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Eur J Cancer. Author manuscript; available in PMC 2014 May 01.

Published in final edited form as:
Eur J Cancer. 2013 May ; 49(8): 1957–1966. doi:10.1016/j.ejca.2013.01.012.

Quantifying fatigue in (long-term) colorectal cancer survivors: a study from the population-based PROFILES registry

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Abstract

Background—Few studies specifically focus on fatigue of (long-term) colorectal cancer (CRC) survivors or compare fatigue levels with a normative population. Association between surviving multiple primary cancers and fatigue is also explored.

Methods—Survivors diagnosed from 1998–2009 were identified from the Eindhoven Cancer Registry. In total, 3739 (79%) respondents and an age- and gender-matched normative population (n=338) completed questionnaires on fatigue and psychological distress.

Results—More survivors reported feeling fatigued than the normative population (39% vs. 22%, p<0.0001). Short-term survivors (<5 years post-diagnosis) had the highest mean fatigue scores compared with long-term survivors (≥5 years post-diagnosis) or the normative population (21±7 vs. 20±7 vs. 18±5, p<0.0001, respectively). Having primary cancers prior to CRC was associated with more fatigue.

Surgery+chemoradiation was independently associated with fatigue (OR: 1.63, 95%CI: 1.17–2.29, p=0.004) as were anxiety (OR: 1.16, 95%CI: 1.12–1.19, p<0.0001) and depressive symptoms (OR: 1.38, 95%CI: 1.33–1.43, p<0.0001).

Conclusions—Fatigue is a significant problem, especially for short-term CRC survivors. The association between chemoradiation and fatigue suggests that patients could benefit from better information on treatment side-effects. When treating fatigue, clinical care should also focus on survivors' psychological needs, especially survivors of multiple primary cancers.

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Conflict of interest
None

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Keywords

colorectal cancer; fatigue; health-related-quality of life; multiple primary cancers; population-based

Introduction

Improved detection and treatment have increased survival after colorectal cancer (CRC).[1,2] In the Netherlands, the number of survivors is projected to increase from 58000 in 2009 to ≈92000 by 2020, of which >50% will be long-term survivors (≥5 years post-diagnosis).[3] With more patients surviving longer, the long-term effects of cancer and its treatment on patients' well-being is of increasing importance.

CRC survivors often report feeling fatigued which could be consequent to their disease and treatment.[4–6] Fatigue can persist long after treatment termination[7] and impacts negatively on quality of life.[8] Breast cancer patients treated with adjuvant therapy report persisting fatigue up to 10 years post-treatment[9] and past chemotherapy treatment has been associated with poorer current quality of life in long-term breast cancer survivors.[10] We postulate that fatigue morbidity will only increase among CRC survivors with the broadening indications and increasing prescription for (neo-)adjuvant treatments.[11,12] Fatigue has been positively correlated with psychological distress among long-term breast and testicular cancer survivors.[13,14] However, few studies look specifically into fatigue and its correlates of (long-term) CRC survivors or compare fatigue levels with a normative population.[15,16]

This study explored fatigue prevalence in a large population-based sample of CRC survivors with up to 10 years after diagnosis and compared fatigue levels with an age- and gender-matched normative population. We also investigated associations of clinical and psychological factors with fatigue. We previously found that multiple primary cancers survivors have poorer health status and more psychological distress than single primary cancer survivors, notably among short-term survivors.[17] Therefore, we were also intrigued if fatigue levels will be associated with surviving previous primary cancers and psychological distress as 1-in-5 CRC survivors have history of a previous primary cancer.[17]

Methods

Setting and Participants

This study pooled data from two patient-reported outcome (PRO) studies conducted in January 2009 and December 2010 on CRC survivors registered in the Eindhoven Cancer Registry (ECR) (Figure 1). Details of studies are reported elsewhere.[18] In both studies, exclusion criteria included cognitive impairment, death prior to start of study (according to the ECR, the Central Bureau for Genealogy and hospital records) or unverifiable addresses. A Medical Ethics Committee approved both studies.

Multiple primary cancer diagnoses, accessed through ECR, were defined as all primary cancer diagnoses *prior* to CRC diagnosis. This study also included all skin cancer diagnoses (except basal cell carcinoma) as possible primary cancer diagnoses.

PRO data was collected via PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) registry.[19] PROFILES is linked directly to clinical data from the ECR, which compiles data of all incident cancer cases in the southern part of the Netherlands, an area with 10 hospitals serving 2.3 million inhabitants.[20]

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Normative population data was accessed from CentERpanel, an online household panel representative of the Dutch population. Details of the annual data collection, started in 2009 by our study group, is described elsewhere.[21] The most recent data wave in 2011 also included a fatigue assessment. From the 2040 (82%) respondents ≥18 years, a random age- and gender-matched normative sample (n=338) was selected for this study, reflecting the distribution of the clinical sample. Sociodemographic data such as age, gender, marital status, and comorbidity were collected.

Data collection

The data collection method of PROFILES has been described.[18,19] In summary, survivors were informed of the study via a letter from their (ex-)attending specialist. Patients were reassured that non-participation had no consequences on follow-up care or treatment. Non-respondents were sent a reminder letter and questionnaire within 2 months.

Fatigue Assessment Scale (FAS)—This 10-item Dutch validated questionnaire assesses how patients *usually* feel about their fatigue. It has good psychometric properties[22] and was previously used with cancer patients.[23] Responses ranged on a 5-point scale (1: never to 5: always).

Hospital Anxiety and Depression Scale (HADS)—Distress was assessed with the HADS questionnaire, with 7 items each assessing anxiety and depression.[24] Caseness for anxiety (HADS-A) or depression (HADS-D) were indicated with 2 cut-off scores: ≥8 [24,25] or ≥11[26] for each subscale.

The ECR routinely collects patients' demographic and clinical data such as date of birth, date of diagnosis, tumor grade,[27] clinical stage,[27] and primary treatment. Comorbidity at time of survey was assessed with the adapted Self-administered Comorbidity Questionnaire (SCQ).[28] Socioeconomic status was determined by an indicator developed by Statistics Netherlands.[29] Patient-reported demographic data included marital status, education, employment, lifestyle factors, weight and height.

PRO data from PROFILES and the normative data will be available for noncommercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

Statistical analyses

We compared the patient and tumor characteristics of respondents, non-respondents and patients with unverifiable addresses, using either t-tests or chi-square analyses. The non-parametric Kruskal-Wallis test was used, where appropriate.

The FAS mean scores of short- and long-term survivors and the normative population were compared with ANCOVA. Confounding variables included for adjustment were determined *a priori*:[30] age at survey, gender, marital status, education, comorbidity at survey (yes/no), HADS-A and HADS-D. ANCOVA analyses with only the survivor groups adjusted for age at survey, gender, marital status, education, socioeconomic status, treatment, multiple primary cancers, comorbidity at survey (yes/no), body mass index, HADS-A and HADS-D.

We made two classifications of the total FAS score as previously done:[31] dichotomous variable, 10–21 (not fatigued) and 22–50 (fatigued); and in tertiles, 10–21 (not fatigued), 22–34 (fatigued) and 35–50 (very fatigued).

Logistic regression models using the dichotomous FAS variable were conducted to identify predictors of fatigue. Predictors were included stepwise into the model: Model 1 consisting

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of demographic variables, clinical variables were added in Model 2 and psychological distress variables in Model 3.

Due to multiple testing, statistical differences were indicated at $p<0.01$. Reported p-values were two-sided. Clinically meaningful differences were determined with Norman's 'rule of thumb', using ≈0.5 SD difference to indicate a threshold discriminant change in scores.[32] All statistical analyses were performed using SAS (version 9.2 for Windows, SAS institute Inc., Cary NC).

Results

From both data collection periods, 4968 eligible survivors received study invitations, of whom 933 did not respond and 490 had non-verified addresses. Comparisons between respondents, non-respondents and survivors with non-verified addresses are reported elsewhere.[18] In short, non-respondents were significantly older, female, were diagnosed with colon cancer, had stage II disease, and were more often treated with surgery only. Patients with non-verified addresses had longer survival time.

Excluded from the 2010 study were 14 respondents who also completed a questionnaire in 2009, and 44 online questionnaires as these respondents also completed a paper version. There were no significant differences between the 44 online and paper questionnaire responses. Of the respondents, 238 diagnosed with other primary cancers *after* their CRC were excluded from further analyses as subsequent treatment for the new cancers could influence fatigue levels. Final analyses included 3739 (79%) respondents.

Comparisons on clinical characteristics of respondents from the 2009 and 2010 studies stratified by years since diagnosis showed that short-term survivors were more likely to have colon cancer, to be treated with surgery+chemotherapy and had previous primary cancer, while long-term survivors were more likely to have stage I cancer (Table 1). Baseline variables that could be compared with the normative population showed differences on education, employment, comorbidity, and anxiety and depressive symptoms. The normative population was more likely to be higher educated and employed at time of survey. For comorbidity, the normative population was more likely to report back pain, with a trend for osteoarthritis but less likely to have anxiety or depressive symptoms when compared with survivors. A trend significance was also noted on the mean age of the whole sample, with long-term survivors being somewhat older compared with short-term survivors and the normative population.

Survivors were more likely to be classified as fatigued when compared with the normative population (39% vs. 22%, $p<0.0001$) (Table 2). In general, short-term survivors had the highest mean fatigue score and the normative population, the lowest. Adjusted results show statistically and clinically significant differences for the items getting tired very quickly and problems with thinking clearly between the normative population and the short- but not long-term survivors.

Comparison between the survivor groups showed statistically significant but not clinically meaningful differences on two FAS items, with short-term survivors more likely to report getting tired very quickly and not doing much during the day.

Survivors with previous primary cancers, especially among long-term survivors, were more likely to be classified as fatigued or very fatigued compared with survivors of only CRC (short-term: 43% versus 41%; long-term: 40% versus 34%, $p=0.002$) (Figure 2). The normative population was significantly less likely to be classified as fatigued or very fatigued when compared with the survivors ($p<0.0001$).

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Survivors had significantly higher mean HADS-A and HADS-D scores than the normative population (both $p<0.0001$), although these differences were not clinically meaningful (Table 3). Survivors were also more likely to meet the HADS-A and HADS-D cut-off score than the normative population. When limited only to the survivor group, a significantly greater percentage of short-term survivors met the cutoff score of 8 for HADS-D ($p=0.0007$) but not HADS-A than the long-term survivors. No differences between the two clinical groups were found when using the more conservative cut-off score.

Using ≥8 points as cut-off, a significantly greater percentage of short-term survivors with previous primary cancers met the HADS-A (29% vs. 20–22%, $p<0.0001$) and HADS-D (27% vs. 13–22%, $p=0.0007$) cut-off scores than short-term survivors without multiple cancer diagnoses and long-term survivors with/without multiple cancer diagnoses. When the cut-off score was ≥11, no differences in psychological distress were found in short- or long-term survivors, with or without multiple cancer diagnoses. On the SCQ, similar depression prevalence rates in the past 12 months were found for the three groups (short-term: 6% vs. long-term: 6% vs. norm: 4%, $p=0.1$). Among survivors who reported having had depression in the past 12 months, 57% short-term survivors, 65% long-term survivors and 75% normative population reported receiving treatment ($p=0.2$). Regarding the burden of depression, a greater percentage of short- and long-term survivors (57% and 54%, respectively) than normative population (33%) felt that depression interfered with their activities, although this difference was not significant ($p=0.2$).

Logistic regression

Model 1 consisting of only socio-demographic variables showed that higher education (odds ratio (OR): 0.61, 95% confidence interval (CI):0.50–0.74, $p<0.0001$), high socioeconomic status (OR: 0.77, 95% CI: 0.66–0.89, $p=0.0005$) and partnered relationship (OR: 0.73, 95% CI: 0.62–0.86, $p=0.0003$) were associated with lower fatigue risk (Table 4).

With the inclusion of clinical variables in Model 2, education and relationship status remained significantly associated with fatigue. The significance of socioeconomic status decreased to a trend ($p=0.01$) while age at survey showed a trend significance whereby older age was associated with less fatigue (OR: 0.99, CI: 0.98–1.00, $p=0.01$). Among the clinical variables, short-term survivorship (OR: 1.29, 95%CI: 1.11–1.49, $p=0.001$) and comorbid conditions (OR: 1.95, 95% CI: 1.65–2.31, $p<0.0001$) were significantly associated with fatigue. Increasing BMI (OR: 1.02, 95%CI: 1.00–1.04, $p=0.02$) and surgery+chemoradiation (OR: 1.36, 95%CI: 1.03–1.81, $p=0.03$) showed a trend significance for increased fatigue. Previous primary cancers were not associated with fatigue.

In Model 3, HADS-A (OR: 1.16, 95%CI: 1.12–1.19, $p<0.0001$) and HADS-D (OR: 1.38, 95%CI: 1.33–1.43, $p<0.0001$) showed strong association with fatigue. Following these psychological factors inclusion, age at survey remained significant while gender gained almost to trend significance (OR: 0.80, 95%CI: 0.66–0.96, $p=0.02$), whereby being male was associated with less fatigue. As for clinical variables, comorbidity (OR: 1.50, 95%CI: 1.22–1.84, $p<0.0001$) remained significant in this model albeit with strongly decreased OR as compared with Model 2. Improved significance was noted for BMI (OR: 1.03, 95%CI: 1.01–1.05, $p=0.007$), and surgery+chemoradiation (OR: 1.63, 95%CI: 1.17–2.29, $p=0.004$) whereby the OR for treatment increased from 1.36 in Model 2.

A subanalysis using only survivors classified as either not fatigued or very fatigued showed a significance for age (OR: 0.96, 95%CI: 0.93–0.98, $p=0.001$), HADS-A (OR: 1.21, 95%CI: 1.13–1.30, $p<0.0001$) and HADS-D (OR: 1.80, 95%CI: 1.64–1.98, $p<0.0001$) in the full model.

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Discussion

This large population-based study among CRC survivors showed that fatigue remains a significant problem even up to 10 years post-diagnosis. In general, regardless of time since diagnosis, CRC survivors reported significantly higher levels of fatigue when compared with an age- and gender-matched normative population. Clinically meaningful differences were found for getting tired quickly and problems with clear thinking. Short-term CRC survivors, especially those with multiple cancer diagnoses, were more likely to report feeling very fatigued compared with long-term survivors. Patients who were younger, had comorbid conditions, and higher HADS-A and HADS-D scores were more likely to report feeling fatigued.

The survivor group had higher levels of fatigue than the normative population which is consistent with other studies on long-term CRC survivors compared with a control group.[15,16] In our sample, 39% of survivors were classified as fatigued or very fatigued. This is comparable to a population-based study of older survivors of colorectal, breast and prostate cancers which approximately 38% reported feeling either little or no energy in a typical week.[33]

Treatment with chemoradiation was strongly associated with fatigue which is in line with previous study on breast cancer survivors.[9] Furthermore, survivors were more likely to report problems thinking clearly than the normative population. This finding suggests cognitive impairments associated with chemotherapy or in combination with other therapies, a phenomenon commonly known as ‘chemobrain’. Cognitive dysfunction consequent to (neo)adjuvant therapy is well studied in breast cancer. Breast cancer patients treated with chemotherapy reported problems with both fatigue and cognitive function up to 2 years post-diagnosis.[34] However a recent review reported that the association between treatment and subjective cognitive dysfunction in breast cancer survivors was inconclusive.[35] Studies on the associations of chemotherapy, cognitive impairment and fatigue among CRC survivors are rare, and even more so among long-term survivors. A murine study on two commonly used chemotherapeutic agents for CRC, oxaliplatin and 5-fluorouracil, found an association with impaired cognitive function.[36]

Survivors with history of previous cancers were more likely to be fatigued or very fatigued. Of interest is the high percentage (40%) of long-term survivors of multiple primary cancers who still feel fatigued years after their last cancer diagnosis. This prevalence is comparable to short-term survivors with (43%) or without (41%) previous cancer diagnoses. Could there be a biologic explanation? Cancer symptoms such as fatigue has been associated with inflammation processes started by the disease and its treatment.[37] A longitudinal study of gastrointestinal cancer patients undergoing chemoradiation found that overexpression of pro-inflammatory cytokines such as sTNF-R1 and IL-6 was associated with fatigue development over course of treatment.[6] Sarcoidosis patients up to 10 years in remission who were still fatigued have less production of the anti-inflammatory Th2 cytokine than their non-fatigued counterparts.[38] Therefore could multiple primary cancer survivors exposed to repeated treatments have residual low-grade inflammation that could increase fatigue?

Anxiety and depressive symptoms were strongly associated with fatigue, consistent with other studies.[13,14] The association between psychological distress and fatigue could be confounded by gender as the significance of this variable improved to almost trend significance after psychological distress variables were included in the regression model.

When the cut-off score of ≥8 was used, short-term survivors with previous primary cancers were most likely to report anxiety or depressive symptoms. This is understandable given that disease progression and need for further treatment could increase psychological distress.

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From the SCQ, only 6% of the short-term survivors reported they had depression within the last 12 months while the HADS results indicate about 20% of survivors would meet HADS-A and HADS-D cut-off scores of ≥8. Furthermore, only 57% of those short-term survivors with depression on the SCQ reported being treated for their depression in comparison to the 75% reported by the normative population. However, when the more conservative cut-off score of ≥11 was used, levels of psychological distress was comparable between short- and long-term survivors. Furthermore, prevalence of depression on the HADS-D using the higher cut-off score was comparable with that on the SCQ. Taken together, this suggests that psychological distress, especially subclinical levels (as identified with the lower HADS cut-off score) could be under-recognized and under-treated in this sample.

Our results have clinical implications. Broadening indication for (neo-)adjuvant treatments in CRC indicate that patients need to be better informed of (late) side effects such as fatigue. Survivors of multiple primary cancers were more likely to have problems with fatigue years after last diagnosis. Furthermore, these survivors (especially short-term) were more likely to meet indicators for psychological distress which were found to be strongly associated with fatigue. Therefore when treating fatigue, clinical practice needs to increase attention to survivors' psychological needs especially survivors who have survived multiple primary cancers as this is no longer a rare clinical picture.

Study limitations include the unavailability of fatigue information from non-respondents and survivors with unverified addresses for comparison and its possible effects on current results remain unknown. In addition, the cross-sectional study design limits the determination of causal association between cancer-related factors and fatigue.

Nevertheless, the present study provides an important contribution to the limited data on fatigue of (long-term) CRC survivors. Strengths of this study include its population-based design with a high response rate from a large sample. Furthermore, we were able to compare fatigue levels with an age- and gender-matched normative sample. Although psychological distress was strongly associated with fatigue, there is evidence to suggest clinical factors such as treatment or getting a new cancer as contributing factors. Further research on potential underlying biologic mechanisms of fatigue among various cancer survivors followed over a longer period of time is needed.

Acknowledgments

Funding

Research supported in part by a Social Psychology Fellowship from the Dutch Cancer Society (#UVT2011-4960) to Melissa Thong, a VENI grant (#451-10-041) from the Netherlands Organization for Scientific Research (The Hague, The Netherlands) to Floortje Mols, a Cancer Research Award from the Dutch Cancer Society (#UVT-2009-4349) to Lonneke van de Poll-Franse, by the MD Anderson Cancer Center Support Grant CA016672 to Ronald DePinho and by NCI R01 CA026582 to Charles S. Cleeland. Comprehensive Cancer Centre South, Eindhoven, the Netherlands; and an Investment Subsidy (#480-08-009) of the Netherlands Organization for Scientific Research (The Hague, The Netherlands) funded data collection. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

We thank all participating patients and doctors. Special thanks to our independent advisor: Dr. M. van Bommel. Thanks to the co-operation of following hospitals: Amphia Hospital, Breda; Bernhoven Hospital, Veghel/Oss; Catharina Hospital, Eindhoven; Elkerliek Hospital, Helmond; Jeroen Bosch Hospital, 's Hertogenbosch; Maxima Medical Centre, Eindhoven/Veldhoven; Sint Anna Hospital, Geldrop; St. Elisabeth Hospital, Tilburg; Twee Steden Hospital, Tilburg/Waalwijk; Viecuri Hospital, Venlo/Venray.

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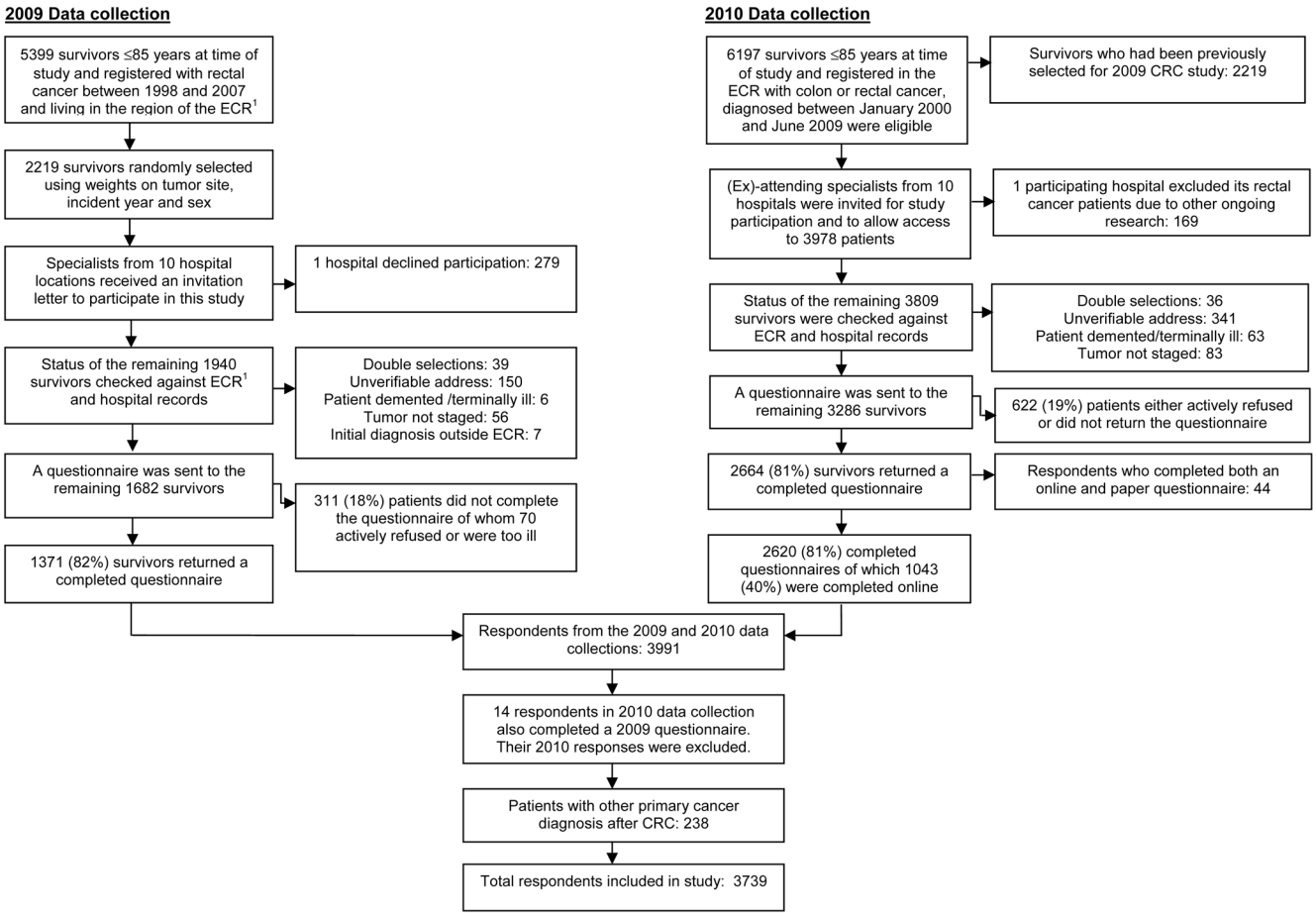

Figure 1.
Flowchart of the patient selection
[1]ECR: Eindhoven Cancer Registry

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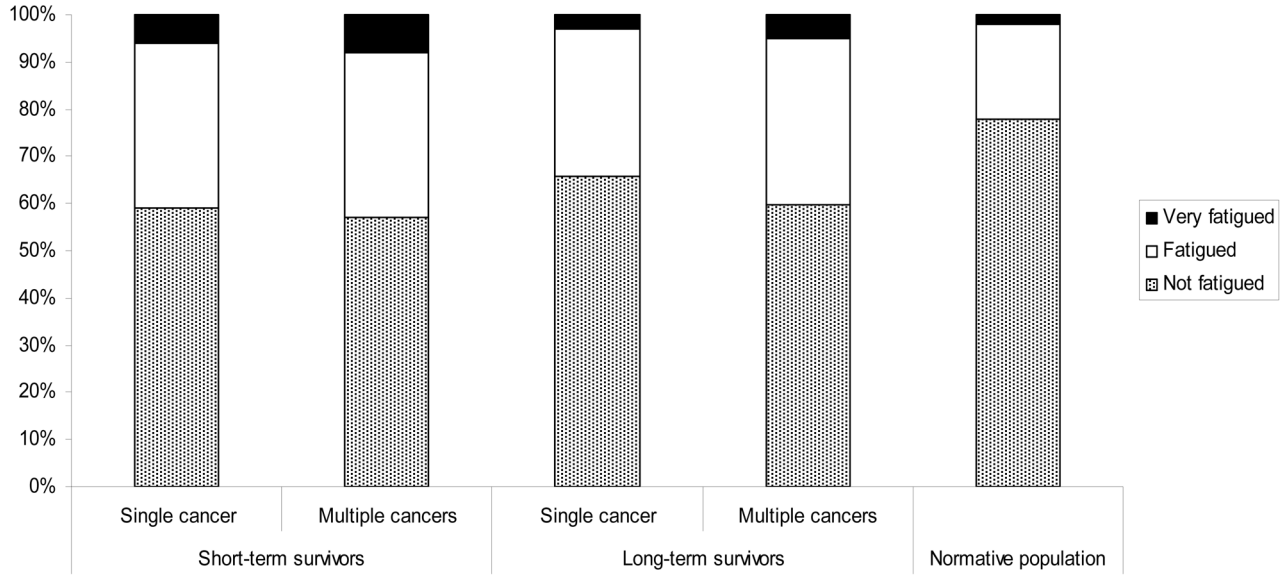

Figure 2.

% Colorectal cancer survivors stratified by years since last diagnosis (short-term: <5 years; long-term: ≥5 years) and multiple primary cancer, and normative population by fatigue levels. FAS total score cut-offs: not fatigued (10–21), fatigued (22–34), very fatigued (35–50).[22,31]

Significant differences noted between the survivors and normative population (p<0.0001) and between short- and long-term survivors with/out multiple primary cancers (p=0.002).

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Table 1

Clinical and demographic characteristics of colorectal cancer survivors stratified by time since diagnosis and the normative population

n (%)	<5 years (n=2320)	≥5 years (n=1419)	Norm (n=338)	*p*-value
Colon cancer	1494 (64)	837 (59)	n.a	**0.001**
Treatment			n.a	**<0.0001**
SU only	1091 (47)	746 (53)		
SU+RT	494 (21)	319 (22)		
SU+CT	535 (23)	245 (17)		
SU+RT+CT	165 (7)	105 (7)		
CT only	24 (1)	1 (0.1)		
RT only	2 (0.1)	1 (0.1)		
Tumor stage			n.a	**<0.0001**
1	624 (27)	470 (33)		
2	826 (36)	543 (38)		
3	668 (29)	369 (26)		
4	158 (7)	23 (2)		
Unknown	44 (2)	14 (1)		
Tumor grade			n.a	0.04
1	169 (7)	118 (8)		
2	1432 (62)	881 (62)		
3	269 (12)	193 (14)		
4	3 (0.1)	1 (0.1)		
Unknown	447 (19)	226 (16)		
Previous primary cancer diagnosis/es (Yes)	310 (13)	139 (10)	n.a	**0.001**
Comorbidity at survey				0.2
None	724 (31)	412 (29)	94 (28)	
1	639 (27)	378 (27)	88 (26)	
> 1	957 (41)	629 (44)	156 (46)	
Most common comorbid conditions at survey				
Heart disease	395 (17)	262 (18)	63 (19)	0.4
Hypertension	729 (31)	472 (33)	114 (34)	0.4
Diabetes	302 (13)	186 (13)	38 (11)	0.6
Osteoarthritis	547 (24)	365 (26)	104 (31)	0.01
Back pain	562 (24)	370 (26)	110 (32)	**0.004**
Mean age at survey (±SD)	69±10	70±10	68±11	0.01
Median years since colorectal cancer diagnosis (IQR)	2.6 (2.1–3.4)	7.6 (6.3–9.1)		
Male	780 (57)	580 (53)	188 (56)	0.09
Married/cohabitating	1753 (76)	1026 (72)	240 (71)	0.03
Education[a]				**<0.0001**
Low	464 (20)	275 (20)	24 (7)	
Medium	1352 (60)	839 (60)	180 (53)	

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n (%)	<5 years (n=2320)	≥5 years (n=1419)	Norm (n=338)	*p*-value
High	443 (20)	274 (20)	134 (40)	
Employment				**0.001**
Working at time of survey	362 (16)	218 (16)	71 (21)	
Socioeconomic status			n.a	0.33
Low	481 (21)	271 (19)		
Medium	917 (41)	569 (41)		
High	800 (36)	535 (38)		
BMI			n.a	0.4
<18.5	30 (1)	14 (1)		
18.5–24.9	753 (33)	491 (36)		
25.0–29.9	1077 (48)	645 (47)		
≥30	389 (17)	223 (16)		
Currently smoke	259 (11)	147 (11)	n.a	0.3
Currently consume alcohol	1229 (63)	800 (66)	n.a	0.3

Some variables exceed 100% due to rounding off; some variables do not add up to 100% due to missing data.

[a]Education: Low (no or primary school); Medium (lower general secondary education or vocational training); High (pre-university education, high vocational training, university)

n.a.: these items were not assessed in the normative population

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Eur J Cancer. Author manuscript; available in PMC 2014 May 01.

Table 2

Mean fatigue scores (± SD) of colorectal cancer survivors by years since diagnosis and the normative population

FAS items (range: 1–5)	**<5 years (n=2320)**	**≥5 years (n=1419)**	**Norm (n=338)**	***p*-value**	
				Only survivors[a]	**Norm+ survivors[b]**
I am bothered by fatigue	2.4±1.0	2.3±1.0	2.0±0.8	0.3	**<0.0001**
I get tired very quickly	2.4±1.1[c]	2.2±1.0	1.8±0.9	**0.0005**	**<0.0001**
I do not do much during the day	2.3±1.1	2.1±1.0	1.9±1.0	**<0.0001**	**<0.0001**
I have enough energy for everyday life *	2.8±1.4	2.7±1.4	2.6±1.4	0.9	0.9
Physically, I feel exhausted	1.8±1.0	1.7±0.9	1.5±0.7	0.6	**0.003**
I have problems starting things	2.0±1.0	1.8±0.9	1.7±0.8	0.1	0.01
I have problems thinking clearly	1.7±0.9[c]	1.6±0.8	1.3±0.6	0.2	**<0.0001**
I feel no desire to do anything	2.0±0.9	1.9±0.8	1.7±0.8	0.02	**0.003**
Mentally, I feel exhausted	1.6±0.9	1.5±0.8	1.3±0.6	0.2	0.03
When I am doing something, I can concentrate quite well *	2.3±1.4	2.3±1.4	2.3±1.3	0.8	0.4
FAS mean total score	21±7	20±7	18±5	0.1	**<0.0001**
%Responders who meet the ≥22 cut-off score for fatigue[31]					
Fatigued	917 (41)	477 (35)	73 (22)		**<0.0001**

[a] *p*-values adjusted for: age at survey, gender, marital status, education, socioeconomic status, treatment, multiple primary cancers, comorbidity, body mass index, HADS-A and HADS-D.

[b] *p*-values adjusted for: age at survey, gender, marital status, education, comorbidity, HADS-A and HADS-D.

[c] Clinically meaningful difference[32] detected between indicated survivors and the normative population.

* Items are reversed scored

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Table 3

Mean scores (± SD) and respondents (%) with anxiety and depressive symptoms

HADS	<5 years (n=2320)	≥5 years (n=1419)	Norm (n=338)	*p*-value
HADS-A	4.8±3.8	4.5±3.8	3.4±3.2	**<0.0001**[a]
HADS-D	4.9±3.7	4.3±3.6	3.8±3.1	**<0.0001**[a]
% above the ≥8 clinical cut-off[24,25]				
HADS-A	22	20	10	**<0.0001**
HADS-D	22	18	12	**<0.0001**
% above the *≥11 clinical cut-off*[26]				
HADS-A	10	8	3	**<0.0001**
HADS-D	9	7	3	**0.0007**

[a] *p*-values for mean HADS-A and HADS-D scores were adjusted for: age at survey, gender, marital status, education and comorbidity.

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Table 4

Logistic model of factors associated with fatigue

		Model 1 (demographics)			Model 2 (Model 1+clinical)			Model 3 (Model 2+psychological)		
		OR	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Block 1 (demographic variables)	Age at survey	0.99	0.99–1.00	0.06	0.99	0.98–1.00	0.01	**0.98**	**0.97–0.99**	**<0.0001**
	Male vs. female	0.89	0.77–1.03	0.1	0.91	0.78–1.06	0.2	0.80	0.66–0.97	0.02
	High vs. medium/low education	**0.61**	**0.50–0.74**	**<0.0001**	**0.61**	**0.50–0.75**	**<0.0001**	0.85	0.67–1.09	0.2
	High vs. medium/low socioeconomic status	**0.77**	**0.66–0.89**	**0.0005**	**0.82**	**0.70–0.96**	**0.01**	0.84	0.70–1.02	0.07
	Partner vs. no partner	**0.73**	**0.62–0.86**	**0.0003**	**0.72**	**0.60–0.86**	**0.0002**	0.83	0.67–1.04	0.1
Block 2 (clinical variables)	Short- vs. long-term survivors				**1.29**	**1.11–1.49**	**0.001**	1.12	0.94–1.35	0.2
	BMI				1.02	1.00–1.04	0.02	**1.03**	**1.01–1.05**	**0.007**
	Comorbidity vs. none				**1.95**	**1.65–2.31**	**<0.0001**	**1.50**	**1.22–1.84**	**0.0001**
	SU+RT vs. SU				1.14	0.94–1.37	0.2	1.19	0.94–1.49	0.1
	SU+CT vs. SU				1.15	0.95–1.39	0.1	1.22	0.96–1.54	0.1
	SU+RT+CT vs. SU				1.36	1.02–1.81	0.03	**1.63**	**1.17–2.29**	**0.004**
	Multiple vs. single primary cancer				1.09	0.88–1.36	0.4	1.07	0.81–1.41	0.6
Block 3 (psychological variables)	HADS-A							**1.16**	**1.12–1.19**	**<0.0001**
	HADS-D							**1.38**	**1.33–1.43**	**<0.0001**

OR: odds ratio; CI: confidence interval.

Continuous variables: time since diagnosis, age at survey, body mass index, HADS-A, HADS-D.

SU: surgery; RT: radiotherapy; CT: chemotherapy