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ORIGINAL ARTICLE

Long-term fatigue and quality of life among epithelial ovarian cancer survivors: a GINECO case/control VIVROVAIRE I study

F. Joly[1,2,3,4*], D. Ahmed-Lecheheb[1,2], E. Kalbacher[5], N. Heutte[6], B. Clarisse[6], J. M. Grellard[6], F. Gernier[2,6], D. Berton-Rigaud[7], O. Tredan[8], M. Fabbro[9], A. M. Savoye[10], J. E. Kurtz[11], J. Alexandre[12], P. Follana[13], V. Delecroix[14], N. Dohollou[15], C. Roemer-Becuwe[16], G. De Rauglaudre[17], A. Lortholary[18], K. Prulhiere[19], A. Lesoin[20], A. Zannetti[21], S. N'Guyen[22], S. Trager-Maury[23], L. Chauvenet[24], S. Abadie Lacourtoisie[25], A. Gompel[26], C. Lhommé[27], A. Floquet[28] & P. Pautier[27]

[1]Department of Oncology, Centre François Baclesse, Caen; [2]INSERM, U1086, Caen; [3]UMR-S1077, University of Caen Basse-Normandie, Caen; [4]Department of Oncology, CHU de Caen, Caen; [5]Department of Oncology, CHU Jean Minjoz, Besançon; [6]Department of Clinical Research, Centre François Baclesse, Caen; [7]Department of Oncology, Institut de Cancérologie de l'Ouest, Site René Gauducheau, Saint Herblain; [8]Department of Oncology, Centre Léon Bérard, Lyon; [9]Department of Oncology, Institut Régional du Cancer, Montpellier; [10]Department of Oncology, Institut Jean Godinot, Reims; [11]Department of Oncology, Hôpitaux Universitaires de Strasbourg, Strasbourg; [12]Department of Oncology, Hôpital Cochin, Paris; [13]Department of Oncology, Centre Antoine Lacassagne, Nice; [14]Department of Oncology, Clinique Mutualiste de l'Estuaire, Saint-Nazaire; [15]Department of Oncology, Polyclinique Bordeaux Nord Aquitaine, Bordeaux; [16]Department of Oncology, Centre d'Oncologie de Gentilly, Nancy; [17]Department of Oncology, Institut Sainte Catherine, Avignon; [18]Department of Oncology, Centre Catherine de Sienne, Nantes; [19]Department of Oncology, Institut du Cancer Courlancy, Reims; [20]Department of Oncology, Centre Oscar Lambret, Lille; [21]Department of Oncology, Centre Hospitalier de Cholet, Cholet; [22]Department of Oncology, CH Pau, Pau; [23]Department of Oncology, GHPSO Senlis, Senlis; [24]Department of Oncology, Centre Hospitalier de Sens, Sens; [25]Department of Oncology, Institut de Cancérologie de l'Ouest, Site Paul Papin, Angers; [26]Department of Oncology, Hôpitaux Universitaires Cochin Hôtel-Dieu Broca, Paris; [27]Department of Oncology, Gustave Roussy, Villejuif; [28]Department of Oncology, Institut Bergonié, Bordeaux, France

Correspondence to: Prof. Florence Joly, Department of Oncology, Centre François Baclesse, 3 avenue du Général Harris, 14076 Caen cedex 5, France. Tel: +33-2-31-45-50-02; E-mail: f.joly@baclesse.unicancer.fr

Background: Few data are available on long-term fatigue (LTF) and quality of life (QoL) among epithelial ovarian cancer survivors (EOCS). In this case–control study, we compared LTF, symptoms and several QoL domains in EOCS relapse-free ≥3 years after first-line treatment and age-matched healthy women.

Patients and methods: EOCS were recruited from 25 cooperative GINECO centers in France. Controls were randomly selected from the electoral rolls. All participants completed validated self-reported questionnaires: fatigue (FACIT-F), QoL (FACT-G/O), neurotoxicity (FACT-Ntx), anxiety/depression (HADS), sleep disturbance (ISI), and physical activity (IPAQ). Severe LTF (SLTF) was defined as a FACIT-F score <37/52. Univariate and multivariate logistic regressions were conducted to analyze SLTF and its influencing factors in EOCS.

Results: A total of 318 EOCS and 318 controls were included. EOCS were 63-year-old on average, with FIGO stage I/II (50%), III/IV (48%); 99% had received platinum and taxane chemotherapy, with an average 6-year follow-up. There were no differences between the two groups in socio-demographic characteristics and global QoL. EOCS had poorer FACIT-F scores (40 versus 45, $P < 0.0001$), lower functional well-being scores (18 versus 20, $P = 0.0002$), poorer FACT-O scores (31 versus 34 $P < 0.0001$), and poorer FACT-Ntx scores (35 versus 39, $P < 0.0001$). They also reported more SLTF (26% versus 13%, $P = 0.0004$), poorer sleep quality (63% versus 47%, $P = 0.0003$), and more depression (22% versus 13%, $P = 0.01$). Fewer than 20% of EOCS and controls exercised regularly. In multivariate analyses, EOCS with high levels of depression, neurotoxicity, and sleep disturbance had an increased risk of developing SLTF ($P < 0.01$).

Conclusion: Compared with controls, EOCS presented similar QoL but persistent LTF, EOC-related symptoms, neurotoxicity, depression, and sleep disturbance. Depression, neuropathy, and sleep disturbance are the main conditions associated with severe LTF.

Key words: epithelial ovarian cancer, cancer treatment, long-term survivorship, chronic fatigue, quality of life

Introduction

Epithelial ovarian cancer (EOC) is a serious gynecological malignancy with poor prognosis and high mortality [1]. However, in recent decades, greater surgical expertise and multimodal therapies have improved the survival rate of these patients, amounting 44% at 5 years [2]. Initial treatment includes extended abdominal and pelvic surgery, mostly followed by chemotherapy, usually platinum–taxane combinations with optional bevacizumab [3–5]. During the treatment periods, EOC patients experience a wide range of symptoms that may persist after chemotherapy: fatigue, pain, nausea, vomiting, abdominal discomfort, peripheral neuropathy, change in body image, anxiety, and depressive symptoms [4]. To date, sparse studies have explored patient-reported outcomes (PROs) including quality of life (QoL) and symptoms during post-treatment periods, and the results are conflicting [6]. Indeed, the physical and psychological consequences of EOC and its treatments were shown to be negatively associated with QoL, including fatigue, sleep problems, pain, anxiety, depression, negative self-concept, and reduced feelings of sexuality [7, 8]. Conversely, other studies have reported that most of epithelial ovarian cancer survivor (EOCS) were satisfied with their global QoL, despite persistent psychological and physical symptoms [9, 10].

Long-term fatigue (LTF) has been described as one of the most common and distressing adverse effects of cancer and its treatment [11–13]. Little is known about the prevalence of LTF in EOCS several years after treatment in comparison with age-matched healthy women. As LTF has a major impact on patients' lives and well-being, a clearer understanding of the effect of LTF on QoL in EOCS is needed. To our knowledge, the factors associated with severe LTF (SLTF) have not yet been assessed in a large group of long-term relapse-free EOCS.

Patients and methods

Study design

A multicenter cross-sectional case–control study was carried out between December 2014 and July 2016 in 25 cancer centers from the French cooperative GINECO (National group of investigators for the study of ovarian and breast cancer) group.

The main objective was to compare LTF and other QoL parameters (EOC-related symptoms, neurotoxicity, anxiety, depression, sleep disturbance, and physical activity) between EOCS and age-matched healthy controls. The second objective was to identify various influencing factors of SLTF among EOCS.

Study participants

EOCS were 18-year old, at least free of cancers for ≥3 years after first-line treatment, having received surgery and chemotherapy for an EOC, whatever the stage at diagnosis, without clinical, biological, or radiological relapse documented for ≥3 years after first-line treatment. Eligible EOCS were identified in the databases of the onco-gynecological departments of the GINECO group that participated in the study.

Controls were randomly selected from electoral rolls of four French regions (North-East, North-West, South-East, and South-West) and were age-matched with EOCS (±2 years). Women having a history of cancer or heavy chronic disease were excluded.

PROs instruments. Standardized validated self-administered questionnaires were sent to all participants: fatigue (FACIT-F), QoL (FACT-G/O), neurotoxicity (FACT-Ntx), anxiety/depression (HADS), sleep disturbance (ISI), and physical activity (IPAQ) (supplementary materials S1 and S2, available at *Annals of Oncology* online).

Assessments

EOCS received information from their oncologists during the follow-up consultation or by mail. They were asked to complete the different self-reported PROs questionnaires. A reminder was sent if necessary. EOCS medical data were collected from patient records.

The 2196 randomly selected controls (ratio 5 : 1) were sent an information letter, self-reported questionnaires and a postage-paid return envelope.

Statistical analysis

For sample size determination, we hypothesized an increase in LTF among EOCS in comparison with controls. A 5% absolute difference in FACIT-F score was considered clinically significant. To demonstrate a statistically significant difference δ equal to 2.5 points between EOCS and controls, at least 215 cases and 215 controls should be included [paired Student's *t*-test; standard deviation (σ) = 13, α = 5%, 1 −β = 80%].

Cases and controls were compared using Mc Nemar χ^2 and paired *t*-tests.

Univariate logistic regression analyses were carried out to evaluate associations between SLTF (defined as FACIT-F score <37/52) [14] and age, education level, time since end of cancer treatment, type of chemotherapy, antiangiogenic therapy, comorbidities, current treatments, physical activity, anxiety, depression, neurotoxicity, sleep disturbance, and digestive symptoms. Multivariate logistic regression analyses were carried out to analyze SLTF and its influencing factors in EOCS. Associations between fatigue used as a continuous variable and the different parameters were also assessed using a mixed model (supplementary material S3, available at *Annals of Oncology* online). To minimize the risk of false-positive results, only associations with a *P*-value ≤0.01 were considered as statistically significant. All reported *P*-values are two-sided. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC).

Ethics

This study was approved by the French consultative committee for data processing concerning research and health (CCTIRS) and the French data protection authority (CNIL).

Results

Participants' characteristics

The 354 and 327 completed questionnaires received from EOCS and controls, respectively, allowed to analyze 318 pairs (Figure 1). The participation rate was 85% for EOCS and 17% for controls. More than 50% of the participants had a high level of education and more than 80% were retired at the time of the study (Table 1). Both groups were similar for body mass index (mean BMI 25.6 ± 5 versus 25.2 ± 5kg/m^2, $P = 0.507$; BMI in the obese range: 11% versus 13%). Controls' comorbidities were cardiac disorders (1%, $n = 4$), diabetes (6%, $n = 18$), thyroid disorders (7%, $n = 19$). At survey, controls were consuming psychotropic medications (8%, $n = 17$), sleep medications (10%, $n = 21$), and pain medications (21%, $n = 44$). Clinical

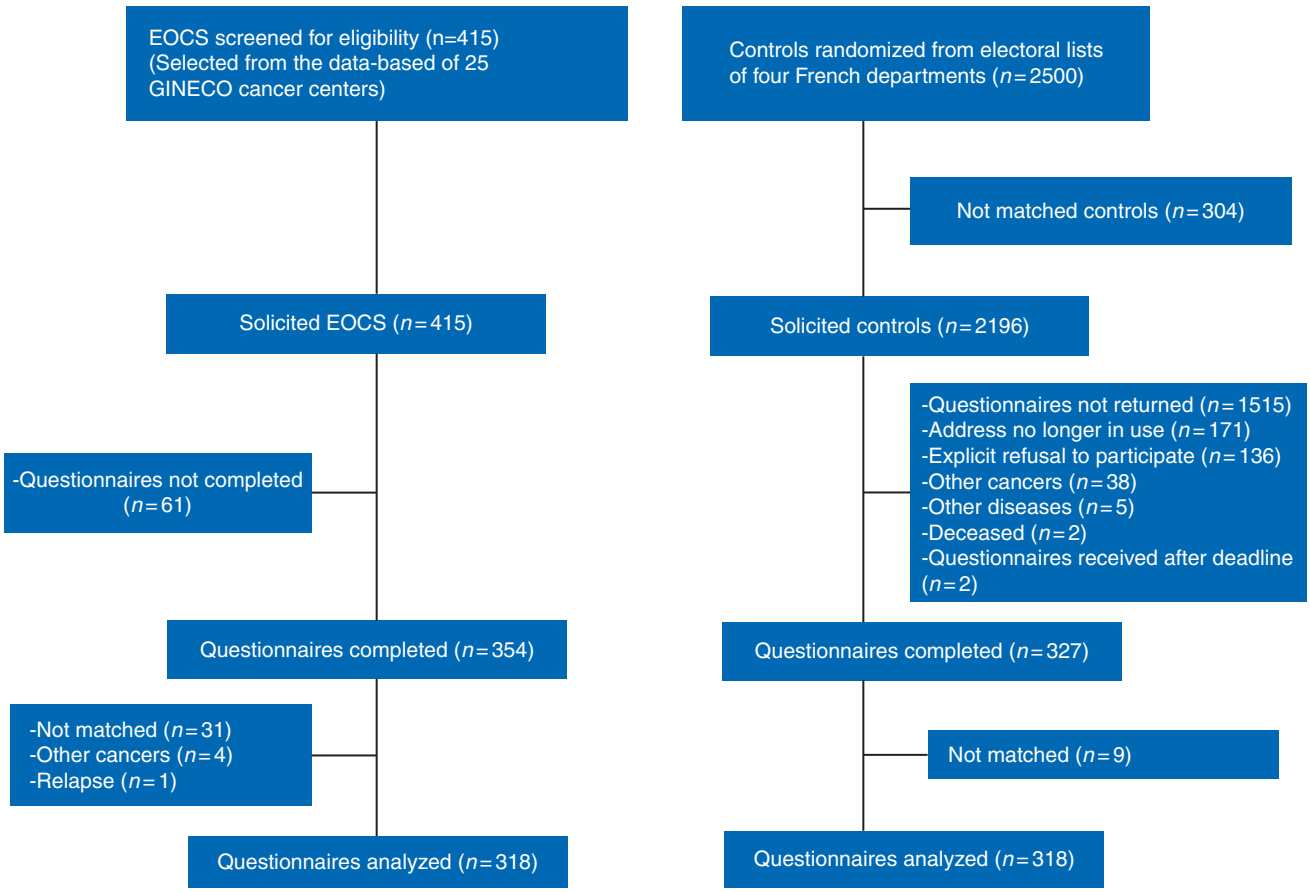

Figure 1. Flowchart of study population. EOCS, epithelial ovarian cancer survivors; GINECO, French group of investigators for the study of ovarian and breast cancer.

characteristics of EOCS are presented in Table 2. The mean time since the end of first-line chemotherapy was 6 years (range 3–24).

Comparison between EOCS and controls

Prevalence of LTF. Compared with controls, EOCS reported significantly higher levels of LTF (mean FACIT-F score: 40 versus 45, $P < 0.0001$), and twice more SLTF, $P = 0.0004$ (Table 3).

Other dimensions of QoL. Compared with controls, EOCS reported significantly poorer levels of FACT-G functional well-being ($P = 0.0002$) and poorer FACT-O scores ($P < 0.0001$). EOCS reported less interest in sex (48.6% versus 72.5%, $P < 0.0001$), but similar satisfaction with their sex life (50% versus 41%, $P = 0.15$).

EOCS reported higher levels of neurotoxicity than controls ($P < 0.0001$), and more complaint about severe neurotoxicity (25% versus 14%, $P < 0.0001$).

EOCS also reported poorer sleep quality (63% versus 47%, $P = 0.0003$), depression (22% versus 13%, $P = 0.01$), and anxiety (53% versus 47%, $P = 0.19$). Both groups reported similar physical activity intensity (around 50% and 20% with moderate/low and high intensity, respectively).

Comparison between EOCS subgroups

Among EOCS, LTF was associated with poorer scores of global QoL (FACT-G scores: 60 versus 80, $P < 0.0001$). FACIT-F scores were not related with cancer stage (stage I-II versus III-IV) or time since end of cancer treatment (<7 versus ≥7 years) (Table 3).

There were no significant differences in levels of LTF, global QoL, neurotoxicity, sleep disturbance, emotional status or physical activity between EOCS with early-stage cancer and advanced-stage EOCS, nor in time since end of cancer treatment (<7 years versus ≥7 years). However, EOCS treated more than 7 years ago reported poorer total FACT-O scores (102 versus 109, $P = 0.01$), and poorer EOC subscale scores (30 versus 32, $P = 0.003$).

The main conditions associated with SLTF among EOCS (univariate and multivariate logistic regression)

In univariate analysis, SLTF was significantly associated ($P < 0.001$) with anxiety and depression, neurotoxicity, sleep disturbance, current psychotropic, and pain medications, higher BMI ($P = 0.01$), physical activity ($P = 0.001$), and comorbidities ($P = 0.003$) (Table 4).

Table 1. Socio-demographic characteristics of EOCS and controls

Characteristics	EOCS $n = 318$ No. (%)	Control group $n = 318$ No. (%)	*P*-value
Age (years)			
Mean±SD	63 ± 11	62 ± 11	
Range	[20–85]	[22–84]	
Education			
High level of education[a]	157 (52)	173 (58)	0.21
Marital status			
Married/in couple	204 (65)	210 (67)	0.09
Employment status			
Employed before disease[b]	162 (52)	145 (47)	0.07
Professional situation at survey			
Retired	97 (82)	104 (88)	0.20
Socio-economic status			
High (>2500€/month)	154 (48)	160 (50)	0.32
Middle (1200–2500€/month)	95 (30)	97 (31)	
Low (<1250€/month)	69 (22)	61 (19)	

[a]High level of education=baccalaureate degree, university or higher education.
[b]For controls: status equivalent at the period of before disease among EOCS group.

In multivariate analyses, depression was the strongest determinant of SLTF [OR = 17.5, 95% CI = (7.8–39.2), $P < 0.0001$]. The two other significant predictors of SLTF were neurotoxicity [OR =6.4, 95% CI = (3.0–13.6), $P < 0.0001$] and sleep disturbance [OR = 3.5, 95% CI = (1.4–8.3), $P = 0.005$]. We globally found the same results when fatigue was analyzed as a continuous variable (supplementary Table S3, available at *Annals of Oncology* online).

Discussion

This large study demonstrates that LTF remains a major issue for EOCS compared with controls. LTF is associated with a decline in functional well-being and EOC treatment-related symptoms. Depression, neurotoxicity, and sleep disturbance are the major predictive factors of SLTF.

Compared with previous studies that explored PROs among EOCS at different stages of the disease [7, 10, 11, 15], our EOCS population was more homogeneous: all patients had received first-line surgery followed by platinum-/taxane-based chemotherapy with a mean 6-year follow-up, and none of them had relapsed. Although long-term EOCS have a global QoL similar to that of controls, they reported poorer LTF scores with more than 25% complaining about high levels of SLTF compared with 13% of controls. EOCS also reported a greater decline in functional well-being and EOC-related symptoms. This is consistent with other studies which argued that despite the persistence of psychological and physical symptoms and treatment sequelae, long-term EOCS are generally satisfied with their global QoL [6].

However, LTF remains a major issue among our population of EOCS. It is also a frequent long-term side-effect reported by survivors of other cancers like testicular [13], breast [16], cervix [17], prostate, and colorectal cancer [18] with similar rates around 25%–28%. Our results corroborate the few available data on LTF in EOCS, as published by Liavaag et al. where LTF was reported by 22% of EOCS with ($n = 59$) and without ($n = 130$) relapses 6 years after diagnosis on average, versus 12% in controls [8]. We also found that EOCS with LTF had a poor global QoL, as in other studies [11, 19].

We found EOCS expressed several other important long-term side-effects: neurotoxicity, sleep disturbance, and depression.

Severe long-term neuropathy, experienced by 25% of our EOCS is often under-evaluated, as reflecting the 51% rate of neuropathy symptoms previously reported among 129 EOCS up to 12 years after carboplatin/paclitaxel, including 20% of relapse and 25% with several lines of chemotherapy [20]. Our results are consistent with published data on survivors of several types of cancers treated with taxanes and platinum derivatives. Indeed, taxanes-induced neuropathy may persist for several years in ~30% of cancer patients [21]. As for the prevalence of neuropathy symptoms amounting 14% in our age-matched control group, it may partly result from the mean age of 62 years or other comorbidities.

Dealing with sleep disturbance, insomnia was reported by 63% of EOCS compared with 47% of controls. Little is known about sleep disturbance in EOCS, and, to our knowledge, without any comparison with controls. Around 2 years after the diagnosis, poor sleep quality was noticed for 67% of 86 EOCS; Sleep disturbance was significantly correlated with poor QoL in all domains but was not correlated with age, time since diagnosis, or number of previous chemotherapy regimens [22]. Another longitudinal study on 108 EOCS with 1-year follow-up highlighted complaint about persistent sleep disturbance for more than 60% of patients without link with depressive symptoms and decline in QoL. Moreover, patients using sleep medications reported poorer

Table 2. Clinical characteristics of EOCS (n = 318)

Characteristics	Value no. (%)
Age at diagnosis (years)	
Mean (±SD) range	56 (±11) [15–81]
Age at menopause	
Mean (±SD) range	49.7 (±5.7) [25–65]
Time since end of chemotherapy (years)	
Mean (±SD) range	6 (±3) [3–24]
Localization	
Ovary	303 (97)
Fallopian tubes	61 (21)
Peritoneum	82 (28)
FIGO stages	
I/II	157 (50)
III/IV	148 (48)
Unknown	6 (2)
Grade	
Low	46 (15)
High	232 (74)
Unknown	33 (11)
Histology	
Serous	145 (49)
Endometrioid	47 (15)
Clear cell	24 (8)
Mucinous	12 (4)
BRCA mutation	
BRCA1	12 (4)
BRCA2	11 (3)
Unknown	169 (54)
Surgery	318 (100)
Completed surgery	218 (68)
Aortic node dissection	89 (88)
Type of chemotherapy	
Paclitaxel/carboplatin (3 weeks)	242 (86)
Paclitaxel/carboplatin (weekly)	37 (13)
Carboplatin mono	1 (0.38)
Antiangiogenic therapy	42 (13)
Most frequent comorbidities	
– High blood pressure	76 (34)
– Hypercholesterolemia	56 (25)
–Depressive syndrome	47 (21)
– Thyroid disease	24 (8)
– Phlebitis	18 (8)
– Diabetes	12 (5)
– Heart disease	11 (5)
–Pulmonary embolism	9 (4)
Current treatments	
– Antidepressants	21 (7)
– Anxiolytics	15 (5)
– Pain medications (opiate)	10 (3)

long-term sleep quality than those who were not taking such medications [23]. Furthermore, depression conferred an increased risk of poor sleep quality. These results highlight the need for continuous screening of sleep disturbance and depression as soon as the diagnosis of EOC is made, and for sleep disturbance interventions in EOCS. As pharmacological treatment seems to have limited efficacy, behavioral interventions should be offered to improve sleep quality and/or depressive symptoms [24].

Although differences are not statistically significant, half of the participants experienced anxiety, whereas depression was more frequently reported by EOCS than controls. EOCS also reported less interest in sex. These findings are in line with those of the literature: most of EOCS experience persistent psychological concerns and sexual inactivity, which do not improve over time [11]. Fewer than 20% of our EOCS and controls exercised regularly, a finding consistent with a recent study conducted in long-term EOCS [15]. Personalized clinical exercise programs were effective in improving fatigue and depression in a heterogeneous population of cancer survivors [25] so they should be promoted in EOCS.

Interestingly, there was no significant difference in LTF, QoL, and side-effects between the EOCS subgroups according to disease stage, thus confirming the findings of Mirabeau-Beal et al. [10]. Most of the two subgroups received the same treatments, which could explain the same range of long-term side-effects. However, whatever the initial stage, patients may adapt to their new life situation over time and develop coping strategies.

Otherwise, a higher correlation of psychological distress with fatigue than with symptoms of distress was reported in a previous meta-analysis of several cancer patients [26]. Our multivariate regression model confirmed that EOCS with high levels of depression, neurotoxicity, and sleep disturbance had an important risk of developing SLTF. Liavaag et al. found a link between LTF and poor body image but not psychological distress. However, sleep quality and neurotoxicity were not assessed, and few patients had depression [8].

Fatigue is a complexity of symptoms modulated by multiple associated factors. The present findings identify some important factors such as depression, sleep disturbance, and neuropathy that contribute to the severity of LTF in EOCS. These somatic and psychological factors should therefore be identified in the follow-up of LTF. They could be detected early and managed during the treatment period to prevent the onset of LTF. The American Society of Clinical Oncology recommends that all cancer patients must be evaluated for the presence of fatigue after completion of primary treatment and be offered specific information and strategies for fatigue management. Physical activity, psychosocial, and mind–body interventions would likely reduce fatigue in cancer survivors [27].

Strengths and limitations

To our knowledge, this is the first large study (using validated self-reported questionnaires) that assessed LTF, global QoL, symptoms, and psychosocial disorders in a homogeneous group of cancer-free EOCS, compared with age-matched controls. The sample size of a rare type of cancer is large, which makes the study unique and gives it sufficient statistical power. In addition, the age-matching of the controls highlights the validity of the findings. The high-response rate of completed questionnaires in EOCS with a mean of 6 years following treatment limits the bias of participation, so the findings can be generalized. The low response rate of controls is in line with similar studies [28]. Furthermore, the study generated a considerable amount of data

Table 3. Comparison of fatigue and QoL between EOCS and controls/EOCS early-stage and advanced-stage/time since end of cancer treatment <7 versus ≥7 years

	Case group	Control group	*P*-value	Clinically significant difference	Early-stage	Advanced-stage	*P*-value	Clinically significant difference	*T**<7 years	*T**≥7 years	*P*-value	Clinically significant difference
Fatigue												
Total FACIT-F score	115.4	115.6	0.6665	**−2.84**	115	116	0.74	−1.04	117	112	0.14	−5.31
FACIT-F subscale score	40	45	**<0.0001**	**−4.52**	39.9	40.9	0.37	−1.04	40.6	40.06	0.67	−0.53
FACIT-F/TOI	81	87	**0.002**	**−7.22**	80	81	0.75	−0.72	81.4	79.5	0.46	−1.88
Severe fatigue < 37 scores *n* (%)	67 (26)	33 (13)	**0.0004**		39 (26)	31 (22)	0.40		47 (22)	24 (28)	0.32	
Global QoL												
Total FACT-G score	76	74	0.83	0.88	76	75	0.70	0.76	77	73	0.06	−4.13
Physical well-being	23	24	0.03	**−1.31**	23	24	0.73	−0.20	23	23	0.58	−0.38
Social/family well-being	18	17	0.10	**1.40**	18	18	0.41	0.51	18	17	0.05	−1.48
Emotional well-being	18	17	0.33	0.77	18	17	0.29	0.58	18	17	0.18	−0.84
Functional well-being	18	20	**0.0002**	**−2.06**	18	17	0.20	0.71	18	17	0.84	−0.12
Ovarian subscale												
Total FACT-O score	107	106	0.89	−0.70	108	106	0.49	1.73	109	102	**0.01**	−6.78
Ovarian cancer subscale	31	34	**<0.0001**	**−2.36**	32	31	0.08	1.10	32	30	**0.003**	−2.18
FACT-O/TOI	72	77	**0.001**	**−6.13**	73	71	0.29	1.63	73	69	0.062	−3.27
Neurotoxicity												
Total FACT/GOG-Ntx score	111	111	0.96	−0.27	111	111	0.98	0.07	113	108	0.10	−4.81
FACT/GOG-Ntx subscale score	3576	3982	**<0.0001**	**−3.64**	3576	3676	0.420.96	−0.70	3677	3676	0.59	0.52
FACT/GOG-Ntx/TOI			**0.007**	**− 5.20**				−0.08			0.65	−0.99
Severe neuropathy <33 scores *n* (%)	69 (25)	40 (14)	**<0.0001**		41 (27)	29 (20)	0.19		55 (25)	21 (24)	0.96	
Sleep disturbance (ISI) *n* (%)												
Prevalence of insomnia	163 (63)	121 (47)	**0.0003**		96 (65)	79 (56)	0.14		125 (60)	53 (63)	0.60	
Emotional status (HADS) *n* (%)												
Anxiety	137 (53)	121 (47)	0.19		79 (53)	74 (53)	0.97		105 (50)	50 (58)	0.22	
Depression	56 (22)	34 (13)	**0.01**		25 (17)	31 (22)	0.30		38 (18)	19 (22)	0.39	
Physical activity (IPAQ) *n* (%)												
High	58 (18)	61 (19)	0.33		32 (20)	24 (16)	0.39		39 (18)	20 (22)	0.43	
Moderate	131 (41)	110 (35)			67 (42)	58 (39)			87 (40)	39 (43)		
Low	129 (41)	147 (46)			59 (37)	66 (45)			94 (41)	32 (35)		

Comparisons were carried out using Mc Nemar χ^2 and paired *t*-tests. Clinically significant difference in boldface (difference of 5%).

*T**, time since end of cancer treatment; EOCS, Epithelial Ovarian Cancer Survivors; QoL, quality of life; FACIT-F, Functional Assessment of Chronic Illness-Fatigue subscale; FACT-G, General Functional Assessment of Cancer Therapy; FACT-O, Functional Assessment of Cancer Therapy-Ovarian subscale; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity subscale; TOI, Trial Outcome Index; ISI, Insomnia Severity Index; HADS, Hospital Anxiety and Depression Scale; IPAQ, International Physical Activity Questionnaire.

Table 4. Univariate and multivariate associations with severe long-term fatigue (FACIT-F score >37)

	Univariate associations with SCF			Multivariate initial model			Multivariate final model		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Age	0.98	[0.96–1.0]	0.09	0.96	[0.92–0.99]	**0.01**			
BMI			**0.01**			0.10			
≤18.5	1.5	[0.3–7.7]		0.8	[0.3–2.1]				
18.5–24.9	1.0			1.0					
25.0–29.9	1.5	[0.8–2.9]		1.3	[0.3–5.1]				
30.0–34.9	2.2	[0.9–5.2]		7.5	[1.3–42.0]				
35–39.9	7.7	[2.1–28.2]		0.2	[0.02–1.4]				
≥40	5.9	[1.2–27.8]		2.5	[0.2–27.8]				
Education (versus low level)High level	0.6	[0.4–1.1]	0.11						
Time since end of cancer treatment	1	[0.99–1.01]	0.27						
Type of chemotherapy[a]	1	[0.4–2.3]	0.95						
Antiangiogenic therapy[b]	0.7	[0.3–1.7]	0.48						
Comorbidities[b,c] (at least one of them)	2.6	[1.4–5.0]	**0.003**	2.4	[0.8–7.2]	0.13			
Digestive symptoms[b]	0.6	[0.2–1.5]	0.29						
Current medications[b,d]	7.4	[3.5–15.7]	**<0.0001**	4.3	[1.3–14.3]	0.02			
Physical activity (versus high)			**0.001**			0.06			
Moderate	3.8	[1.6–8.7]		0.9	[0.3–3.3]				
Low	1.3	[0.6–3.2]		2.7	[1.1–6.8]				
Anxiety[b]	5.9	[3.1–11.1]	**<0.0001**	2.6	[1.0–6.6]	0.05			
Depression[b]	20.7	[10.2–42.2]	**<0.0001**	14.0	[5.1–38.5]	**<0.0001**	17.5	[7.8–39.2]	**<0.0001**
Neurotoxicity[b]	0.8	[0.81–0.9]	**<0.0001**	7.8	[2.9–20.7]	**<0.0001**	6.4	[3.0–13.6]	**<0.0001**
Sleep disturbance[b]	6.6	[3.1–13.9]	**<0.0001**	2.4	[0.8–6.9]	**0.11**	3.5	[1.4–8.3]	**0.005**

In the final multivariate analysis, only significant variables ($P \leq 0.01$) were kept in the model. Bold values correspond to *P*-values below the significance level of 0.05 of the corresponding odds ratio.

[a]Paclitaxel/carboplatin (3 weeks), paclitaxel/carboplatin (weekly) (reference class).

[b]Yes versus no.

[c]Antidepressants, anxiolytics, pain medications (opiate).

[d]Diabetes, thyroid disease, heart disease, depressive syndrome, obesity, chronic obstructive pulmonary disease.

BMI, body mass index.

on a cancer with a poor prognosis and high risk of relapse. Follow-up of EOCS usually focuses on the tumor and relapse risk without guidelines dedicated to post-treatment side-effects. However, our findings do not provide insights into how fatigue and QoL change over time.

In conclusion, compared with controls, EOCS have a globally similar QoL despite the persistence of sequelae. They presented more LTF with poorer functional well-being and EOC-related symptoms, depression, sleep disturbance, and more long-term complaints about neuropathy. Depression, neuropathy, and sleep disturbance may therefore be considered as the main conditions associated with SLTF among EOCS. They should be detected early and treated.

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