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OVQUEST – Life after the diagnosis and treatment of ovarian cancer - An international survey of symptoms and concerns in ovarian cancer survivors

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HIGHLIGHTS

- There are a growing number of long term ovarian cancer survivors for whom quality of life is an important issue.
- The health related quality of life of the study cohort was inferior to general population norms.
- A strong association has been seen between obesity, physical inactivity and quality of life.
- Recurrent disease status did not appear to be a significant contributor to symptom burden.

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ABSTRACT

Objectives. Our aim was to investigate the prevalence and potential risk factors for persistent and troublesome physical and psychological symptoms following treatment for ovarian cancer (OC).

Methods. OvQuest is an international, internet-based, cross-sectional questionnaire which explored symptom burden and quality of life (QOL) after treatment for OC. Eligible women were aged 18 and over, diagnosed with OC at least 6 months previously and had received chemotherapy. Self-report data were collected including demographics, diagnosis and treatment, and standardised instruments for treatment-related toxicities, QOL, physical activity (PA) and supportive care needs.

Results. The survey included 1360 patients, of whom 421 (31%) had been treated for recurrent OC. 78% reported symptoms of peripheral neuropathy, 60% significant fatigue, 48% mood disturbance and 59% moderate-severe insomnia. Rates of fatigue, mood disorders, neuropathy and insomnia did not differ between women with or without recurrence. The majority of respondents were overweight or obese (high BMI, 59%) and 35% reported low PA. Low PA and high BMI were associated with poorer QOL scores and higher symptom burden across a range of domains.

Conclusion. Women living after a diagnosis of OC report a substantial and ongoing symptom burden which impacts significantly on their quality of life across multiple domains. The reported associations between obesity, physical inactivity and poor QOL warrant prospective evaluation of lifestyle interventions to improve QOL.

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1. Introduction

There are a large and growing number of women who are long term survivors after a diagnosis of ovarian cancer [1–3]. The number of ovarian cancer survivors is expected to increase worldwide, due to the continued development of novel active therapeutics [4]. Ovarian cancer survivors are a relatively understudied population with limited data published on the long-term impact of the diagnosis and treatment on quality of life, and the major issues that concern women living with recurrent ovarian cancer (ROC) as well as long-term disease-free survivors. Survivorship concerns expressed by women include symptoms of the disease and symptoms related to adverse effects of treatment. The psychosocial challenges of living with recurrent ovarian cancer as well as fear of recurrence following chemotherapy are also substantial concerns [5,6].

Standard treatment of ovarian cancer includes radical surgery with an attempt to resect all macroscopically visible disease and platinum and taxane-based combination chemotherapy. [7]. Although treatment-related toxicity is routinely reported by clinicians in clinical trials, relatively few studies have focussed on patient-reported outcomes including the prevalence and trajectory of adverse effects after treatment in ovarian cancer survivors. Most reports have included only small cohorts, with sample sizes of one hundred patients or fewer [8–10]. Better understanding of the symptoms and concerns of ovarian cancer survivors, along with early identification of the subset of patients at high risk of ongoing morbidity after treatment for ovarian cancer could lead to better utilisation of resources and facilitate targeted interventions to address and manage symptoms in these patients.

2. Methods

The OvQuest survey was an international, internet-based, cross-sectional questionnaire to explore the follow-up care, symptoms and quality of life concerns of women after treatment for ovarian cancer. The survey was developed in cooperation with the Australia New Zealand Gynaecological Oncology Group (ANZGOG) and Ovarian Cancer Australia in collaboration with ovarian cancer consumer groups in the USA, United Kingdom, Canada and Germany (NOGGO). Eligible participants were women over the age of 18 who had been diagnosed with ovarian cancer at least six months previously and had received chemotherapy. Participating women were enrolled between October 2013 and July 2017.

2.1. Study procedures and survey content

The internet-based survey was developed using the KeySurvey platform (WorldAPP, USA) at the University of New South Wales (UNSW). Potential participants were referred to the survey link, which was hosted securely on a UNSW server. The survey included self-reported data on demographics (age, residential remoteness, marital status, highest level of education attained, employment status, nationality, height and weight), and cancer details (year of diagnosis, first surgery and most recent chemotherapy, cancer stage, cancer recurrence, number of lines of chemotherapy, chemotherapy agents received, intraperitoneal chemotherapy, participation in clinical trials, genetic testing). Validated instruments were used for the assessment of health-related quality of life (HR-QoL), symptoms, physical activity and supportive care needs. The expected time to complete the survey was approximately 30 min.

The primary outcome was HR-QoL as measured by the Functional Assessment of Cancer Therapy (FACT-G) [11]. The FACT-G comprises subscales for physical well-being (PWB), functional (FWB), social/family (SWB) and emotional (EWB) aspects of well-being as well as a total FACT-G score. As part of the primary outcome analysis the total FACT-G score has been compared to population-based normative scores. The FACT-G is a well-validated and widely used cancer-related quality of life measure and can be combined with a subscale of common symptoms related to ovarian cancer, the Ovarian Cancer Subscale (OCS), to form the FACT-O [12]. The FACT/Gynaecologic Oncology Group–Neurotoxicity (FACT/GOG-NTX) is an additional 11-item FACT subscale, developed for the assessment of chemotherapy-related neurotoxicity [13]. It does not have a cut-off for the presence or absence of clinical neuropathy. In the present study, the method devised by Richardson et al., has been applied, whereby neuropathic symptoms were considered to be present on the basis of positive responses to the NTX items 1–4, 8 or 9 [14]. The 12-item Somatic and Psychological Health Report (SPHERE) was developed to assess common somatic and psychiatric symptoms in medical and psychiatric settings [15]. It has six psychological items (PSYCH-6) and six somatic/fatigue items (SOMA-6). A score of two or more on the PSYCH-6 scale indicates a possible psychological disorder, and a score of three or more on the SOMA-6 scale suggests a possible somatic/fatigue disorder. The Insomnia Severity Index (ISI) is a brief, 7-item self-report screening tool, which has been extensively used for the assessment of insomnia in both clinical and research settings [16]. A clinical cut-off score of 8 has been recommended for the detection of sleep difficulties in patients with cancer. The International Physical Activity Questionnaire–short form (IPAQ-SF) uses self-reported physical activity in the past week to calculate an estimate of total physical activity in MET-minutes/week, and to stratify physical activity levels into low, moderate or high activity [17]. The Supportive Care Needs Survey (SCNS-34) is a cancer-related measure of unmet need [18]. Items are reported as standardised summated Likert scores with a range of 0–100, with higher scores reflecting greater unmet needs.

2.2. Statistical analysis

Descriptive statistics were prepared for each of the demographic and clinical details of participants, as well as the self-reported questionnaire outcomes. Analyses were conducted for the study population as a whole, with planned subset analyses for patients without evidence of recurrence compared to those with recurrent disease. For differences between women with and without recurrent cancer, *t*-tests were used for continuous variables with effect size calculated by Cohen's *d*, while categorical variables were assessed with Chi-squared tests with adjusted standardised residuals and Yates continuity correction where appropriate. Kruskal-Wallis tests with pairwise comparisons by Dunn's procedure were used for ordinal variables. For the primary endpoint of HR-QOL, participant FACT-G scores were converted to T-scores with reference to published norms for the United States (US) and Australian general female populations and compared to these norms using one-sample *t*-tests [19,20]. Effect sizes were defined as "small, $d = 0.2$," "medium, $d = 0.5$," and "large, $d = 0.8$". Univariable associations between QOL scales, symptoms and potential clinical and demographic predictor variables (Table 1) were sought using Mann-Whitney *U* tests for categorical variables and Spearman's correlations for continuous variables. Multivariate analyses were performed using multiple regression models, selecting those potential predictor variables with $p < 0.1$ on univariate analysis for inclusion.

3. Results

Surveys were submitted by 1360 eligible women, whose clinical and demographic characteristics are shown in Table 1. Respondents had a median age of 51 to 60 years. The majority had been diagnosed with stage III/IV OC (62.5%) and had received platinum and taxane chemotherapy (83%). The average duration since the last chemotherapy was 2.3 years (SD 3.7). Almost one third had received treatment for recurrent OC (31%), and one in five (21.7%) were currently on treatment. Just over half (53.7%) reported having had genetic testing (BRCA1/BRCA2) and 20.4% of the women had received treatment on a clinical

Table 1
Clinical and demographic characteristics of respondents, with comparisons by recurrent disease status.

Characteristic	OvQuest cohort (n = 1360) n (%)	No disease recurrence (n = 939)	Recurrent ovarian cancer (n = 421)	p
Demographic				
Age (median)	51–60	51–60	51–60	<**0.001**
18–40	101 (7.4)	**83 (8.8)**	**18 (4.3)**	
41–50	296 (21.8)	215 (22.9)	81 (19.2)	
51–60	532 (39.2)	370 (39.5)	162 (38.5)	
61–70	327 (24.1)	**199 (21.2)**	**128 (30.4)**	
Over 70	102 (7.5)	70 (7.5)	32 (7.6)	
Married/de facto	1002 (74.3)	701 (75.4)	301 (71.8)	0.19
Tertiary educated	972 (72.9)	661 (71.5)	311 (76.0)	0.10
Working or studying	594 (44.8)	462 (50.4)	132 (32.1)	<**0.001**
Rural residence	296 (22.0)	204 (22.0)	92 (22.2)	0.97
International sites				0.57
Australia	208 (15.3)	147 (15.7)	61 (14.5)	
Canada	94 (6.9)	69 (7.3)	25 (5.9)	
Germany	195 (14.3)	126 (13.4)	69 (16.4)	
United Kingdom	444 (32.6)	306 (32.6)	138 (32.8)	
United States	419 (30.8)	291 (31.0)	128 (30.4)	
Cancer and treatment				
Stage (median)	III	III	III	<**0.001**
I	263 (19.4)	**234 (25.0)**	**29 (7.0)**	
II	178 (13.2)	**144 (15.4)**	**34 (8.2)**	
III	675 (49.9)	**410 (43.8)**	**265 (63.5)**	
IV	171 (12.6)	**103 (11.0)**	**68 (16.3)**	
Don't know	66 (4.9)	45 (4.8)	21 (5.0)	
Years since diagnosis (mean, SD)	3.8 (4.0)	**3.3 (3.9)**	**5.1 (3.8)**	<**0.001**
Years since last chemo (mean, SD)	2.3 (3.7)	**2.8 (4.0)**	**1.1 (2.6)**	<**0.001**
Chemotherapy at diagnosis	1303 (95.8)	**931 (99.1)**	**372 (88.4)**	<**0.001**
Chemotherapy for recurrence	421 (31.0)	939	421	–
If recurrent, number of lines of chemo (median)	2 (Range 1–6+)	N/A	2 (Range 1–6+)	–
Current chemotherapy	295 (21.7)	**77 (8.2)**	**218 (51.8)**	<**0.001**
Chemotherapy agents				
Carboplatin	**1197 (88.0)**	**804 (85.6)**	**393 (93.3)**	<**0.001**
Cisplatin	**257 (18.9)**	**137 (14.6)**	**120 (28.5)**	<**0.001**
Paclitaxel	**1129 (83.0)**	**757 (80.6)**	**372 (88.4)**	<**0.001**
Docetaxel	**107 (7.9)**	**54 (5.8)**	**53 (12.6)**	<**0.001**
Gemcitabine	**207 (15.2)**	**15 (1.6)**	**192 (45.6)**	<**0.001**
PLD	**177 (13.0)**	**8 (0.9)**	**169 (40.1)**	<**0.001**
Topotecan	**56 (4.1)**	**8 (0.9)**	**48 (11.4)**	<**0.001**
Bevacizumab	**252 (21.8)**	**101 (12.8)**	**151 (41.7)**	<**0.001**
Other[a]	120 (8.8)			
Don't know	84 (6.2)	57 (6.1)	27 (6.4)	0.90
Intraperitoneal chemotherapy	202 (15.0)	130 (14.0)	72 (17.1)	0.15
Participation in a clinical trial	276 (20.4)	**131 (14.0)**	**145 (34.4)**	<**0.001**
Genetic testing (BRCA1/BRCA2)	651 (53.7)	**402 (48.0)**	**249 (66.4)**	<**0.001**
Second cancer	177 (14.7)	119 (14.2)	58 (15.5)	0.63
Physical activity and obesity				
BMI (kg/m^2) mean (SD)	27.9 (7.0)	28.1 (7.0)	27.4 (6.9)	0.107
BMI category				
Underweight	29 (2.2)	17 (1.9)	12 (3.0)	
Normal	503 (38.5)	345 (38.2)	158 (39.0)	
Overweight	380 (29.1)	248 (27.5)	132 (32.6)	
Obese	396 (30.3)	293 (32.4)	103 (25.4)	
Physical activity (MET minutes/week) mean (SD)	1687 (1894)	1749 (1935)	1544 (1792)	0.09
PA category				
Low	415 (34.7)	273 (32.9)	142 (38.8)	
Intermediate	531 (44.4)	373 (45.0)	158 (43.2)	
High	249 (20.8)	183 (22.1)	66 (18.0)	

Comparisons with pairwise adjusted standardised residuals of >2 or <−2 for significant X^2 tests are indicated in bold to reflect the source of significant differences.
[a] Includes chemotherapy agents not listed here and regimens for rare ovarian cancer subtypes (e.g., bleomycin/etoposide/cisplatin (BEP), 5-fluorouracil and oxaliplatin (FOLFOX)); PLD: pegylated liposomal doxorubicin.

trial. Women with recurrent cancer were more likely to be older, not working, had been initially diagnosed with advanced stage disease, have received chemotherapy more recently and to have received each of the chemotherapy drugs of interest. They were also less likely to have received chemotherapy at diagnosis, but more likely to have participated in a clinical trial and had genetic testing.

3.1. Quality of life and comparison to population norms

The mean FACT-G and subscale scores of the entire OvQuest cohort, and comparisons between scores of participants with and without recurrent OC are shown in Table 2. Participants with recurrent OC had significantly lower scores on all domains except social well-being,

Table 2
FACT quality of life scores for the OvQuest cohort and by recurrent disease status.

FACT scale	OvQuest cohort n = 1327 Mean (SD)	No recurrence n = 916 Mean (SD)	Recurrent ovarian cancer n = 411 Mean (SD)	Effect size (*d*)	*P*
FACT-G (/108)	74.5 (18.0)	75.9 (17.6)	71.3 (18.4)	0.26	<**0.001**
PWB (/28)	20.1 (6.4)	20.9 (6.1)	18.3 (6.7)	0.41	<**0.001**
SWB (/28)	20.3 (5.6)	20.2 (5.7)	20.6 (5.5)	−0.07	0.266
EWB (/24)	16.2 (4.9)	16.5 (4.7)	15.4 (5.1)	0.22	<**0.001**
FWB (/28)	17.8 (6.2)	18.2 (6.2)	17.0 (6.1)	0.20	**0.001**
OCS (/44)	31.4 (6.2)	32.0 (5.9)	30.1 (6.7)	0.30	<**0.001**
FACT-O (/152)	106.0 (22.7)	108.0 (22.0)	101.5 (23.7)	0.28	<**0.001**

FACT-G: Functional Assessment of Cancer Therapy–General; PWB: physical well-being; SWB: social well-being; EWB: emotional well-being; FWB: functional well-being; OCS: ovarian cancer subscale; FACT-O: total FACT-G and OCS.

however the effect sizes for each of these comparisons were small (*d* 0.20 to 0.41). Multivariable models for the clinical and demographic features associated with each of the FACT scales are shown in Table 3. Recurrent disease was not independently associated with any of the QOL measures or subscales, although there was a trend to a negative impact on EWB. Physical inactivity was independently associated with the FACT-G and PWB, EWB, FWB and OCS subscales, as well as the overall FACT-O score, whereas overweight/obesity was associated with PWB and SWB.

FACT-G overall and subscale T-scores for the OvQuest cohort were compared to published norms for the Australian and US female general unaffected populations (Fig. 1). Quality of life scores for OC patients were significantly inferior to US and Australian general population norms across all domains, with the exception of social well-being (SWB), which was preserved compared to both populations and functional well-being (FWB), which was preserved compared to the US data. These findings were upheld both for the overall cohort, and the cohort restricted to participants from the source country of the normative datasets. Effect sizes for these comparisons were large for the comparison of the physical well-being (PWB) and emotional well-being (EWB) of the OvQuest cohort to the Australian norms ($d = 0.91$ and 1.04 respectively), and moderate for the EWB of the OvQuest population to the US norms ($d = 0.64$) and the FACT-G of the OvQuest participants to Australian norms ($d = 0.70$). Effect sizes for all other comparisons to population norms were small ($d < 0.4$).

3.2. Symptoms

Mean symptom scores on each of the relevant instruments are shown in Table 4, while the proportion of individuals scoring above the pre-defined cut-off ranges on each instrument are shown in Fig. 2. Final multivariable models for features associated with each of the symptom domains are shown in Table 3.

3.3. Peripheral neuropathy

The mean FACT/GOG-NTX score for all participants was 33.0 (SD 9.1, n = 1356). There were no significant differences in NTX scores according to recurrent disease status (mean 32.9 vs 33.1, p = 0.71). More than three-quarters of participants reported the presence of neuropathic symptoms (78.1%, Fig. 1), with no significant differences between participants with or without recurrent ovarian cancer (77.6% vs 78.4%, p = 0.80). The final multivariable model demonstrated statistically significant independent associations between neuropathy and higher educational level, not working/studying, fewer years since last chemotherapy, rural residence, being overweight/obese and low physical activity (Table 3) ($R^2 = 0.089$, $p < 0.001$).

3.4. Fatigue

More than half of participants (60.4%) met criteria for clinically significant fatigue on the SOMA-6 scale, reflected by an above threshold mean score of 4.0 (SD 3.4, n = 1347, Table 3). There were no significant differences in either case rates or mean SOMA-6 scores between women with, and without, recurrent ovarian cancer (case rate 64.0% vs 58.8%, p = 0.08). On multivariable analysis younger age, women without a partner, higher education, not working/studying, fewer years since last chemotherapy, being overweight/obese and low physical activity were significantly associated with fatigue, in a model which was also statistically significant ($R^2 = 0.127$, $p < 0.001$). There was no significant difference for patients receiving current treatment.

3.5. Mood disorders

Almost half of women (47.8%) met criteria for significant mood disorders on the PSYCH-6 scale, with an above threshold mean score of 2.6 (SD 3.2, n = 1346). Although women with recurrent cancer had a lower mean PSYCH-6 score (2.4 ± 2.9 vs 2.8 ± 3.3, p = 0.036), there were no significant differences in reporting mood disorders between participants with and without ROC (45.3% vs 48.9%, p = 0.25). The multivariable model was statistically significant ($R^2 = 0.072$, $p < 0.001$), with independent associations found between mood disorders and younger age, higher education and those with low physical activity.

3.6. Insomnia

Over half of participants (59.8%) were found to have significant insomnia as measured by the ISI, with a mean ISI score for the cohort above the clinical cut-off at 9.6 (SD 6.2, n = 1360) and no differences between women with and without recurrent disease (57.0% vs 61.0%, p = 0.181). On multivariable analysis younger age, higher education, earlier stage at diagnosis, overweight/obesity and low physical activity were associated with insomnia. The model was also statistically significant ($R^2 = 0.053$, $p < 0.001$).

3.7. Unmet supportive care needs

The unmet supportive care needs of the cohort were measured by the SCNS-SF34. Women with recurrent ovarian cancer reported higher unmet needs in relation to physical function and lower needs in relation to sexuality (p = 0.001 and <0.001 respectively), but effect sizes were small (Cohen's *d* −0.23 and 0.25). No differences were seen between women with or without recurrent disease on other unmet supportive care needs domains, and there were no significant differences between patients on treatment vs surveillance.

Table 3
Final multivariable models for quality of life and symptom scales.

Domain	Model R^2	p	Variables	p	B	95% CI
Quality of life domains						
FACT-G	0.148	<0.001	**Age**	**<0.001**	4.42	3.43–5.40
(n = 1104)			**Married or partnered**	**0.002**	3.50	1.27–5.72
			Working or studying	**<0.001**	7.01	4.87–9.14
			Low physical activity	**<0.001**	−5.01	−7.12 to −2.91
			Years from last chemo	**<0.001**	0.48	0.21–0.75
			Current chemo	**<0.001**	−5.39	−7.87–2.91
PWB	0.180	<0.001	**Age**	**<0.001**	1.23	0.89–1.57
(n = 1084)			Married or partnered	0.064	0.73	−0.04–1.51
			Working or studying	**<0.001**	2.57	1.82–3.31
			Low physical activity	**<0.001**	−1.91	−2.62 to −1.12
			Overweight/obesity	**0.001**	−1.21	−1.90 to −0.52
			Years from last chemo	**<0.001**	0.21	0.11–0.31
			Current chemo	**<0.001**	−2.99	−3.86 to −2.13
SWB	0.038	<0.001	**Age**	**<0.001**	0.76	0.48–1.04
(n = 1288)			**Married or partnered**	**<0.001**	1.23	0.54–1.92
			Overweight/obesity	**0.046**	−0.62	−1.24 to −0.01
			Clinical trial participant	**0.013**	0.90	−0.19 to −1.60
EWB	0.097	<0.001	**Age**	**<0.001**	0.94	0.66–1.23
(n = 1067)			**Married or partnered**	**0.044**	0.66	0.02–1.30
			Working or studying	0.053	0.60	−0.01–1.21
			Low physical activity	**0.012**	−0.74	−1.32 to −0.16
			Years from last chemo	**<0.001**	0.21	0.13–0.30
			Recurrent disease	0.075	−0.57	−1.20–0.06
			Stage at diagnosis	**0.004**	−0.45	−0.75 to −0.15
FWB	0.164	<0.001	**Age**	**<0.001**	1.24	0.90–1.57
(n = 1105)			**Married or partnered**	**0.009**	1.01	0.26–1.76
			Tertiary educated	**0.002**	−1.19	−1.94 to −0.43
			Working or studying	**<0.001**	3.03	2.29–3.76
			Low physical activity	**<0.001**	−1.83	−2.52 to −1.15
			Years from last chemo	**<0.001**	0.18	0.09–0.27
			Current chemo	**<0.001**	−1.86	−2.71 to −1.02
OCS	0.129	<0.001	**Age**	**<0.001**	0.91	0.59–1.27
(n = 1125)			**Married or partnered**	**0.005**	1.10	0.34–1.86
			Working or studying	**<0.001**	1.52	0.81–2.28
			Low physical activity	**<0.001**	−1.78	−2.50–1.11
			Years from last chemo	**<0.001**	0.17	0.08–0.26
			Current chemo	**<0.001**	−2.79	−3.63 to −1.94
FACT-O	0.160	<0.001	**Age**	**<0.001**	5.37	4.13–6.60
(n = 1103)			**Married or partnered**	**0.001**	4.55	1.76–7.33
			Working or studying	**<0.001**	8.62	5.96–11.29
			Low physical activity	**<0.001**	−6.88	−9.42 to −4.34
			Years from last chemo	**<0.001**	0.65	0.31–0.99
			Current chemo	**<0.001**	−8.18	−11.28 to −5.07
Symptom domains						
Neuropathy	0.089	<0.001	**Rural residence**	**0.002**	−1.98	−0.32 to −0.74
(n = 1078)			**Tertiary education**	**0.017**	−1.45	−2.64 to −0.26
			Working or studying	**<0.001**	2.70	1.66–3.75
			Years from last chemo	**0.017**	0.16	0.02–0.30
			Overweight/obese	**<0.001**	−3.19	−4.23 to −2.14
			Low physical activity	**0.002**	−1.67	−2.76 to −0.59
Fatigue	0.127	<0.001	**Age**	**<0.001**	−0.84	−1.03 to −0.64
(n = 1073)			**Married or partnered**	**0.048**	−0.44	−0.87 to −0.04
			Rural residence	**0.037**	0.48	0.03–0.94
			Tertiary education	**<0.001**	1.05	0.61–1.48
			Working or studying	**<0.001**	−1.24	−1.66 to −0.82
			Years from last chemo	**0.017**	−0.06	−0.11 to −0.01
			Overweight/obese	**<0.001**	0.72	0.34–1.10
			Low physical activity	**0.002**	0.63	0.23–1.03
Mood disturbance	0.072	<0.001	**Age**	**<0.001**	−0.77	−0.94 to −0.61
(n = 1175)			**Tertiary education**	**0.028**	0.45	0.05–0.85
			Low physical activity	**0.024**	0.42	0.06–0.79
Insomnia	0.053	<0.001	**Age**	**<0.001**	−0.88	−1.23 to −0.53
(n = 1078)			**Tertiary education**	**0.020**	0.99	0.15–1.83
			Stage at diagnosis	**0.012**	−0.47	−0.86 to −0.09
			Overweight/obese	**0.007**	1.01	0.28–1.75
			Low physical activity	**0.001**	1.29	0.52–2.06

FACT-G: Functional Assessment of Cancer Therapy–General; PWB: physical well-being; SWB: social well-being; EWB: emotional well-being; FWB: functional well-being; OCS: ovarian cancer subscale; FACT-O: total FACT-G and OCS. Positive associations indicate better QOL for FACT subscales. Positive associations indicate lower likelihood of symptoms for neuropathy; greater likelihood of symptoms for all other measures.

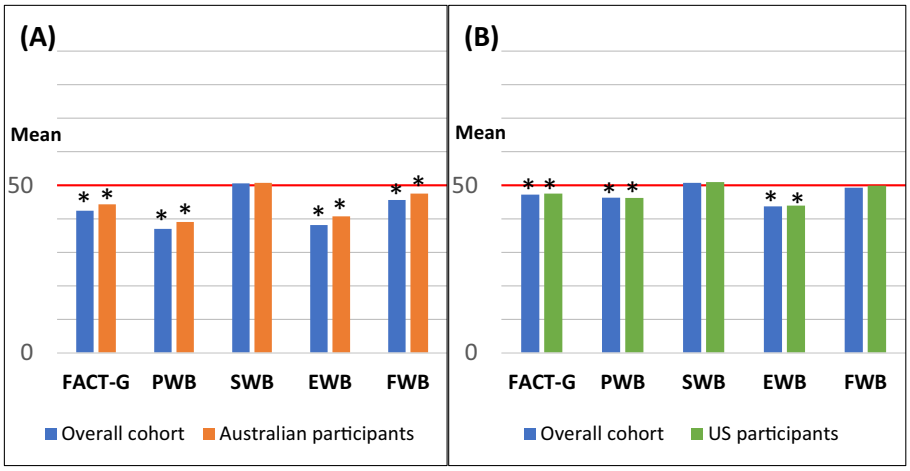

Fig. 1. FACT-G and subscale T-scores for OvQuest cohort compared to (A) Australian and (B) US female population norms. Transformed mean scores for reference populations are 50 on all domains, indicated by red line, with SD ± 10. *comparison to population mean, $p < 0.001$. FACT-G: Functional Assessment of Cancer Therapy – General; PWB: physical well-being; SWB: social well-being; EWB: emotional well-being; FWB: functional well-being.

4. Discussion

To the best of our knowledge this is the largest international survey of the health status of women treated for ovarian cancer reported to date. It provides a clear insight of life for women following diagnosis and treatment for ovarian cancer using validated questionnaires and symptom scales. On the whole, the health-related quality of life of the study cohort was inferior to the Australian and US population norms, as measured by the FACT-G. This deficit was seen in overall, physical and emotional well-being between the study cohort and both comparator populations, with relatively preserved social well-being. This finding underscores the relevance and focus of this study on physical and psychological symptom burden reported by patients.

While expected differences were seen between a number of clinical and demographic factors and recurrent disease, it is noteworthy that ROC was not independently associated with poorer quality of life overall or on any of the QOL subscales, nor was recurrent disease status a significant contributor to symptom burden on any of the four symptom domains of interest. These findings are consistent with results of other studies [8,21,22]. It is possible that this relates to adaptation and altered expectations in patients with ROC, rather than the absence of symptoms in these women. For example, a level of fatigue which may be tolerable for an individual with recurrent cancer on chemotherapy may be disproportionately disabling for a disease-free survivor who expects to return to her previous activities. It is also likely that while the experience of women with ROC may be different to women without recurrence, there are other clinical and demographic features like age, being partnered, having children or financial issues that may play a greater role in determining quality of life and long-term symptom burden. In short, the relative similarities of the concerns of women with and without ROC supports the notion that in ovarian cancer, it is reasonable to consider a broader definition of "survivorship" than simply being alive with or without evidence of recurrent disease.

Table 4
Neurotoxicity, fatigue, mood disturbance and insomnia symptom scores.

Symptom measure	OvQuest cohort Mean (SD)
FACT/GOG-NTX (/44)	33.0 (9.1)
SOMA-6 (/12)	4.0 (3.4)
PSYCH-6 (/12)	2.6 (3.2)
ISI (/28)	9.6 (6.2)

Higher scores indicate fewer symptoms for FACT/GOG-NTX; higher scores indicate more symptoms for all other measures. Cut-points for clinically significant symptoms were SOMA-6 ≥ 3; PSYCH-6 ≥ 2; ISI ≥ 8. The cut-off for the FACT/GOG-NTX was derived from a subset of items on this measure [16].

The prevalence of each of the symptoms of interest in the OvQuest study was higher than may have been expected. The rate of neurotoxicity of 78% in this study was markedly higher than the rates reported in many randomised clinical trials of ovarian cancer chemotherapy, where neuropathy is commonly reported and rated by treating clinicians rather than by patients [23,24], and patients with greater then grade 2 neurotoxicity are usually excluded. The high rate is due in part to the inclusive definition of neuropathy adopted in this study, based on positive responses to items regarding key symptoms of neuropathy (e.g. numbness and tingling, pain in the hands and feet) rather than a cut-off score on the FACT/GOG-NTX scale, as no such cut-off has been derived. This approach was considered reasonable, given that while a certain background level of symptoms such as fatigue, mood disturbance and insomnia might be part of the normal human experience, one would not ordinarily consider any degree of neuropathy to be normal. Reporting in clinical trials generally relies upon clinician ratings using CTCAE which incorporates the degree neuropathy has on functionality and favours reporting only higher grade (2–4) symptoms. By contrast, assessments using patient reported outcome (PRO) measures typically find much higher rates of neuropathy reported by patients, with clinicians significantly underestimating the prevalence and severity of symptoms [23]. The finding that obesity is independently associated with neuropathy is of interest, because historical patterns of chemotherapy prescribing with "capping" of doses for larger patients are generally thought to have resulted in under-dosing in the obese based on true body surface area [25]. It is possible that this finding of neuropathy in the obese may relate to pre-existing subclinical neuropathy due to metabolic syndrome and insulin resistance, aggravated by the cumulative insult of neurotoxic chemotherapy. Guidelines now recommend against dose capping, which underscores the importance that obese patients receiving neurotoxic chemotherapy should be carefully monitored for symptoms of neuropathy [26].

The case rates of 60% and 48% for fatigue and mood disorders found in the OvQuest population were higher than that reported using the SPHERE as a screening instrument in a large Australian general practice study, where the rates were 37% and 35% respectively [27]. Cancer and treatment-related variables appeared to have less of a role in the prevalence of fatigue and mood disturbance in this population, as evidenced by the final multivariable models. No treatment variables featured in the final model for mood disturbance, while increasing time from last chemotherapy was the only treatment-related factor associated with

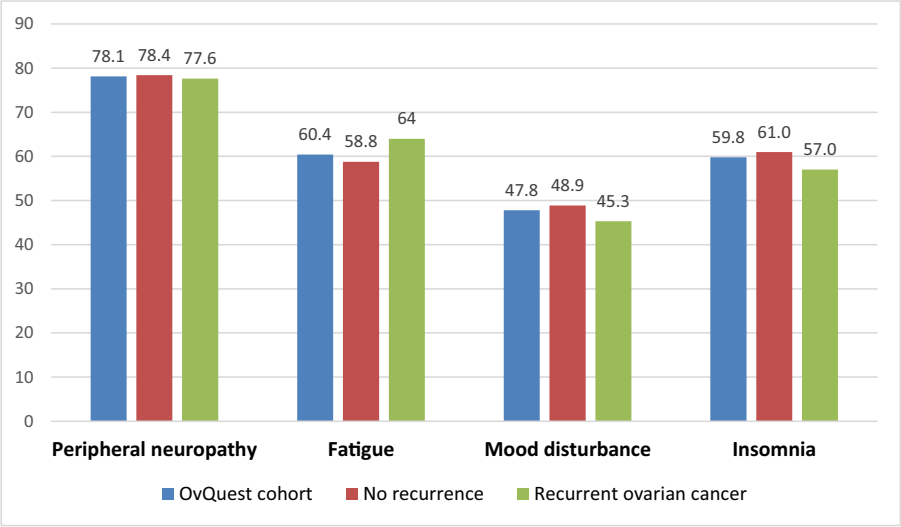

Fig. 2. Proportion of participants with above threshold symptom levels. No comparisons were significant at $p < 0.05$ based on recurrent disease status.

fatigue, in keeping with the clinical experience of recovery post-chemotherapy [28]. Demographic factors such as younger age, education and employment status featured prominently in these models. It is plausible that premature menopause in premenopausal women due to surgery contributes to the risk of fatigue and mood disorders. Adjuvant hormone replacement therapy after ovarian cancer treatment has demonstrated safety and may be associated with improved overall survival [29]. Clinicians may therefore be alerted to the presence of demographic risk factors for the development of these symptoms for early referral to supportive care services and consideration of oestrogen replacement therapy where appropriate.

The rate of clinical insomnia of 59.8% was higher than that seen in the Australian Ovarian Cancer Study cohort (17.1%) [30] and other international studies [31] however these studies have not used the lower cut-off value recommended for cancer patients [16]. General population rates of significant insomnia are reported to be in the order of 10% [32]. In the present study, younger women and those with higher levels of education experienced more sleep problems. These factors were both also associated with mood disturbance, and thus may reflect an interaction between depression and/or anxiety with sleep.

Younger and more highly educated women seem to be more troubled by fatigue, mood disorders and insomnia in the present study. Premature menopause may play a role, and oestrogen replacement therapy may be a reasonable consideration for affected women [29], along with other evidence-based interventions targeting these symptoms such as physical activity, cognitive behavioural therapy and where appropriate, medications [33–35]. It is also possible that younger survivors and those with higher educational levels may have both higher health literacy and a lower tolerance for symptoms given competing demands at home and at work. For example, younger women may be more likely to have young children and the need to return to work, which may produce greater psychological and physical burden.

The relationships of obesity and physical inactivity to symptoms and quality of life among women with ovarian cancer are perhaps the most striking findings of this study, and importantly are amenable to specific interventions. The overweight/obesity rate in this study of 59% is slightly lower than the Australian general population rate (63.4%) [36]. The physical inactivity rate of 35% was lower than the Australian population rate of 45% [37]. Physical activity is typically overestimated by self-report compared to objective measurements, particularly among individuals who are also obese [38]. The results of this study are therefore likely to underestimate both physical activity and obesity. Nevertheless, physical inactivity was associated with inferior quality of life and independently associated with all of the symptom domains of interest. Overweight and obesity were associated with poorer physical functional quality of life and independently associated with neuropathy, fatigue and insomnia. The beneficial effects of physical activity on mood and fatigue are well described [39] and it is likely that increasing activity led to improved symptoms or conversely that high levels of symptoms contributed to inactivity.

In a cross-sectional study such as this it is not possible to infer causality. It is possible that high levels of symptoms contributed to inactivity, or conversely, that increasing activity led to improved symptoms. The present study however adds to a growing body of evidence of a positive relationship between physical activity, quality of life and symptoms after ovarian cancer and is the largest study of its kind to date to support such a relationship. Exercise is safe in individuals with cancer and is a low cost, readily accessible intervention which can be implemented in almost any clinical setting. The finding that physical activity was independently associated with fewer symptoms of fatigue, depression and insomnia in the present study, and with superior quality of life across multiple domains should encourage clinicians to support their at-risk patients to remain, or become, physically active after an ovarian cancer diagnosis.

In addition to the symptom and quality of life concerns described in this study, it was notable that only 54% of participants had undergone genetic testing for BRCA1/BRCA2. This represents a missed opportunity with prognostic and treatment implications for affected women, as well as a lost opportunity to prevent cancer in unsuspecting relatives through risk-reduction intervention in mutation carriers and to provide appropriate reassurances to noncarriers [40]. Clinicians should be alerted to the importance of offering genetic testing to affected women and their families.

The strengths of this study lie in its large sample size, international base and the breadth of the issues explored, along with the selection of validated instruments with available normative data. It is noted that the FACT normative populations were on average younger that the OvQuest cohort, which could contribute to the superior QOL seen in the general population. Conversely, among participants, younger age was associated with poorer QOL on each of the FACT subscales. The relative contribution of these factors to the QOL differences noted cannot be quantified in the present study.

The most significant limitation of the study is its reliance on self-report data for clinical and anthropometric data. This was a limitation by design, as anonymous online completion of the questionnaire was preferred in order to facilitate response by a broad cross section of women with ovarian cancer, including those for whom recruitment via a cancer centre may not be feasible. Other limitations of this study

include the potential for selection bias in the cohort, which arises in part due to recruitment via consumer organisations (thus selecting for women already engaged with supportive care services), and also due to the potential for response bias among those women with higher levels of symptoms and concerns. A possible selection bias can be identified for healthier recurrent cancer patients while women with ROC in a poor state of health might not have been willing to participate in this survey. The method of recruitment may also have under-sampled the socially disadvantaged, less well-educated and those from culturally and linguistically diverse backgrounds, and these potential biases are also acknowledged, and are supported by the high engagement with clinical trial enrolment in this population. The internet-based nature of the survey may also have favoured a younger age group, although the number of responses among women aged 70 and older was pleasing.

5. Conclusions

The OvQuest study has demonstrated that women living after a diagnosis of ovarian cancer experience a substantial and often persisting physical and psychosocial symptom burden which impacts significantly on their quality of life across multiple domains. The strong associations seen between obesity, physical inactivity and quality of life argue for prospective evaluation of lifestyle interventions in this at-risk population as there are effective strategies available that may lead to significant reduction in symptoms and improvement in quality of life.

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Declaration of competing interest

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Author contributions

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Data collection – KW, JM, SB, RC, TH, JS, SN, GI, MF.

Data analysis and interpretation – KW, EC, LM, DS, JM, SB, RC, TH, JS, SN, GI, MF.

Drafting the article – KW, EC, MF.

Critical revision of the article - KW, EC, LM, DS, JM, SB, RC, TH, JS, SN, GI, MF.

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