. First, patient-reported HRQoL might better reflect survival-related functioning and well-being than traditional prognostic (clinician-reported) indicators (e.g. performance status, toxicity)[8]. This may be because PRO measures, especially the EORTC summary score, are composed of different questions with more sensitive response scales that reflect distinct and unique aspects of well-being. Recent studies have shown that clinicians miss up to half of the self-reported subjective toxicities reported by cancer patients[26]. Second, HRQoL measures might be more sensitive to prognostically relevantly lowered patient well-being than other measures like performance status. Third, PROs also reflect individual characteristics (e.g. coping with stressful circumstances, personality, illness perceptions) that might affect the disease process. For example, some studies suggest that stress-related adaptation processes could have physiological consequences such as alterations in cellular

immune function and pro-inflammatory signaling during cancer survivorship which in turn could influence disease progression[27]. Finally, higher HRQoL scores are linked with more positive behaviors, such as treatment adherence and healthy lifestyles that may affect survival.

The finding that the EORTC QLQ-C30 summary score provides distinct prognostic information beyond known sociodemographic and clinical measures, not only around cancer diagnosis (baseline) but also at follow-up, has implications for clinical practice and future research. Recent studies have shown that the availability of PRO data can improve symptom management, patient-clinician communication, shared decision-making and patients' satisfaction with care[28-31]. A randomized clinical trial by Basch et al[32,33] of 766 cancer patients demonstrated that a simple intervention, a web-based tool that enables patients to report their symptoms in real time and triggers alerts to clinicians, can have major benefits, including less frequent admissions to the emergency room or hospitalizations, remaining longer on chemotherapy and longer survival. These and our findings highlight the need for routine cancer survivorship PRO monitoring systems[34]. PRO's reflect how cancer and its treatment affect patients, which will help to direct health care professionals to areas of concern. Early detection via routine monitoring of deterioration in functional health and symptom burden would enable timely patient-specific supportive care interventions that may improve HRQoL and possibly survival of cancer survivors. Our findings indicate that the availability of the QLQ-C30 summary score alongside other prognostic variables allows for a more holistic approach. When a cut-off score for the QLQ-C30 summary score becomes available in the future, it might even be possible to use the summary score for screening purposes. However, more detailed HRQoL assessments should always be carried out in the interest of more personalized care.

To date, many studies of the prognostic value of HRQoL were based on retrospective analysis of clinical trial data. Although this is one of the best-known methodologies to evaluate treatment outcomes, results are limited by the selected study samples (e.g. some or no comorbid conditions, good performance status, strict follow-up and surveillance). Our study adds to the current "real-world" evidence[24] by demonstrating that the QLQ-C30 summary score is a significant prognostic factor for survival in specific tumor types. Moreover, our results also show that the summary score, global QoL scale and physical functioning scale are stronger predictors of all-cause mortality than the other functioning and symptom scales of the QLQ-C30, although some scales are shown to be particularly relevant for specific cancer types. The use of data from the PROFILES registry provides several advantages: population-based study samples; uniform patient recruitment procedures; use of a single, validated HRQoL measure; and availability of clinical registry data for linkage with HRQoL data.

Secondary data analysis of registry data also has some limitations. First, our study sample is a collection of separate study samples, with different inclusion criteria and sample sizes, and therefore heterogeneous with regard to years since initial cancer diagnosis. However, data collection method was similar across studies, we corrected for clustering and we addressed possible survivorship bias by using a left-truncated Cox regression model. Second, for most cancer types, pre-treatment HRQoL data of the patients were lacking. It could be argued that pre-treatment HRQoL is more likely to reflect (premorbid) disease specific characteristics, while follow-up HRQoL reflect treatment-specific characteristics, and that changes in HRQoL over time might be more interesting than only a single measure at one time point. Third, we only had information on primary treatment, and not on treatment following recurrence or for emergent metastatic disease. Therefore mortality estimates should be interpreted with

caution. Fourth, although we corrected for a range of generic sociodemographic and clinical covariates, there is still the possibility of residual confounding by additional, condition-specific clinical variables. We cannot rule out that HRQoL scales became significant simply because other well-established (disease-specific) variables (e.g. performance status) were not included in the prognostic models. However, other prognostic studies that have included performance status in the statistical models have supported the independent, prognostic value of QLQ-C30 data[24]. Finally, the sample size for some patient groups was relatively small resulting in limitations of statistical power, and some prevalent cancer types (e.g. breast cancer) were not available.

## Conclusion

In conclusion, this population-based study indicates that, for a number of cancer patient populations, a summary score reflecting different domains of HRQoL has a strong prognostic value for overall survival above and beyond that of sociodemographic and clinical variables . Furthermore, the summary score appears to have more prognostic value than the global QoL, physical functioning, or any other scale within the QLQ-C30.

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**Conflict of interest:**

The authors have no conflict of interest to declare. This manuscript is original research and it has not been submitted or published elsewhere.

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**Figure legends**

**Figure 1:** Flow-chart

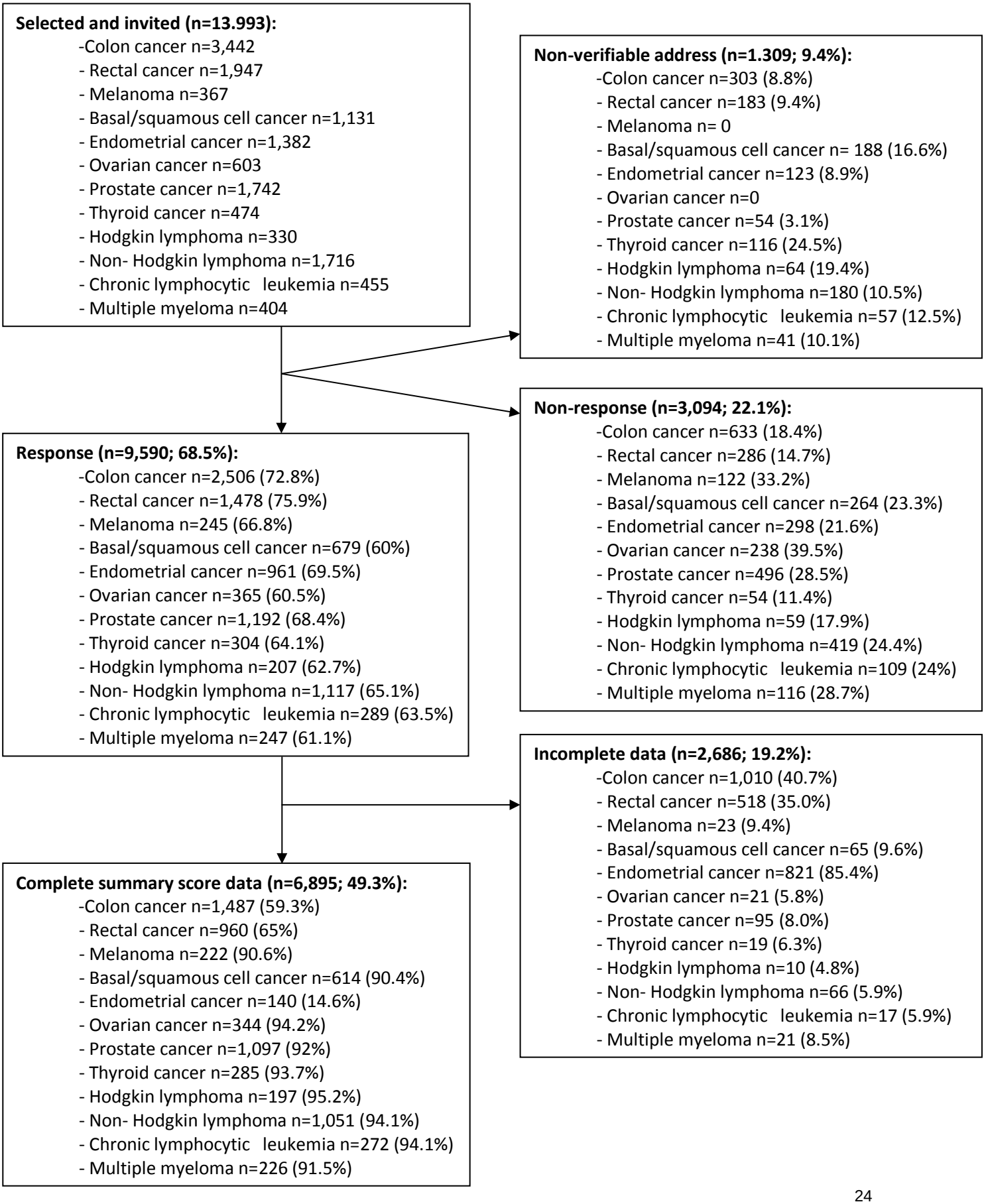
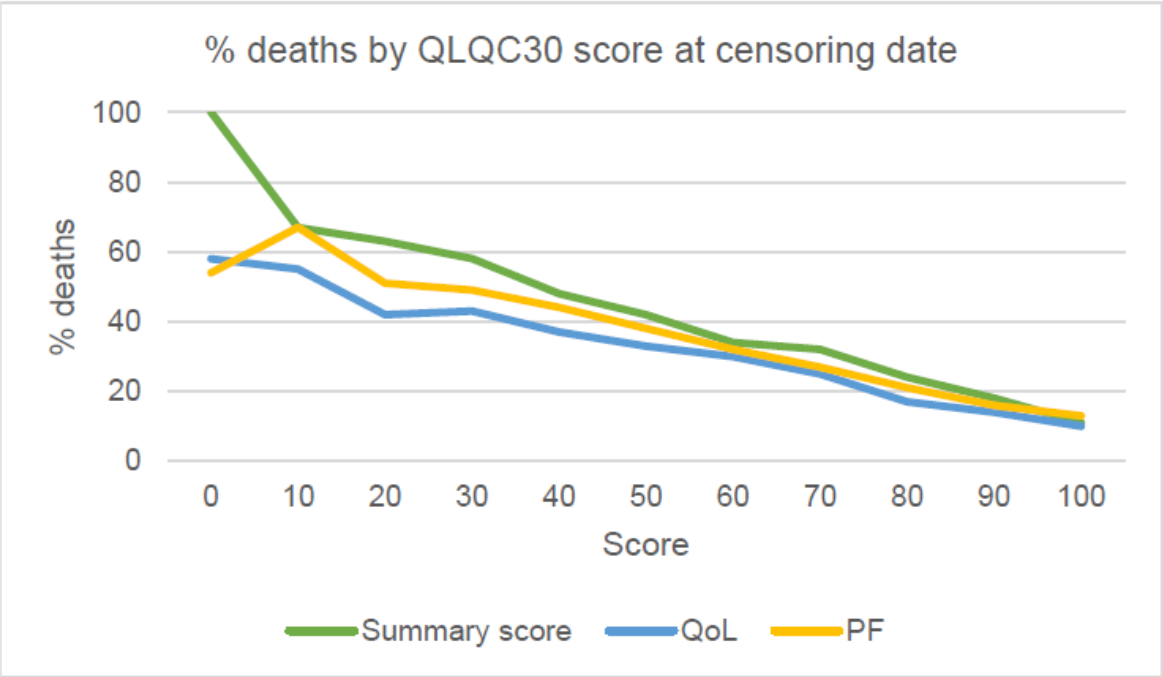


**Figure 2:** Proportions of deaths at censuring date by the score distribution of summary score, global QoL and physical functioning scale




| Summary score | | | | Global QoL (QoL) | | | | Physical functioning (PF) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Score* | *Death N* | *Alive N* | *Total N* | *Score* | *Death N* | *Alive N* | *Total N* | *Score* | *Death N* | *Alive N* | *Total N* |
| 0 | 0 | 1 | 1 | 0 | 10 | 14 | 24 | 0 | 6 | 7 | 13 |
| 10 | 1 | 2 | 3 | 10 | 5 | 6 | 11 | 10 | 13 | 26 | 39 |
| 20 | 3 | 5 | 8 | 20 | 36 | 26 | 62 | 20 | 20 | 21 | 41 |
| 30 | 10 | 14 | 24 | 30 | 124 | 95 | 219 | 30 | 86 | 84 | 170 |
| 40 | 40 | 37 | 77 | 40 | 80 | 46 | 126 | 40 | 90 | 72 | 162 |
| 50 | 101 | 72 | 173 | 50 | 318 | 160 | 478 | 50 | 306 | 189 | 495 |
| 60 | 257 | 135 | 392 | 60 | 249 | 106 | 355 | 60 | 243 | 112 | 355 |
| 70 | 421 | 196 | 617 | 70 | 797 | 261 | 1058 | 70 | 644 | 242 | 886 |
| 80 | 863 | 278 | 1141 | 80 | 2196 | 437 | 2633 | 80 | 478 | 128 | 606 |
| 90 | 1795 | 395 | 2190 | 90 | 512 | 87 | 599 | 90 | 1695 | 325 | 2020 |
| 100 | 2014 | 255 | 2269 | 100 | 1160 | 141 | 1301 | 100 | 1920 | 181 | 2101 |

**Tables**

**Table 1:** Sociodemographic and clinical characteristics of study participants

| | Total | Colon cancer | Rectal cancer | Melanoma | Basal/squamous cell cancer | Endometrial cancer | Ovarian cancer | Prostate cancer | Thyroid cancer | Hodgkin lymphoma | Non-Hodgkin lymphoma | Chronic lymphocytic leukemia | Multiple myeloma |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 6895 | 1487 | 960 | 222 | 614 | 140 | 344 | 1097 | 285 | 197 | 1051 | 272 | 226 |
| Age at diagnosis, mean (SD) | 62.1 (12.2) | 64.4 (9.7) | 62.1 (9.6) | 55.2 (13.3) | 66.8 (11.8) | 67.0 (8.5) | 60.0 (11.6) | 66.6 (7.3) | 46.4 (15.1) | 41.9 (16.0) | 60.3 (13.2) | 63.9 (10.4) | 63.4 (9.8) |
| <50 years | 974 (14) | 111 (7) | 99 (10) | 81 (36) | 57 (9) | 3 (2) | 61 (18) | 10 (1) | 167 (59) | 132 (67) | 206 (20) | 27 (10) | 20 (9) |
| 50-60 | 1687 (24) | 362 (24) | 307 (32) | 49 (22) | 100 (16) | 27 (19) | 116 (34) | 229 (21) | 64 (22) | 35 (18) | 267 (25) | 65 (24) | 66 (29) |
| 60-70 | 2448 (36) | 567 (38) | 358 (37) | 62 (28) | 215 (35) | 65 (46) | 100 (29) | 513 (47) | 31 (11) | 20 (10) | 335 (32) | 99 (36) | 83 (37) |
| 70-80 | 1581 (23) | 412 (28) | 187 (19) | 27 (12) | 174 (28) | 38 (27) | 59 (17) | 314 (29) | 22 (8) | 10 (5) | 211 (20) | 75 (28) | 52 (23) |
| >80 | 205 (3) | 35 (2) | 9 (1) | 3 (1) | 68 (11) | 7 (5) | 8 (2) | 31 (3) | 1 (0) | 0 (0) | 32 (3) | 6 (2) | 5 (2) |
| Age at questionnaire, mean (SD) | 66.7 (11.8) | 69.9 (9.4) | 67.9 (9.6) | 58.6 (13.6) | 68.4 (11.8) | 67.7 (8.5) | 63.8 (11.2) | 71.1 (7.3) | 56.1 (14.6) | 46.8 (16.0) | 64.3 (12.9) | 67.8 (10.3) | 66.4 (9.4) |
| <50 years | 636 (9) | 51 (3) | 41 (4) | 59 (27) | 50 (8) | 3 (2) | 39 (11) | 2 (0) | 105 (37) | 115 (58) | 146 (14) | 17 (6) | 8 (4) |
| 50-60 | 980 (14) | 159 (11) | 144 (15) | 50 (23) | 80 (13) | 21 (15) | 80 (23) | 57 (5) | 72 (25) | 34 (17) | 195 (19) | 38 (14) | 50 (22) |
| 60-70 | 2261 (33) | 471 (32) | 344 (36) | 57 (26) | 192 (31) | 62 (44) | 125 (36) | 427 (39) | 52 (18) | 29 (15) | 333 (32) | 87 (32) | 82 (36) |
| 70-80 | 2267 (33) | 590 (40) | 334 (35) | 44 (20) | 193 (31) | 45 (32) | 79 (23) | 476 (43) | 36 (13) | 17 (9) | 281 (27) | 98 (36) | 74 (33) |
| >80 | 744 (11) | 216 (15) | 96 (10) | 12 (5) | 99 (16) | 9 (6) | 20 (6) | 134 (12) | 19 (7) | 2 (1) | 95 (9) | 31 (11) | 13 (5) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex, N (%) | | | | | | | | | | | | | |
| male | 4020 (58) | 804 (54) | 572 (60) | 99 (45) | 313 (51) | 0 (0) | 0 (0) | 1097 (100 | 71 (25) | 107 (54) | 633 (60) | 187 (69) | 137 (61) |
| female | 2875 (42) | 683 (46) | 388 (40) | 123 (55) | 301 (49) | 140 (100) | 344 (100) | 0 (0) | 214 (75) | 90 (46) | 418 (40) | 85 (31) | 89 (39) |
| Disease stage[a], N (%) | | | | | | | | | | | | | |
| I | 1778 (26) | 333 (22) | 318 (33) | 170 (77) | 51 (8) | 122 (87) | 149 (43) | 146 (13) | 159 (56) | 37 (19) | 305 (29) | 0 (0) | 0 (0) |
| II | 1974 (29) | 622 (42) | 286 (30) | 34 (15) | 2 (0) | 4 (3) | 34 (10) | 639 (58) | 55 (19) | 101 (51) | 189 (18) | 0 (0) | 0 (0) |
| III | 1350 (20) | 439 (30) | 301 (31) | 10 (5) | 1 (0) | 6 (4) | 107 (31) | 214 (20) | 46 (16) | 36 (18) | 181 (17) | 0 (0) | 0 (0) |
| IV | 617 (9) | 72 (5) | 38 (4) | 2 (1) | 0 (0) | 5 (4) | 27 (8) | 95 (15) | 19 (7) | 20 (10) | 299 (28) | 0 (0) | 0 (0) |
| Not applicable/ unknown | 1154 (17) | 21 (1) | 17 (2) | 6 (3) | 560 (91) | 3 (2) | 27 (8) | 3 (9) | 6 (2) | 3 (2) | 77 (7) | 272 (100) | 226 (100) |
| Primary treatments received, N (%) | | | | | | | | | | | | | |
| Surgery | 3837 (56) | 1475 (99) | 946 (99) | 221 (100) | 102 (17) | 139 (99) | 332 (97) | 339 (31) | 283 (99) | 0 (0) | 0 (0) | 0 (0) | (0) |
| Systemic therapy[b] | 2216 (32) | 490 (32) | 275 (29) | 0 (0) | 5 (1) | 5 (4) | 251 (73) | 0 (0) | 0 (0) | 186 (94) | 768 (73) | 60 (22) | 176 (78) |
| Radiotherapy | 1832 (27) | 24 (2) | 692 (72) | 0 (0) | 0 (0) | 53 (38) | 2 (1) | 396 (36) | 206 (72) | 117 (59) | 263 (25) | 8 (3) | 72 (32) |
| Hormonal therapy | 318 (5) | 1 (0) | 2 (0) | 0 (0) | 0 (0) | 1 (0) | 1 (0) | 306 (28) | 6 (2) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| No therapy/active surveillance | 585 (9) | 4 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 221 (20) | 2 (1) | 4 (2) | 117 (11) | 202 (74) | 35 (15) |
| Time between diagnosis and invitation, N (%) | | | | | | | | | | | | | |
| <2 years | 1789 (26) | 125 (8) | 55 (6) | 34 (15) | 610 (99) | 140 (100) | 172 (50) | 44 (4) | 5 (2) | 55 (28) | 359 (34) | 84 (31) | 106 (47) |
| 2-3 years | 1411 (21) | 427 (29) | 222 (23) | 41 (19) | 1 (0) | 0 (0) | 30 (9) | 237 (22) | 32 (11) | 34 (17) | 239 (23) | 82 (30) | 66 (29) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3-5 years | 1537 (22) | 284 (19) | 210 (22) | 84 (38) | 2 (0) | 0 (0) | 37 (11) | 551 (51) | 45 (16) | 31 (16) | 212 (20) | 48 (18) | 33 (15) |
| >5 years | 2126 (31) | 641 (43) | 471 (49) | 61 (28) | 1 (0) | 0 (0) | 105 (31) | 258 (24) | 202 (71) | 77 (39) | 233 (22) | 57 (21) | 20 (9) |
| Comorbidities, N (%) | | | | | | | | | | | | | |
| 0 | 2113 (31) | 401 (27) | 307 (32) | 81 (36) | 341 (55) | 32 (23) | 115 (33) | 284 (26) | 72 (25) | 86 (44) | 296 (28) | 52 (19) | 46 (20) |
| 1 | 1843 (27) | 406 (27) | 269 (28) | 63 (28) | 82 (13) | 38 (27) | 88 (26) | 362 (33) | 89 (31) | 49 (25) | 284 (27) | 59 (22) | 52 (24) |
| >1 | 2939 (43) | 690 (46) | 384 (40) | 78 (35) | 191 (31) | 70 (50) | 141 (41) | 451 (41) | 124 (43) | 62 (31) | 471 (45) | 161 (59) | 126 (56) |
| Partner, N (%) | | | | | | | | | | | | | |
| Yes | 5328 (78) | 1119 (76) | 760 (79) | 181 (83) | 469 (78) | 102 (74) | 235 (70) | 920 (85) | 222 (78) | 147 (75) | 785 (76) | 210 (78) | 178 (80) |
| No | 1500 (22) | 359 (24) | 198 (21) | 37 (17) | 136 (22) | 36 (26) | 103 (30) | 166 (15) | 63 (22) | 49 (25) | 249 (24) | 59 (22) | 45 (20) |
| Educational level, N (%) | | | | | | | | | | | | | |
| Low | 1119 (16) | 284 (19) | 176 (18) | 15 (7) | 159 (26) | 22 (16) | 48 (14) | 147 (14) | 28 (7) | 13 (7) | 153 (15) | 44 (16) | 30 (13) |
| Middle | 4202 (62) | 905 (61) | 575 (60) | 135 (62) | 395 (65) | 99 (72) | 221 (67) | 647 (60) | 183 (64) | 122 (62) | 623 (60) | 151 (56) | 146 (65) |
| High | 1487 (22) | 284 (19) | 203 (21) | 68 (31) | 52 (9) | 16 (12) | 67 (20) | 288 (27) | 73 (26) | 61 (31) | 255 (25) | 73 (27) | 47 (21) |
| Employment status, N (%) | | | | | | | | | | | | | |
| Employed | 1628 (24) | 218 (15) | 178 (19) | 109 (50) | 151 (26) | 27 (20) | 91 (28) | 151 (14) | 146 (52) | 97 (54) | 369 (38) | 47 (19) | 44 (20) |
| Not employed | 5022 (76) | 1249 (85) | 770 (81) | 108 (50) | 433 (74) | 105 (80) | 230 (72) | 915 (86) | 133 (46) | 84 (46) | 613 (62) | 207 (82) | 175 (80) |
| Deceased, N (%) | | | | | | | | | | | | | |
| Yes | 1390 (20) | 324 (22) | 218 (23) | 6 (3) | 22 (4) | 25 (18) | 113 (33) | 148 (13) | 26 (9) | 22 (11) | 263 (25) | 82 (30) | 141 (62) |
| No | 5505 (80) | 1163 (78) | 742 (77) | 216 (97) | 592 (96) | 115 (82) | 231 (67) | 949 (87) | 259 (91) | 175 (75) | 788 (75) | 190 (70) | 85 (38) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Follow-up time in years, M (SD) | 4.6 (2.0) | 5.3 (1.5) | 5.2 (1.6) | 2.4 (1.3) | 2.4 (0.2) | 4.5 (1.1) | 3.8 (1.5) | 3.6 (1.6) | 5.9 (0.9) | 6.5 (1.8) | 5.3 (2.2) | 5.0 (2.3) | 3.8 (2.3) |
| Median (min-max) | 5.2 (0-7.9) | 5.9 (0.1-6.2) | 5.9 (0-6.2) | 2.0 (0.6-7.7) | 2.5 (0.3-3.9) | 4.7 (0.7-5.8) | 4.6 (0.2-5.8) | 4.3 (0.1-5.3) | 6.2 (1.0-6.3) | 7.6 (0.8-7.8) | 5.4 (0.1-7.8) | 4.6 (0.2-7.7) | 3.6 (0-7.7) |

[a]According to TNM. Ann Arbor Code was used for Hodgkin lymphoma and Non-Hodgkin lymphoma. For Chronic lymphocytic leukemia and Multiple myeloma tumor stage was not determined or registered.
[b]Systemic therapies were: chemotherapy, targeted therapy and immune therapy.
SD= Standard deviation

**Table 2:** Overall EORTC QLQ-C30 summary scores according to vital status at censoring date

| | Summary score | | | | | Global QoL | | | | | Physical functioning | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Alive at censoring date | | Deceased at censoring date | | P-value | Alive at censoring date | | Deceased at censoring date | | P-value | Alive at censoring date | | Deceased at censoring date | | P-value |
| | N | Mean (SD) | N | Mean (SD) | | N | Mean (SD) | N | Mean (SD) | | N | Mean (SD) | N | Mean (SD) | |
| Total sample | 5505 | 87.7 (12.9) | 1390 | 79.6 (16.9) | **<0.01** | 5505 | 79.8 (69.7) | 1390 | 68.4 (21.7) | **<0.01** | 5505 | 84.5 (18.2) | 1390 | 69.8 (23.6) | **<0.01** |
| Colon cancer | 1163 | 87.5 (12.5) | 324 | 80.8 (15.6) | **<0.01** | 1163 | 79.7 (16.9) | 324 | 69.2 (21.6) | **<0.01** | 1163 | 84.5 (18.2) | 324 | 69.4 (23.7) | **<0.01** |
| Rectum cancer | 742 | 87.7 (12.6) | 218 | 80.4 (16.7) | **<0.01** | 742 | 79.6 (17.7) | 218 | 69.3 (22.7) | **<0.01** | 742 | 83.5 (18.0) | 218 | 69.8 (24.8) | **<0.01** |
| Melanoma | 216 | 92.4 (10.0) | 6 | 85.4 (16.2) | 0.10 | 216 | 82.6 (17.4) | 6 | 84.7 (16.2) | 0.76 | 216 | 91.5 (15.6) | 6 | 90.0 (13.2) | 0.81 |
| Basal/squamous cell cancer | 592 | 92.6 (10.9) | 22 | 82.9 (17.0) | **0.03** | 592 | 82.1 (16.9) | 22 | 67.9 (22.1) | **<0.01** | 592 | 87.6 (18.3) | 22 | 73.0 (25.9) | **<0.01** |
| Endometrial cancer | 115 | 88.1 (9.3) | 25 | 88.2 (8.5) | 0.98 | 115 | 81.0 (14.5) | 25 | 75.7 (16.8) | 0.11 | 115 | 90.8 (7.7) | 25 | 90.9 (7.0) | 0.96 |
| Ovarian cancer | 231 | 83.4 (13.3) | 113 | 72.2 (18.1) | **<0.01** | 231 | 74.5 | 113 | 62.1 | **<0.01** | 231 | 79.8 | 113 | 64.7 | **<0.01** |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | (18.2) | | (21.7) | | | (20.1) | | (22.6) | |
| Prostate cancer | 949 | 88.9 (12.4) | 148 | 80.1 (18.2) | **<0.01** | 949 | 79.3 (17.4) | 148 | 69.5 (21.1) | **<0.01** | 949 | 86.7 (17.2) | 148 | 69.5 (24.3) | **<0.01** |
| Thyroid cancer | 259 | 85.9 (13.8) | 26 | 78.7 (16.0) | **0.01** | 259 | 76.4 (19.8) | 26 | 67.3 (19.0) | **0.03** | 259 | 84.7 (18.2) | 26 | 67.8 (24.4) | **<0.01** |
| Hodgkin lymphoma | 175 | 87.2 (14.1) | 22 | 86.4 (10.9) | 0.79 | 175 | 79.0 (17.2) | 22 | 70.1 (17.8) | **0.03** | 175 | 87.6 (16.2) | 22 | 81.9 (15.5) | 0.12 |
| Non-Hodgkin lymphoma | 788 | 85.5 (13.3) | 263 | 80.3 (17.9) | **<0.01** | 788 | 76.5 (18.2) | 263 | 69.0 (22.3) | **<0.01** | 788 | 81.5 (18.6) | 263 | 71.5 (22.2) | **<0.01** |
| Chronic lymphocytic leukemia | 190 | 86.1 (15.4) | 82 | 82.3 (15.6) | 0.06 | 190 | 76.5 (19.7) | 82 | 72.1 (19.5) | 0.10 | 190 | 84.1 (18.0) | 82 | 72.1 (22.3) | **<0.01** |
| Multiple myeloma | 85 | 78.8 (18.6) | 141 | 75.4 (16.7) | 0.15 | 85 | 68.1 (22.5) | 141 | 64.1 (22.2) | 0.20 | 85 | 70.8 (22.9) | 141 | 63.5 (23.4) | **0.02** |

EORTC QLQ-C30= European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30; SD= Standard deviation

**Table 3:** Adjusted Cox regression analysis of survival for EORTC QLQ-C30 summary score, global QoL scale and physical functioning scale

| | **Total**[a] | **Colon cancer** | **Rectal cancer** | **Melanoma** | **Basal/squamous cell cancer** | **Endometrial cancer** | **Ovarian cancer**[a] | **Prostate cancer**[a] | **Thyroid cancer** | **Hodgkin lymphoma**[a] | **Non-Hodgkin lymphoma**[a] | **Chronic lymphocytic leukemia**[a] | **Multiple myeloma**[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 6895 | 1487 | 960 | 222 | 614 | 140 | 344 | 1097 | 285 | 197 | 1051 | 272 | 226 |
| Person-years | 31422.97 | 7815.64 | 4995.92 | 525.09 | 1488.58 | 623.09 | 1295.82 | 3906.50 | 1684.08 | 1281.75 | 5584.17 | 1367.58 | 854.74 |
| Deaths | 1390 | 324 | 218 | 6 | 22 | 25 | 113 | 148 | 26 | 22 | 263 | 82 | 141 |
| **Unadjusted cox regression HR (99%CI)** | | | | | | | | | | | | | |
| EORTC QLQ-C30 summary score (per 10 points) | **0.75 (0.71-0.81)*** | **0.75 (0.69-0.82)*** | **0.76 (0.69-0.84)*** | 0.71 (0.30-1.68) | **0.65 (0.47-0.90)*** | 1.05 (0.59-1.85) | **0.75 (0.66-0.85)*** | **0.72 (0.64-0.81)*** | 0.77 (0.58-1.03) | 0.95 (0.81-1.12) | **0.81 (0.76-0.87)*** | 0.86 (0.74-1.01) | **0.90 (0.82-0.99)*** |
| Global QOL (per 10 points) | **0.80 (0.77-0.84)*** | **0.79 (0.74-0.83)*** | **0.80 (0.74-0.87)*** | 1.01 (0.50-2.05) | **0.71 (0.56-0.90)*** | 0.82 (0.60-1.13) | **0.83 (0.72-0.96)*** | **0.79 (0.78-0.80)*** | **0.84 (0.68-1.04)** | **0.80 (0.77-0.83)*** | **0.85 (0.81-0.88)*** | 0.89 (0.81-0.98) | 0.92 (0.82-1.03) |
| Physical functioning (per 10 points) | **0.77 (0.75-0.80)*** | **0.78 (0.73-0.82)*** | **0.77 (0.72-0.83)*** | 1.04 (0.42-2.59) | **0.77 (0.63-0.94)*** | 1.02 (0.45-2.29) | **0.83 (0.79-0.86)*** | **0.73 (0.68-0.78)*** | **0.76 (0.63-0.91)*** | **0.85 (0.73-0.98)*** | **0.81 (0.79-0.84)*** | **0.79 (0.75-0.83)*** | **0.89 (0.8-0.99)*** |
| **Adjusted cox regression**[b] **HR (99%CI)** | | | | | | | | | | | | | |
| EORTC QLQ-C30 summary score (per | **0.77 (0.71-0.82)*** | **0.75 (0.67-0.83)*** | **0.77 (0.69-0.85)*** | 0.58 (0.11-3.00) | 0.77 (0.54 1.17) | 1.09 (0.52-2.26) | 0.85 (069-1.06) | **0.78 (0.66-0.92)*** | 0.77 (0.52-1.13) | 0.82 (0.49-1.38) | **0.81 (0.75-0.87)*** | **0.78 (0.76-0.81)*** | **0.89 (0.82-0.97)*** |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 points) | | | | | | | | | | | | | |
| Global QOL (per 10 points) | **0.82 (0.77-0.86)*** | **0.80 (0.75-0.86)*** | **0.80 (0.73-0.87)*** | 0.95 (0.27-3.30) | 0.81 (0.60-1.04) | 1.00 (0.63-1.59) | 0.92 (0.73-1.16) | **0.83 (0.82-0.84)*** | 0.86 (0.66-1.13) | **0.70 (0.56-0.87)*** | **0.86 (0.81-0.90)*** | **0.87 (0.81-0.94)*** | 0.90 (80-1.00) |
| Physical functioning (per 10 points) | **0.81 (0.77-0.85)*** | **0.81 (0.76-0.86)*** | **0.80 (0.74-0.86)*** | 1.60 (0.33-7.66) | 0.93 (0.68-1.25) | 1.93 (0.71-5.25) | 0.88 (0.72-1.09) | **0.79 (0.69-0.90)*** | 0.83 (0.63-1.11) | 1.00 (0.91-1.08) | **0.84 (0.81-0.88)*** | **0.78 (0.74-0.83)*** | 0.90 (0.83-0.98) |

[a]Analyses included multiple studies/cohorts and were therefore cluster-adjusted for study

[b]adjusted for covariates: age, sex, disease stage, treatments received, number of comorbid conditions, partner, educational level, employment status

EORTC QLQ-C30= European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30; QoL= Quality of Life; HR = Hazard Ratio; CI = confidence interval

HR is significant at $p < 0.01$

Table 4: Likelihood ratio tests of Cox regression analyses for other EORTC QLQ-C30 scales

| | Total[a] N=6895 | Colon cancer N=1487 | Rectal cancer N=960 | Melanoma N=222 | Basal/squamous cell cancer N=614 | Endometrial cancer N=140 | Ovarian cancer[a] N=344 | Prostate cancer[a] N=1097 | Thyroid cancer N=285 | Hodgkin lymphoma[a] N=197 | Non-Hodgkin lymphoma[a] N=1051 | Chronic Lymphocytic leukemia[a] N=272 | Multiple myeloma[a] N=226 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Unadjusted cox regression, -2 Log Likelihood ratio** | | | | | | | | | | | | | |
| EORTC QLQ-C30 summary score | | | | | | | | | | | | | |
| *Full model* | **21207.7 -** | **4087.3 -** | **2543.5 -** | 42.0 - | **267.4 -** | 232.1 - | **1052.5 -** | **1807.1 -** | 223.0 - | 182.6 - | **3146.3 -** | 769.6 - | 1263.5 - |
| *Null model* | **21504.1*** | **4147.2*** | **2586.9*** | 42.9 | **276.6*** | 232.2 | **1076.6*** | **1852.6*** | 227.7 | 182.7 | **3175.3*** | 774.3 | 1268.6 |
| Global QOL | | | | | | | | | | | | | |
| *Full model* | **19928.5 -** | **3862.0 -** | **2409.9 -** | 27.7 - | **222.0 –** | **172.1 -** | **928.4 -** | **1637.6 -** | **169.6 -** | **131.8 -** | **2869.8 -** | **673.4 -** | **1162.1 -** |
| *Null model* | **20840.4*** | **4085.0*** | **2582.3*** | 42.6 | **262.5*** | **230.5*** | **1012.1*** | **1784.4*** | **227.4*** | **182.4*** | **3014.1*** | **733.6*** | **1194.6*** |
| Physical functioning | | | | | | | | | | | | | |
| *Full model* | **20956.3 -** | **4037.2 -** | **2512.1 -** | 42.8 - | **254.8 -** | 232.2 - | **1054.9 -** | **1770.4 -** | **215.3 -** | 180.8 - | **3121.0 -** | **741.9 -** | 1**247.8 -** |
| *Null model* | **21453.6*** | **4147.2*** | **2586.9*** | 42.9 | **263.7*** | 232.2 | **1076.6*** | **1852.1*** | **227.7*** | 182.7 | **3174.8*** | **763.7*** | **1256.9*** |
| **Adjusted cox regression[b], -2 Log Likelihood ratio** | | | | | | | | | | | | | |
| EORTC QLQ-C30 summary score | | | | | | | | | | | | | |
| *Full model* | **20073.7 -** | **3874.8 –** | **2419.1 -** | 27.0 - | **239.7 -** | **172.0 -** | **934.2 -** | **1636.8 -** | **168.5 -** | **136.2 -** | **2895.3 -** | **675.9 -** | **1204.4 -** |
| *Null model* | **20987.7*** | **4086.3*** | **2583.4*** | 42.6 | **275.7*** | **230.5*** | **1022.8*** | **1784.8*** | **227.4*** | **182.5*** | **3039.5*** | **740.9*** | **1235.8*** |
| Global QOL | | | | | | | | | | | | | |
| *Full model* | **19928.5 -** | **3862.0 -** | **2409.9 -** | 27.7 - | **222.0 -** | **172.1 -** | **928.4 -** | **1637.6 -** | **169.6 -** | **131.8 -** | **2869.8 -** | **673.4 -** | **1162.1 -** |
| *Null model* | **20840.4*** | **4085.0*** | **2582.3*** | 42.6 | **262.5*** | **230.5*** | **1012.1*** | **1784.4*** | **227.4*** | **182.4*** | **3014.1*** | **733.6*** | **1194.6*** |
| Physical functioning | | | | | | | | | | | | | |
| *Full model* | **19977.3 -** | **3857.4 -** | **2406.9 -** | 27.0 - | **225.9 -** | **169.1 -** | **933.9 -** | **1623.4 -** | **168.7 -** | **136.9 -** | **2889.0 -** | **667.9 -** | **1190.8 -** |
| *Null model* | **20953.5*** | **4086.3*** | **2583.4*** | 42.6 | **262.8*** | **230.5*** | **1022.8*** | **1784.4*** | **227.4*** | **182.5*** | **3039.0*** | **740.9*** | **1224.2*** |

[a]Analyses included multiple studies/cohorts and were therefore cluster-adjusted for study

[b]adjusted for covariates: age, sex, disease stage, treatments received, number of comorbid conditions, partner, educational level, employment status

Likelihood ratio test is significant at p< 0.01

Online appendix 1: Adjusted Cox regression analysis of survival for other EORTC QLQ-C30 scales

| | **Total**[a] | **Colon cancer** | **Rectal cancer** | **Melanoma** | **Basal/squamous cell cancer** | **Endometrial cancer** | **Ovarian cancer**[a] | **Prostate cancer**[a] | **Thyroid cancer** | **Hodgkin lymphoma**[a] | **Non-Hodgkin lymphoma**[a] | **Chronic lymphocytic leukemia**[a] | **Multiple myeloma**[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 6895 | 1487 | 960 | 222 | 614 | 140 | 344 | 1097 | 285 | 197 | 1051 | 272 | 226 |
| Person-years | 31422.97 | 7815.64 | 4995.92 | 525.09 | 1488.58 | 623.09 | 1295.82 | 3906.50 | 1684.08 | 1281.75 | 5584.17 | 1367.58 | 854.74 |
| Deaths | 1390 | 324 | 218 | 6 | 22 | 25 | 113 | 148 | 26 | 22 | 263 | 82 | 141 |
| **Unadjusted cox regression HR (99%CI)** | | | | | | | | | | | | | |
| Role functioning (per 10 points) | **0.85 (0.83-0.88)*** | **0.86 (0.83-0.90)*** | **0.86 (0.81-0.91)*** | 0.92 (0.56-1.52) | **0.82 (0.68-0.98)*** | 0.92 (0.65-1.30) | **0.88 (0.81-0.96)*** | **0.82 (0.77-0.87)*** | 0.86 (0.74-1.00) | 0.98 (0.86-1.13) | **0.89 (0.87-0.91)*** | **0.92 (0.86-0.99)**** | 0.94 (0.87-1.02) |
| Emotional functioning (per 10 points) | **0.90 (0.87-0.93)*** | **0.92 (0.86-0.99)*** | **0.87 (0.81-0.94)*** | 1.47 (0.46-4.78) | 0.94 (0.69-1.27) | 0.85 (0.74-1.41) | **0.87 (0.84-0.90)*** | **0.90 (0.84-0.97)*** | 0.98 (0.77-1.26) | 0.99 (0.90-1.10) | **0.95 (0.92-0.97)*** | 0.96 (0.90-1.03) | **0.90 (0.82-1.00)*** |
| Cognitive functioning (per 10 points) | **0.92 (0.90-0.94)*** | **0.92 (0.86-0.97)*** | 0.93 (0.86-1.01) | 1.01 (0.40-2.59) | 0.83 (0.67-1.03) | 1.26 (0.84-1.87) | 0.96 (0.92-1.02) | **0.88 (0.83-0.93)*** | 1.03 (0.82-1.30) | 1.00 (0.92-1.08) | **0.93 (0.90-0.97)*** | 0.97 (0.90-1.04) | **0.93 (0.92-0.94)*** |
| Social functioning (per 10 points) | **0.88 (0.85-0.91)*** | **0.88 (0.83-0.93)*** | **0.89 (0.83-0.95)*** | 0.98 (0.48-2.02) | 0.91 (0.67-1.25) | 1.10 (0.79-1.55) | **0.86 (0.82-0.89)*** | **0.84 (0.78-0.90)*** | 0.98 (0.81-1.19) | 1.10 (0.99-1.21) | **0.93 (0.91-0.96)*** | 0.92 (0.82-1.03) | 0.97 (0.91-1.03) |
| Fatigue (per 10 points) | **1.00 (1.00-1.00)*** | **1.20 (1.14-1.26)*** | **1.18 (1.11-1.25)*** | 1.32 (0.87-1.98) | 1.19 (0.97-1.46) | 0.90 (0.71-1.14) | **1.14 (1.01-1.28)*** | **1.22 (1.16-1.28)*** | 1.11 (0.92-1.34) | 0.98 (0.99-1.01) | 1.00 (1.00-1.00)** | **1.05 (1.03-1.08)*** | **1.08 (1.03-1.12)*** |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pain (per 10 points) | **1.00 (1.00-1.00)*** | **1.07 (1.02-1.13)*** | **1.09 (1.02-1.16)*** | 1.09 (0.67-1.76) | 1.16 (0.93-1.45) | 1.00 (0.76-1.34) | **1.07 (1.07-1.07)*** | **1.11 (1.02-1.22)*** | 1.13 (0.95-1.34) | 1.06 (0.98-1.15) | 1.00 (1.00-1.00) | 1.04 (0.97-1.11) | **1.00 (1.00-1.00)*** |
| Nausea and vomiting (per 10 points) | **1.00 (1.00-1.01)*** | **1.22 (1.12-1.33)*** | **1.22 (1.11-1.34)*** | 1.29 (0.85-1.96) | 1.97 (0.77-1.87) | 1.14 (0.85-1.52) | **1.27 (1.16-1.40)*** | **1.23 (1.15-1.32)*** | 1.22 (0.86-1.71) | 1.11 (0.97-1.27) | 1.03 (0.99-1.07) | **1.10 (1.06-1.14)*** | **1.00 (1.00-1.00)*** |
| **Adjusted cox regression[b] HR (99%CI)** | | | | | | | | | | | | | |
| Role functioning (per 10 points) | **0.86 (0.83-0.89)*** | **0.87 (0.83-0.91)*** | **0.86 (0.81-0.91)*** | 0.99 (0. 46-2.13) | 0.85 (0.68-1.06) | 1.03 (0.66-1.03) | 0.93 (0.78-1.11) | **0.85 (0.79-0.92)*** | 0.87 (0.72-1.06) | 0.85 (0.60-1.20) | **0.89 (0.87-0.91)*** | **0.92 (0.89-0.94)*** | 0.94 (0.86-1.02) |
| Emotional functioning (per 10 points) | **0.89 (0.86-0.93)*** | **0.91 (0.84-0.98)*** | **0.86 (0.79-0.92)*** | 5.01 (0.20-127.83) | 0.99 (0.70-1.41) | 1.07 (0.72-1.58) | **0.91 (0.87-0.95)*** | 0.96 (0.89-1.03) | 0.95 (0.70-1.29) | 0.97 (0.84-1.12) | **0.94 (0.90-0.98)*** | **0.91 (0.91-0.91)*** | **0.85 (0.74-0.98)*** |
| Cognitive functioning (per 10 points) | **0.93 (0.91-0.95)*** | **0.93 (0.87-0.99)*** | 0.94 (0.86-1.02) | 1.11 (0.38-3.25) | 0.98 (0.75-1.29) | 1.04 (0.69-1.54) | 0.97 (0.93-1.01) | **0.96 (0.92-0.99)*** | 1.12 (0.84-1.51) | 0.96 (0.86-1.08) | **0.93 (0.90-0.95)*** | **0.96 (0.95-0.98)*** | **0.91 (0.89-0.94)*** |
| Social functioning (per 10 points) | **0.88 (0.85-0.91)*** | **0.88 (0.83-0.94)*** | **0.89 (0.84-0.95)*** | 0.71 (0.22-2.30) | 1.02 (0.74-1.41) | 1.12 (0.74-1.69) | **0.90 (0.83-0.97)*** | **0.84 (0.78-0.90)*** | 0.96 (0.74-1.23) | 0.91 (0.82-1.02) | **0.92 (0.91-0.93)**** | **0.88 (0.88-0.89)*** | 0.96 (0.88-1.04) |
| Fatigue (per 10 points) | **1.00 (1.00-1.00)*** | **1.19 (1.12-1.26)*** | **1.17 (1.17-1.09)*** | 1.52 (0.68-3.41) | 1.07 (0.84-1.35) | 0.86 (0.56-1.32) | 1.08 (0.90-1.29) | **1.15 (1.10-1.22)**** | 1.22 (0.95-1.55) | 1.00 (0.99-1.01) | **1.00 (1.00-1.00)*** | **1.11 (1.08-1.14)*** | **1.08 (1.06-1.11)*** |
| Pain (per 10 points) | 1.00 (1.00-1.00) | **1.07 (1.01-1.13)*** | **1.09 (1.02-1.17)*** | 0.92 (0.43-1.98) | 1.08 (0.83-1.39) | 0.95 (0.66-1.35) | 1.02 (0.95-1.09) | 1.07 (0.98-1.16) | 1.13 (0.89-1.43) | 1.12 (0.94-1.35) | 0.98 (0.99-1.00) | 1.06 (0.97-1.16) | 1.00 (1.00-1.00) |
| Nausea and vomiting (per 10 points) | 1.00 (0.99-1.00) | **1.22 (1.12-1.34)*** | **1.20 (1.08-1.34)*** | 2.57 (0.89-7.77) | 1.02 (0.65-1.61) | 1.22 (0.90-1.65) | **1.13 (1.02-1.25)*** | **1.13 (1.03-1.23)*** | 1.08 (0.77-1.52) | **1.91 (1.04-3.51)*** | 1.01 (0.97-1.06) | **1.27 (1.22-1.32)*** | 1.00 (0.99-1.00) |

[a]Analyses included multiple studies/cohorts and were therefore cluster-adjusted for study

[b]adjusted for covariates: age, sex, disease stage, treatments received, number of comorbid conditions, partner, educational level, employment status

EORTC QLQ-C30= European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30; QoL= Quality of Life; HR = Hazard Ratio; CI = confidence interval

HR is significant at $p < 0.01$.

Online appendix 2: Likelihood ratio tests of Cox regression analyses for other EORTC QLQ-C30 scales

| | **Total[a]** | **Colon cancer** | **Rectal cancer** | **Melanoma** | **Basal/squamous cell cancer** | **Endometrial cancer** | **Ovarian cancer[a]** | **Prostate cancer[a]** | **Thyroid cancer** | **Hodgkin lymphoma[a]** | **Non-Hodgkin lymphoma[a]** | **Chronic Lymphocytic leukemia[a]** | **Multiple myeloma[a]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N=6895** | **N=1487** | **N=960** | **N=222** | **N=614** | **N=140** | **N=344** | **N=1097** | **N=285** | **N=197** | **N=1051** | **N=272** | **N=226** |
| **Unadjusted cox regression, -2 Log Likelihood ratio** | | | | | | | | | | | | | |
| Role functioning | | | | | | | | | | | | | |
| *Full model* | **21118.8 -** | **4079.3 -** | **2539.6 -** | 42.7 - | 257.6 - | 231.8 - | **1060.9 -** | **1795.7 -** | 221.9 - | 182.7 - | **3143.5 -** | 759.3 - | 1250.8 - |
| *Null model* | **21453.6*** | **4147.2*** | **2586.9**** | 42.9 | 263.7 | 232.2 | **1076.6*** | **1852.1*** | 227.723 | 182.7 | **3174.8*** | 763.7 | 1256.9 |
| Emotional functioning | | | | | | | | | | | | | |
| *Full model* | **21383.0 -** | **4138.4 –** | **2565.8 -** | 41.8 - | 2634 | 232.2 - | **1065.5 -** | **1844.4 -** | 227.7 - | 182.7 - | 3171.0 - | 763.1 - | 1251.2 - |
| *Null model* | **21454.0*** | **4147.2*** | **2586.9*** | 42.9 | - 263.7 | 232.2 | **1076.6*** | **1852.1*** | 227.7 | 182.7 | 3174.8 | 763.7 | 1258.5 |
| Cognitive functioning | | | | | | | | | | | | | |
| *Full model* | **21402.2 -** | **4134.5 -** | 2581.7 - | 42.9 - | 259.7 - | 229.4 - | 1075.8 - | 1839.8 - | 227.6 - | 182.7 - | **3167.2 -** | 763.3 - | 1253.1 - |
| *Null model* | **21453.8*** | **4147.2*** | 2586.9 | 42.9 | 263.7 | 232.2 | 1076.6 | 1852.1 | 227.7 | 182.7 | **3174.8*** | 763.7 | 1256.9 |
| Social functioning | | | | | | | | | | | | | |
| *Full model* | **21303.7 -** | **4115.5 -** | **2566.1 -** | 42.9 - | 263.3 - | 231.6 - | **1059.1 -** | **1823.2 –** | 227.7 - | 182.1 - | **3167.4 -** | 760.0 - | 1255.5 - |
| *Null model* | **21454.0*** | **4147.2*** | **2586.9*** | 42.9 | 263.7 | 232.2 | **1076.6*** | **1852.1*** | 227.7 | 182.6 | **3175.3*** | 763.7 | 1256.9 |
| Fatigue | | | | | | | | | | | | | |
| *Full model* | 21470.6 - | **4075.5 -** | **2546.3 -** | 40.6 - | 259.6 - | 231.4 - | **1063.4 -** | **1810.7 -** | 225.7 - | 182.6 - | 3174.9 - | 761.9 - | 1261.3 - |
| *Null model* | 21471.0 | **4147.2*** | **2586.9*** | 42.9 | 263.7 | 232.2 | **1076.6*** | **1852.1*** | 227.7 | 182.7 | 3175.3 | 763.7 | 1267.1 |
| Pain | | | | | | | | | | | | | |
| *Full model* | 21469.1 - | **4136.6 -** | **2577.3 –** | 42.6 - | 261.3 - | 232.2 - | 1072.6 - | **1839.2 -** | 224.9 - | 182.2 - | 3175.3 - | 763.1 - | 1267.0 - |
| *Null model* | 21470.6 | **4147.2*** | **2586.9*** | 42.9 | 263.7 | 232.2 | 1076.6 | **1852.1*** | 227.7 | 182.6 | 3175.3 | 763.7 | 1267.1 |
| Nausea and vomiting | | | | | | | | | | | | | |
| *Full model* | 21465.5 - | **4120.8 -** | **2567.4 -** | 41.4 - | 262.9 - | 231.2 - | **1050.9 -** | **1839.3 -** | 226.0 - | 182.4 - | 3174.1 - | 762.5 - | 1267.0 - |
| *Null model* | 21470.6 | **4147.2*** | **2586.9*** | 42.9 | 263.7 | 232.2 | **1076.6*** | **1852.1*** | 227.7 | 182.6 | 3175.3 | 763.7 | 1267.1 |
| **Adjusted cox regression[b], -2 Log Likelihood ratio** | | | | | | | | | | | | | |
| Role functioning | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Full model* | **20006.5 -** | **3873.5 -** | **2411.9 -** | 27.7 - | **223.1 -** | **172.1 -** | **936.4 -** | **1626.3 -** | **168.5 -** | **135.7 -** | **2888.5 -** | **680.7 -** | **1191.6 -** |
| *Null model* | **20953.5*** | **4086.3*** | **2583.4*** | 42.6 | **262.8*** | **230.5*** | **1022.8*** | **1784.4*** | **227.4*** | **182.5*** | **3039.0*** | **740.7*** | **1224.2*** |
| Emotional functioning | | | | | | | | | | | | | |
| *Full model* | **20185.3 -** | **3912.9 -** | **2429.2 -** | 23.2 - | **226.3 -** | **171.9 -** | **936.8 -** | **1655.1 -** | **171.3 -** | **136.9 -** | **2912.2 -** | **681.5 -** | **1185.9 -** |
| *Null model* | **20954.0*** | **4086.3*** | **2583.4*** | 42.6 | **262.9*** | **230.5*** | **1022.8*** | **1784.4*** | **227.4*** | **182.5*** | **3039.0*** | **740.7*** | **1225.8*** |
| Cognitive functioning | | | | | | | | | | | | | |
| *Full model* | **20225.0 -** | **3915.1 -** | **2451.0 -** | 27.6 - | **226.4 -** | **172.1 -** | **940.4 -** | **1654.9 -** | **170.4 -** | **136.9 -** | **2909.4 -** | **684.0 -** | **1192.6 -** |
| *Null model* | **20953.8*** | **4086.3*** | **2583.4*** | 42.6 | **262.9*** | **230.5*** | **1022.8*** | **1784.4*** | **227.4*** | **182.5*** | **3039.0*** | **740.7*** | **1224.2** |
| Social functioning | | | | | | | | | | | | | |
| *Full model* | **20128.1 -** | **3897.6 -** | **2437.2 -** | 27.2 - | **226.4 -** | **171.6 -** | **933.1 -** | **1633.1 -** | **171.3 -** | **136.5 -** | **2907.5 -** | **678.5 -** | **1196.1 -** |
| *Null model* | **20953.9*** | **4086.3*** | **2583.4*** | 42.6 | **262.9*** | **230.5*** | **1022.8*** | **1784.4*** | **227.4*** | **182.4*** | **3039.7*** | **740.7*** | **1224.2*** |
| Fatigue | | | | | | | | | | | | | |
| *Full model* | **20273.6 -** | **3871.9 -** | **2422.5 -** | 25.7 - | **225.9 -** | **171.3 -** | **937.1 -** | **1639.4 -** | **167.2 -** | **136.9 -** | **2917.0 -** | **679.5 -** | **1202.0 -** |
| *Null model* | **20970.9*** | **4086.3*** | **2583.4*** | 42.6 | **262.9*** | **230.5*** | **1022.8*** | **1784.4*** | **227.4*** | **182.5*** | **3039.5*** | **740.7*** | **1234.3*** |
| Pain | | | | | | | | | | | | | |
| *Full model* | **20275.3 -** | **3916.6 -** | **2445.1 -** | 27.6 - | **225.9 -** | **172.0 -** | **940.6 -** | **1652.5 -** | **169.8 -** | **136.0 -** | **2917.6 -** | **683.0 -** | **1207.8 -** |
| *Null model* | **20970.5*** | **4086.3*** | **2583.4*** | 42.6 | **262.9*** | **230.5*** | **1022.8*** | **1784.4*** | **227.4*** | **182.4*** | **3039.5*** | **740.7*** | **1234.3*** |
| Nausea and vomiting | | | | | | | | | | | | | |
| *Full model* | **20274.2 -** | **3899.4 -** | **2440.0 -** | 23.3 - | **226.4 -** | **169.9 -** | **935.3 -** | **1651.9 -** | **171.2 -** | **133.1 -** | **2917.8 -** | **678.0 -** | **1207.8 -** |
| *Null model* | **20970.5*** | **4086.3*** | **2583.4*** | 42.6 | **262.9*** | **230.5*** | **1022.8*** | **1784.34*** | **227.4*** | **182.4*** | **3039.5*** | **740.7*** | **1234.3*** |

[a]Analyses included multiple studies/cohorts and were therefore cluster-adjusted for study

[b]adjusted for covariates: age, sex, disease stage, treatments received, number of comorbid conditions, partner, educational level, employment status

Likelihood ratio test is significant at $p < 0.01$