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Presence of gastro-intestinal symptoms in ovarian cancer patients during survivorship: a cross-sectional study from the PROFILES registry

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Abstract

Objective To assess the association between gastro-intestinal (GI) symptoms and health-related quality of life (HRQoL) in ovarian cancer (OC) survivors.

Methods Women diagnosed with OC between 2000 and 2010 as registered in the Netherlands cancer registry ($n = 348$), received a questionnaire on socio-demographic characteristics, HRQoL (EORTC-QLQ-C30), ovarian cancer-specific symptoms including GI (EORTC-QLQ OV28), and psychological distress (HADS). Data collection took place in 2012.

Results Of 348 women diagnosed with ovarian cancer, 191 (55%) responded. Of all participants, 69% were eligible for analysis ($n = 131$). In 25% of all women, high level GI symptoms occurred ($n = 33$). In 23% of all women, recurrence of OC occurred ($n = 30$). Regression analysis showed that presence of high levels of GI symptoms during survivorship was associated with lower functioning on all HRQoL domains (except for emotional functioning), more symptoms, and higher levels of distress. QoL was negatively affected in those who had few and high levels of GI symptoms. QoL of those with recurrent disease was worse than those without recurrent disease.

Conclusion A substantial proportion of OC survivors experience GI symptoms, regardless of the recurrence of disease. Health care professionals should be aware of GI symptoms during survivorship in order to refer their patients for supportive care interventions to reduce symptoms or help survivors to cope. Further research should examine the cause of GI symptoms during OC survivorship among those with non-recurrent disease.

Keywords Gastro-intestinal symptoms · Ovarian cancer · Survivorship

Introduction

Ovarian cancer (OC) is the third most common gynecological malignancy worldwide and the fifth leading cause of cancer-

related death among women [1, 2]. In the Netherlands, about 1300 cases of OC are diagnosed annually [3, 4]. Due to vague nature of symptoms, the disease is usually diagnosed at an advanced disease stage: up to 70% of all patients is diagnosed

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with stage III/IV disease, with extensive involvement of the abdominal cavity [5, 6]. Up to 70% of all patients experience recurrent disease [7, 8]. Overall, the most frequently reported symptoms at time of OC diagnosis and eventual recurrence are pain, abdominal swelling or distension, unusual fatigue, bloating, weight change, dyspepsia, vomiting, altered bowel habits, urinary, and gastro-intestinal (GI) symptoms [5, 9–11]. Standard therapy consists of surgery and chemotherapy [12]. Despite effective initial treatment, overall 5-year survival rates fluctuate from 90% for early-stage disease to 40% for late-stage disease [6, 13].

Some OC survivors may return to their normal functioning and life after the initial treatment, but others survivors will experience a wide range of sequelae related to cancer or its treatment that do not dissipate with time and may result in diminished post-treatment functioning [9, 10].

The most frequently reported problems among OC survivors are fatigue, pain, neuropathy, and concerns about getting cancer under control, recurrence, and death [14–19]. Two recent studies revealed that GI symptoms are a common problem among OC survivors who underwent surgery alone or surgery followed by chemotherapy [12, 16]. Research among survivors of other cancer types who received abdominal radiotherapy revealed that up to 40% reported moderate or severe GI symptoms, which had a negative impact on their health-related quality of life (HRQoL) [20]. GI symptoms are commonly reported as symptoms at first presentation of OC or disease recurrence; experiencing these symptoms during survivorship may cause significant distress and deteriorated HRQoL among OC survivors as these symptoms remind them of their disease [21]. However, up to now, no studies address this issue in population-based cohort of both short- and long-term cancer survivors. Therefore, the aims of this study were to assess (1) the prevalence of GI symptoms stratified by recurrence status and (2) the relationship of GI symptoms with HRQoL and distress among OC survivors.

Methods

Setting and participants

A cross-sectional study was conducted among women diagnosed with ovarian cancer between January 1, 2000 and July 1, 2010, as registered in the Netherlands Cancer Registry (NCR), in six hospitals in the southern region of the Netherlands. To be eligible, women had to have been diagnosed with ovarian cancer between January 1, 2000 and July 1, 2010, have an adequate literacy level to understand the questionnaire, speak and understand Dutch, have been treated in one of the affiliated hospitals, and had to be alive at the time of the study. Vital status was established either by the hospital patient file or by linking the NCR with the Central Bureau of

Genealogy; 693 were deceased according to the Central Bureau of Genealogy and therefore excluded. Of 1147 registered women, 693 were identified as deceased according to the Central Bureau of Genealogy and 106 were identified as deceased, hospitalized, or staying in a nursing home according to the hospital patient file. The remaining 348 received a questionnaire (Fig. 1). This study was approved by a regional ethical committee (St. Elisabeth Hospital, no. 1149).

Procedures/data collection

All patients received an information letter from their gynecologist, and after signing the informed consent form about linking the results of the questionnaires with the NCR data, the questionnaires were completed. Data collection took place in 2012 and was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry to study the physical and psychosocial impact of cancer and its treatment in a dynamic, growing population-based cohort of both short- and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the NCR. Details of the data collection method have been previously described [22]. Data from the PROFILES registry are available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration (www.profilesregistry.nl).

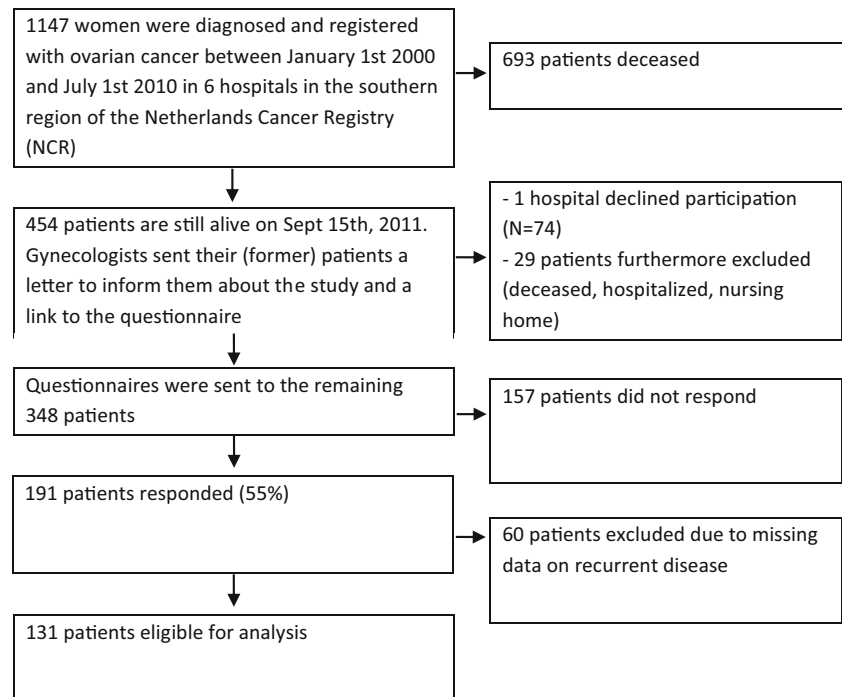
Measures

Socio-demographic and clinical characteristics

Clinical and patient information was obtained from the NCR (i.e., date of birth, date of diagnosis, disease stage, and primary treatment) [23]. The questionnaire included questions on socio-demographic characteristics (i.e., marital status, employment status, and educational level). Comorbidity at the time of survey was assessed using the self-administered comorbidity questionnaire (SCQ) [24].

HRQoL

The EORTC QLQ-C30 version 3.0 (European Organization for Research and Treatment of Cancer Quality of Life, quality of life core questionnaire) was used to assess HRQoL [25]. It contains five functional scales on physical, role, cognitive, emotional, and social functioning, a global health status/QoL scale; three symptom scales on fatigue, nausea and vomiting, and pain; and six single items. The questions were framed as “during the past week...”. Response scales included: “Not at all,” “A bit,” “Quite a bit,” and “Very much,” except for the global QoL scale, which ranges from “Very poor” to “Excellent.” Scores were linearly transformed to a 0–100 scale [26].

Fig. 1 Flowchart of the data collection process

Presence of GI symptoms

Disease-specific HRQoL, including GI symptoms, were assessed with the EORTC QLQ-OV28 (Ovarian cancer module) [27]. The QLQ-OV28 module contains seven scales: abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning. Abdominal symptoms are abdominal pain, feeling bloated, clothes too tight, changed bowel habit, flatulence, fullness when eating, indigestion. Peripheral neuropathy symptoms are tingling, numbness, and weakness. Other chemotherapy-related side effects are hair loss and upset by hair loss, taste change, muscle pain, hearing problem, urinary frequency, and skin problems. Hormonal/menopausal symptoms are hot flashes and night sweat. Body image-related symptoms are feeling less attractive and dissatisfied with the body. Attitude towards disease and treatment are described using disease burden, treatment burden, and worry about future. Symptoms of sexual dysfunctioning are rated using interest in sex, sexual activity, enjoyment of sex, and lubrication [27, 28].

The GI symptoms scale consists of six questions: “Did you have abdominal pain?,” “Did you have a bloated feeling in your abdomen/stomach?,” “Did you have problems with your clothes feeling too tight?,” “Did you experience change in bowel habit as a result of your disease and treatment?,” “Were you troubled by passing wind/gas/flatulence” and “Did you feel full too quickly after beginning to eat.” The questions were framed as “during the past week...”. Response scales included “Not at all,” “A bit,” “Quite a bit,” and “Very much.” Scores were

linearly transformed to a 0–100 scale [26]. Our data revealed a Cronbach’s alphas of 0.80 for the GI symptom subscale.

Psychological distress

The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress. The HADS is a 14-item, self-report measure of anxiety and depression [29, 30]. Each item is rated on a scale from 0 (not at all) to 3 (very much). The HADS has two subscales (anxiety and depression) and a total score. Meta-analysis of Norton et al. showed that the HADS does not provide good separation between the subscales anxiety and depression [31]. Therefore, we only used the total score to describe the psychological distress of the patients [32]. Higher scores imply more psychological distress.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA). *p* values of < 0.05 were considered statistically significant. Multi-item scales of the EORTC QLQ-C30 were only computed if at least half of the items from a scale were completed, according to the EORTC QLQ-C30 scoring guidelines [24].

The GI symptom scale was dichotomized as 0 to 30 (high level of GI symptoms) versus ≥ 30 to 100 (low level of GI symptoms). This conservative cut-off point was pragmatically chosen.

Frequencies and percentages were used to summarize categorical data. Means and standard deviations were used to

summarize continuous data. Socio-demographic and clinical characteristics of patients who had GI symptoms during survivorship versus those who had lower levels of GI symptoms were compared using independent samples *t* tests for continuous variables and chi-square tests for categorical variables (Table 1).

Descriptives of items of the GI symptom scale were presented stratified by patients with versus those without recurrent disease and were compared using *t* tests for continuous and chi-square tests for categorical variables (Fig. 2).

Descriptives were presented for the total group (Table 2). Patients who had high levels of GI symptoms during survivorship versus those who had low levels of GI symptoms were compared using *t* tests for continuous and chi-square tests for categorical variables. Thereafter, clinically important differences were determined between the low and high GI symptom groups based upon published guidelines for the EORTC QLQ-C30 and upon Norman's rule of thumb for the OV-28 questionnaire [33]. Norman's rule of thumb states that differences between groups of half a SD or more can be regarded clinically significant [34]. Descriptives were presented stratified by patients with versus those without recurrent disease (supplement Table 3).

Multiple linear regression analyses were performed to evaluate the association between low or high level of GI symptoms (dichotomized item) and the HRQoL scales (dependent variable). A priori we included presence of recurrent disease (no vs. yes), total psychological distress (total score on HADS), presence of comorbidities (no vs. yes), time since diagnosis (years), and age at time of questionnaire completion (years) as confounders.

Results

Patient characteristics

Of the 348 OC survivors, 191 responded to the questionnaire (55%, Fig. 1). Sixty women (17%) were excluded due to lacking information on the presence of recurrent disease, 131 participants were eligible for analysis (38% of the invited patients, 69% of the respondents) of which 101 (77%) had non-recurrent disease and 30 (23%) experienced recurrent disease. Socio-demographic and clinical characteristics did not differ between patients with high and low levels of GI symptoms (Table 1).

GI symptoms

Twenty five percent of the patients ($n = 33$) reported high levels of GI symptoms (Table 1). Of the 101 patients who had non-recurrent disease, 20 (20%) experienced high levels of GI symptoms, while 13 of the 30 (43%) patients with recurrent

disease experienced high levels GI symptoms. Women who were suffering from recurrent disease more often significantly experienced high levels of GI symptoms (odds ratio 6.3 $p = 0.01$; not tabulated) and scored significantly higher on three (presence of abdominal pain, bloated feeling, and change in bowel habits) of six of the GI symptom items (Fig. 2).

HRQoL domains of functioning and symptoms

Descriptive statistics on HRQoL scores were tabulated for the total group (Table 2) and stratified for patients with versus those without recurrent disease (Supplement Table 3).

In univariate analyses, significant differences were found between survivors with high and low levels of GI symptoms in all HRQoL functional scales (Table 2). Furthermore, patients suffering from high level of GI symptoms reported a worse overall QoL ($p = 0.00$) and higher levels of (cancer-related) symptoms ($0.00 \leq p \leq 0.04$). Lastly, patients suffering from GI symptoms more often had distress ($p = 0.00$) compared to those without GI problems. All differences were of small to large clinical importance. Descriptives of recurrent versus non recurrent disease have been described in supplement Table 3. Presence of recurrent disease in those with high levels of GI symptoms did not change the levels of HRQoL (functioning and symptoms) or distress. In those with low levels of GI symptoms with recurrent disease, HRQoL scores revealed to be worse compared to those with high level of GI symptoms and recurrent disease (supplement Table 3).

In multivariate analyses, patients with higher levels of GI symptoms scored lower on all HRQoL functioning scales and higher on all symptom scales, except emotional functioning ($p = 0.15$), financial problems ($p = 0.67$), and sexuality ($p = 0.18$), compared to patients without GI symptoms.

Discussion and conclusions

In this study, 25% of OC survivors reported having high levels of GI symptoms, regardless of presence of recurrent disease. GI symptoms may have an impact on the well-being of survivors because they are debilitating and act as a reminder of disease and treatment [21] and as a presenting symptom for recurrent disease [5, 9, 10]. In line with this, we found that OC survivors without recurrent disease with high GI complaints reported higher levels of distress than patients with low levels of GI symptoms. Those with low levels of GI symptoms and recurrent disease have a worse level of functioning and more symptoms on various domains compared to those with low levels of GI symptoms without recurrent disease or those with high levels of GI symptoms.

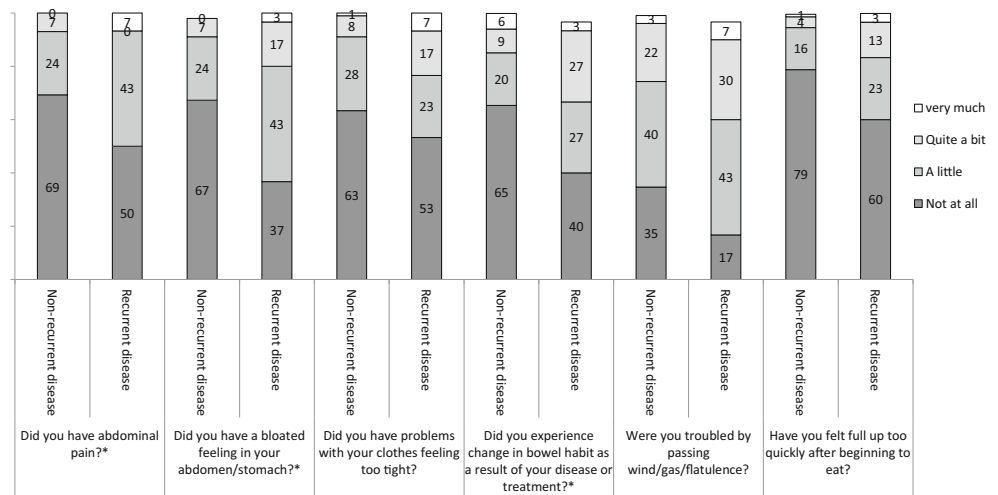
Our study adds to the current literature by showing that OC survivors with and without recurrent disease who experience GI complaints reported significantly more symptoms, including

Table 1 Socio-demographic and clinical characteristics of ovarian cancer survivors, according to presence of abdominal symptoms (*n*, %)

	High level of GI symptoms ^A (<i>n</i> = 33, 25%)	Low level of GI symptoms ^A (<i>n</i> = 98, 75%)	<i>p</i> value*
Age at time of survey, years (mean, range, SD)	65 (48–88, 11)	65 (40–85, 10)	0.84
Years since diagnosis years (mean, range, SD)	5.7 (1.9–12.2, 3.2)	6.3 (1.93–12.3, 3.1)	0.37
FIGO stage at diagnosis (<i>n</i> , %)			
I	11 (33)	46 (47)	
II	7 (21)	14 (14)	
III	12 (36)	32 (33)	
IV	3 (9)	5 (5)	0.22
Treatment (<i>n</i> , %)			
Surgery	1 (3)	4 (4)	
Surgery+ CTx	32 (97)	92 (94)	
CTx	0 (0)	1 (1)	
Other	0 (0)	1 (1)	0.72
Comorbidities (<i>n</i> , %)			
No	9 (27)	35 (36)	
Yes	24 (73)	63 (64)	0.38
Most frequent comorbidities (<i>n</i> , %)			
Backache	13 (39)	22 (22)	0.38
Arthritis	12 (36)	30 (31)	
Hypertension	7 (21)	25 (26)	
Socio-economic status (<i>n</i> , %)			
High	8 (24)	35 (36)	
Middle	16 (49)	38 (39)	
Low	9 (27)	22 (22)	
Missing	0 (0)	3 (3)	0.42
Educational level (<i>n</i> , %)			
High	3 (9)	13 (13)	
Medium	23 (70)	64 (65)	
Low	4 (12)	19 (19)	
Missing	3 (9)	2 (2)	0.58
Employed (<i>n</i> , %)			
No	21 (64)	73 (75)	
Yes	7 (21)	19 (19)	
Missing	5 (15)	6 (6)	0.61
Marital status at time of survey (<i>n</i> , %)			
Partner	22 (67)	63 (64)	
No partner	9 (27)	35 (36)	
Missing	2 (6)	0 (0)	0.52
Marital status at time of diagnosis (<i>n</i> , %)			
Partner	22 (67)	61 (62)	
No partner	3 (9)	3 (3)	
Missing	8 (24)	34 (35)	0.22
Presence of recurrent disease (<i>n</i> , %)			
No	20 (61)	81 (83)	
Yes	13 (39)	17 (17)	0.22

**T* tests for continuous and chi-square test for categorical data; educational level: high = university or higher education, medium = vocational training, low = primary or secondary education or less; Marital status: partner = married or cohabiting, no partner = divorced, widowed, or never married/cohabited; A: Low level defined as GI symptom scale score < 30, high level defined as GI symptom scale score ≥ 30

Fig. 2 Ovarian cancer survivors' (recurrent and non-recurrent disease) responses to QLQ-OV28 symptom scale items. Chi-square tests were performed, Asterisk shows a significant ($p < 0.05$) difference between patients with and without recurrent disease



fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation or diarrhea, hormonal symptoms, neuropathy, and other chemotherapy side effects compared to those without GI complaints. One other study showed that GI symptoms appeared to be moderately correlated with HRQoL including social functioning, pain, and the nausea/vomiting [27]. It is unclear whether these issues are fully due to OC or due to treatment (surgery or chemotherapy) or other physiologic causes.

Our study showed that prevalence of GI symptoms in patients with recurrent disease is higher in those of survivors without recurrent disease. OC survivors with recurrent disease had lower scores on HRQoL scales for global QoL and higher scores on symptom scales. This could be interpreted as side effects of further treatment that patients have to undergo because of recurrent disease. Initial treatment as well as treatment for recurrent OC includes chemotherapy that causes considerable toxicity, such as nausea, vomiting, lack of appetite, alopecia, weakness, and fatigue [35]. Symptoms such as peripheral neuropathy are to a large extent irreversible, while others such as GI symptoms, pain, and fatigue or psychological problems can potentially be treated if identified early [36]. These symptoms usually disappear over time after treatment completion.

GI symptoms were associated with HRQoL, regardless of the presence of recurrent disease. GI complaints might probably be related to the sequelae of the initial treatment consisting of surgery followed by systemic treatment with chemotherapy or recurrent disease. Unfortunately, we did not record specific data on chemotherapeutic regimen, surgical outcome, pre-existent performance status, or complications during treatment as possible explanations for persisting GI symptoms during survivorship.

Clinical implications

Care provided to OC patients should not be stopped when the treatment ends because many women continue to experience complaints after their cancer treatment [36]. During transition

from patient to survivor, patients lose contact with their cancer caregiver and they are challenged to resume former roles in life, even while they experience problems [37]. Therefore, symptom management is important to maintain HRQoL of OC survivors. A recently published review [38] showed benefits of interventions such as cognitive behavioral therapy and motivational interviewing as effective interventions to help patients to cope with physical and psychological problems, especially for women in whom the presence of GI symptoms acts as a reminder of the disease. As of yet, no instrument for symptom monitoring or interventions for persistent GI symptoms exist, except interventions that reduce burden of sequelae. Therefore, further research after causes of GI symptoms is warranted to uncover possibilities for symptom management and patient consultation.

Strengths and limitations

The strengths of the current study are that it is a population-based multicenter study design and it uses standardized and validated questionnaires. However, our study also has several limitations. The findings are based on cross-sectional data; this means that causal relationships could not be determined. In a study performed with a longitudinal design, analyses stratified by surgical outcomes would be possible. In addition, the results could have been affected by survivorship bias due to aggressiveness of the disease and low survival rates [39]. Of all selected patients, only 40% was still alive at time of inclusion. Detailed information about the health status of non-respondents is lacking (our response rate was 55% of whom we had to exclude 31% due to lacking data on recurrent disease). Furthermore, analyses on recurrent disease could not be performed due to small numbers of participants. Still, our sample may be considered representative for the OC population: from literature 5-year survival rate is at around 40%, but 90% for early stage disease [6, 13]. Prior research revealed

Table 2 Mean HRQoL and distress scores (SD) for ovarian cancer survivors with high and low levels of GI symptoms, for the total group. Difference in HRQoL and distress according to GI symptoms (as continuous scale variable) were assessed using univariate and multivariate linear regression analyses

	High level of abdominal symptoms	Low level of abdominal symptoms	Mean difference	CID	Beta univariate	p value univariate	Beta multivariate ^D	p value multivariate ^D
QLQ-C30		GI scale score > 30 (n = 20)						
Physical functioning ^A	64 (24)	84 (18)	20.3	Medium	-0.5	0.00	-0.3	0.00
Role functioning ^A	57 (32)	84 (22)	26.9	Medium	-0.5	0.00	-0.3	0.00
Emotional functioning ^A	72 (26)	85 (20)	12.5	Small	-0.4	0.00	-0.8	0.15
Cognitive functioning ^A	69 (26)	87 (17)	18.7	Large	-0.4	0.00	-0.3	0.00
Social functioning ^A	73 (25)	89 (20)	16.1	Medium	-0.4	0.00	-0.1	0.04
Global health status/QoL ^A	41 (22)	20 (14)	-20.6	Large	0.5	0.00	0.3	0.00
Fatigue ^B	45 (26)	21 (22)	-24.2	Large	0.5	0.00	0.3	0.00
Nausea/vomiting ^B	15 (25)	4 (12)	-11.3	Medium	0.4	0.00	0.2	0.02
Pain ^B	39 (29)	15 (23)	-24.5	Large	0.5	0.00	0.3	0.00
Dyspnea ^B	23 (30)	10 (22)	-12.6	Medium	0.4	0.00	0.3	0.00
Insomnia ^B	43 (38)	22 (27)	-21.0	Medium	0.3	0.00	0.2	0.02
Appetite loss ^B	21 (34)	4 (11)	-17.1	Medium	0.3	0.00	0.2	0.01
Constipation ^B	39 (32)	6 (14)	-32.3	Large	0.7	0.00	0.7	0.00
Diarrhea ^B	15 (25)	4 (16)	-10.1	Medium	0.3	0.00	0.2	0.01
Financial problems ^B	15 (24)	8 (20)	-6.6	Small	0.2	0.03	0.0	0.67
QLQ-OV28								
Body image ^B	35 (29)	15 (21)	-19.4	Yes	0.4	0.00	0.3	0.00
Sexuality ^A	25 (26)	34 (32)	9.3	No	-0.2	0.04	-0.1	0.18
Attitude to disease and treatment ^B	58 (23)	41 (26)	-17.4	No	0.4	0.00	0.2	0.01
Hormonal, menopausal symptoms ^B	34 (33)	19 (26)	-15.1	No	0.3	0.00	0.3	0.00
Neuropathy ^B	41 (37)	23 (26)	-18.6	No	0.3	0.00	0.2	0.02
Other chemotherapy side effects ^B	39 (18)	17 (13)	-21.1	Yes	0.6	0.00	0.5	0.00
HADS distress ^C	13 (7)	9 (7)	-4.0	No	0.4	0.00	-0.1	0.24

Functional scales and symptom scores range from 0 to 100. Standardized betas have been reported. A higher score on functional scales (A) and global QoL (A) means better functioning, whereas a higher score on symptom scale (B) mean more complaints and a higher score on HADS (C) implies more psychological distress; Analyses (D) were adjusted for confounding variables presence of recurrent disease, psychological distress, presence of comorbidities, time since diagnosis and age at time of questionnaire completion; SD standard deviation, CID clinically important difference, GI gastro-intestinal

that 10 to 50% of the OC survivors reported GI symptoms [19, 36, 40]. We interpret these differences due to different survival time from previous studies, and we included a heterogeneous population including patients with and without recurrent disease and we excluded those with missing data.

In conclusion, a substantial proportion (20%) of OC survivors experience GI symptoms that are similar to first presentation, despite the fact that a large proportion does not have recurrent disease. Health care professionals should be aware of the persistence of presenting symptoms during survivorship, affecting domains of functioning in daily life.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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