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Quality of life among borderline ovarian tumor survivors: A comparison with survivors of early-stage ovarian cancer and a cancer-free population: A cross-sectional population-based PROFILES study

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HIGHLIGHTS

- BOT survivors' HRQoL is between that of ovarian cancer survivors and a cancer-free population.
- BOT survivors reported significantly less insomnia than early-stage ovarian cancer survivors.
- BOT survivors reported significantly more dyspnea than the cancer-free population.
- Other differences in HRQoL were not significantly different and mostly of trivial clinical importance.
- Future studies should evaluate the group of women that is premenopausal by diagnosis.

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ABSTRACT

Objective. This study assessed the health-related quality of life (HRQo) of women surviving a borderline ovarian tumor (BOT) in comparison with early-stage ovarian cancer survivors treated surgically alone and with a matched cancer-free population.

Methods. Survivors of BOT and ovarian cancer were invited in two Dutch cross-sectional, population-based studies. Ovarian cancer survivors with tumor stage I who were treated surgically only were included. A random sample from the cancer-free population was matched on sex, age and education to the sample of BOT survivors. The EORTC QLQ-C30 (version 3.0) and the EORTC QLQ-OV28 were completed by the cancer-free population and the BOT and ovarian cancer survivors in study 1 and 2. The Hospital Anxiety and Depression Scale (HADS) was only completed by the cancer-free population and the survivors of BOT and ovarian cancer in study 1. BOT survivors were compared to early-stage ovarian cancer survivors and the general population using linear regression analyses and effect sizes regarding clinical importance.

Results. 83 BOT (42%), 88 early-stage ovarian cancer survivors (52%), and 82 women from the general population were included. In most HRQoL domains, BOT survivors were not significantly different from early-stage ovarian cancer survivors and the cancer-free population, except that BOT survivors reported significantly less insomnia than early-stage ovarian cancer survivors and more dyspnea than the cancer-free population (small clinical difference).

Conclusion. In general, BOT survivors' HRQoL lies between the HRQoL of early-stage ovarian cancer survivors and of the cancer-free population, but clinical effect sizes between the groups were mostly only trivial.

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1. Introduction

Borderline ovarian tumors (BOTs) are a distinct group of epithelial ovarian tumors characterized by atypical proliferation of the ovary epithelium, but without stromal infiltration [1–4]. BOTs represent 10–15% of epithelial ovarian tumors [5]. BOT often affect patients at a relatively young age compared with ovarian cancer [2,4,6,7]. They have low malignant potential and a low growth rate [7–9]. Nearly 80% of the BOT patients are diagnosed at FIGO stage I [2]. Consequently, BOTs are associated with a more favorable prognosis than ovarian cancer and a 5-year survival rate of 98% [10]. Generally, ovarian cancer has a poor prognosis with a 5-year survival rate of 38–46%. This is partly caused by a relatively late diagnosis [10–12]. 75% of all patients are diagnosed at FIGO (Federation of Gynecology and Obstetrics) stage II or higher [11].

Patients with a BOT generally receive surgical treatment, aimed at complete removal of the ovarian tumor and staging [5,13,14]. A decision has to be made between conservative or more radical treatment, depending on lateralization, menopausal status and childbearing potential [2,15]. Radical surgery involves removal of the uterus and both ovaries, as opposed to conservative surgery where the uterus and at least one ovary are preserved [16]. This decision may have long-term consequences, for example, regarding side effects, follow-up, fertility aspect, maintenance of hormonal function, as well as the risk of recurrence [2,5,16]. If both ovaries are removed, another consequence may be related to surgical menopause, causing menopausal symptoms to occur earlier and also become more severe, associated with a decreased quality of life [17]. To date, only two studies have been conducted on HRQoL in BOT patients and survivors (Pubmed; search terms borderline ovarian tumor AND quality of life, April 17th 2023). Previous research examined levels of anxiety and depression in ovarian cancer survivors, including survivors with all stages of disease, compared to survivors of BOT. Although higher levels of anxiety and depression were observed in ovarian cancer survivors compared with BOT survivors, HRQoL of BOT survivors has not previously been assessed in comparison with ovarian cancer survivors or the general population [5,10].

In contrast to BOT, ovarian cancer is often diagnosed at a relatively late stage and therefore most patients need intensive treatment with both chemotherapy and surgery [11,12,18,19]. Approximately 20% of patients are diagnosed at stage I or II and undergo surgery, although adjuvant chemotherapy may be recommended in case of unfavorable tumor characteristics and suboptimal staging procedure [19–21]. The diagnosis and treatment of ovarian cancer seriously impair patients' health-related quality of life (HRQoL), including ongoing physical and psychological problems during treatment with chemotherapy, such as negative feelings towards sickness, fatigue and pain, all of which negatively affected HRQoL [19,22,23]. In contrast to what might be expected HRQoL was not better for ovarian cancer patients who did not receive chemotherapy [22].

To date, only a single other study has evaluated HRQoL in BOT survivors, but it has not been previously assessed in comparison with another patient group or the general population (Pubmed; search terms borderline ovarian tumor AND quality of life, April 17th 2023). Women diagnosed with BOT constitute a substantial portion of gynecological cancer cases, and patients often undergo invasive treatments, partly due to its impact on hormonal function. Moreover, the exact relationship with ovarian cancer is still not well known. To obtain a deeper understanding of the impact of the disease and treatment of this patient group, the current study aimed to compare HRQoL of BOT survivors with that of early-stage ovarian cancer survivors and a cancer-free population. Based on previous research, it is expected that BOT survivors report better HRQoL than early-stage ovarian cancer survivors, but worse HRQoL than the cancer-free population.

2. Methods

2.1. Design, setting and participants

We combined data from two cross-sectional, population-based studies within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) (Fig. 1). PROFILES is a registry for studying the physical and psychosocial impact of cancer and its treatment from a population-based cohort of cancer survivors [24,25]. It is linked to clinical data from the Netherlands Cancer Registry (NCR) [26]. In addition, a matched sample from the cancer-free population was obtained from the CentERpanel, an online household panel representative of the Dutch population in the Netherlands [27].

Data collection of study 1 took place in 2012 and included women diagnosed with ovarian cancer or a BOT between 2000 and 2011 within six hospitals as registered in the NCR [24]. Study 2 is the InCHARGE study (International collaboration of the Healthcare Professionals and Researchers for Gynecologic Cancer Survivors' Empowerment); of which only data were used from the Dutch women diagnosed with early-stage ovarian cancer between 2011 and 2016 within four hospitals as registered in the NCR. Those women were invited to participate between October 2018 and June 2019. According to the medical ethical committees (St. Elisabeth 2011/129/METC Brabant 18.239), full ethical review was not applicable, as the research is not covered by Medical Research Involving Human Subjects Act. In both studies, all survivors diagnosed or treated in the selected hospitals in the Netherlands, aged 18 years and older who could read and understand the Dutch language were invited. Women who died prior to the commencement of the study and those whose addresses were unverifiable were excluded [19,28].

To obtain a sample of ovarian cancer survivors that were comparable to BOT survivors on extensiveness of treatment, only ovarian cancer survivors with stage I disease were included and ovarian cancer survivors who received treatment other than surgery alone were excluded. To be included in the current study, participants had to have completed the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.

2.2. Data collection

The approach and questionnaires used in both studies were similar. All survivors were invited through their (ex-)medical specialist, from whom they received an information letter, a questionnaire and an informed consent form. In study 1, women received a paper questionnaire as opposed to study 2 where women received a link to an online questionnaire, with an option to receive a paper questionnaire if preferred. Informed consent was obtained by returning the informed consent form and questionnaire (Fig. 1).

As previously mentioned, a sample from the cancer-free population was obtained from the CentERpanel, which also has included data on HRQoL and anxiety and depression. Of the 950 available women in the general population, 864 women were cancer-free. A random sample from the cancer-free population was drawn and education- (low, medium or high), sex- and 5-years age-matched (range 30 to 80 years) to the sample of BOT survivors using frequency matching. In 2011, the selected women completed the same questionnaires as BOT and ovarian cancer survivors in the two studies.

2.3. Clinical and sociodemographic characteristics

For the current study, NCR data on clinical characteristics were used (i.e. diagnosis, date of diagnosis, tumor stage, lateralization and primary treatment) [29]. The self-administered questionnaire included questions on age at time of survey (as a continuous variable), marital status

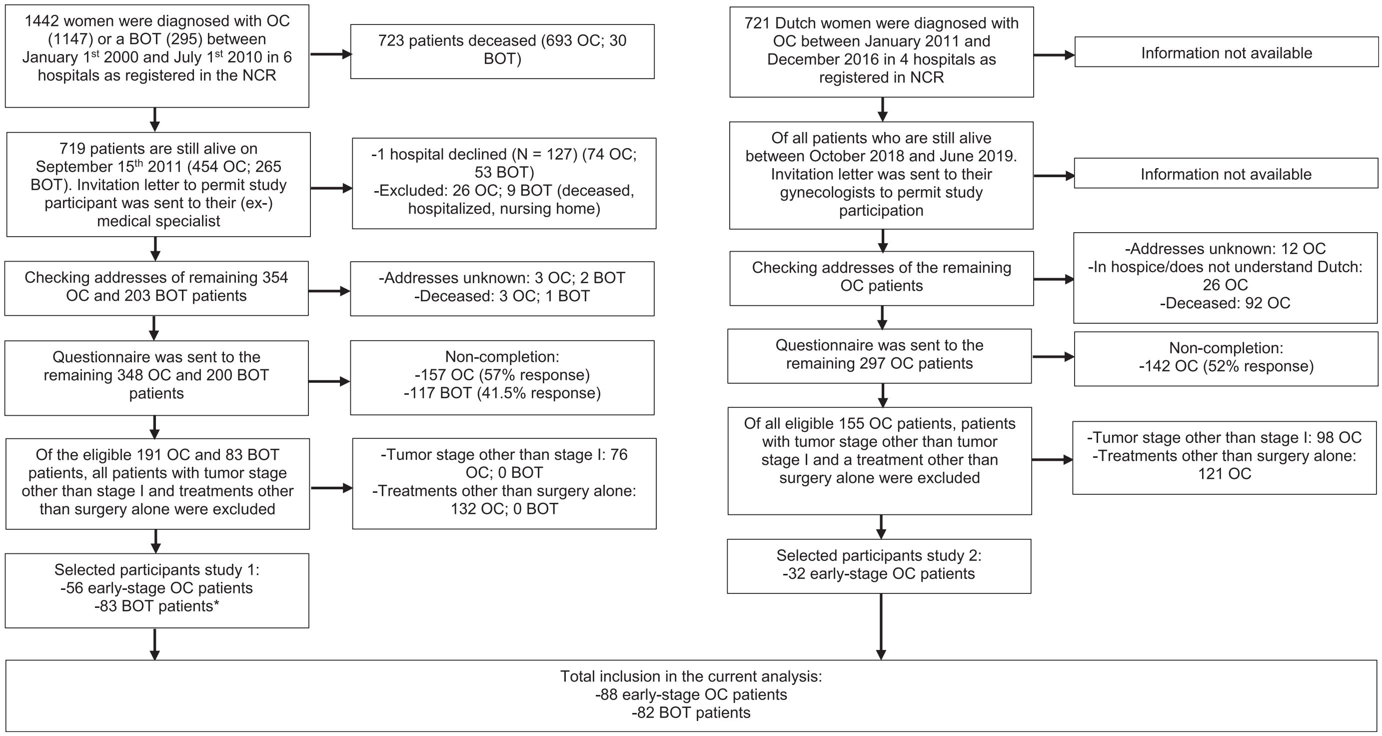

Fig. 1. flowchart of data collection in study 1 (left) and study 2 (right).
* 1 BOT survivors has a missing value on education level, therefore this participant cannot be matched and was excluded. OC = ovarian cancer; BOT = borderline ovarian tumor; NCR = Netherlands Cancer Registry.

(partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabiting) and education level (high = university, higher education or higher vocational; medium = vocational training; low = primary or secondary education or less), as well as the adapted Self-Administered Comorbidity Questionnaire (SCQ) to assess the number of comorbidities at the time of the study (0, 1 or ≥ 2) [30].

2.4. HRQoL

HRQoL in BOT and ovarian cancer patients from study 1 and 2 and the cancer-free population was assessed using the EORTC QLQ-C30 [31]. The questionnaire contains five functioning scales regarding physical, emotional, cognitive, role and social functioning. In addition, it includes a global health status scale and several questions on symptom experience regarding fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial problems. The items on global health status are scored on a 7-point scale ranging from 1 (very bad) to 7 (excellent). The other items are measured on a 4-point scale ranging from 1 (not at all) to 4 (very much). Only among women in study 1 and the cancer-free population, sexual functioning was additionally assessed using the EORTC QLQ-OV28, which is a module specifically for ovarian cancer to supplement the core EORTC. It was measured using 5 items and response scales included 'Not at all', 'A bit', 'Quite a bit' and 'Very much' [26,32,33]. Both the EORTC QLQ-C30 and the EORTC QLQ-28 are considered to be valid measurements of overall quality of life in cancer patients, and also specifically in ovarian cancer patients [22]. Scores on all domains were converted to a 0–100 score. Higher scores on the global health status and functioning scales represent better functioning outcome and HRQoL, while higher scores on the symptom scales represent more symptoms and a poorer HRQoL.

2.5. Anxiety and depressive symptoms

Anxiety and depressive symptoms in BOT and ovarian cancer patients from study 1 only, and the cancer-free population were assessed using the Dutch translation of the Hospital Anxiety and Depression Scale (HADS) [34]. It contains 7 items on anxiety and 7 items on depressive symptoms, each scored on a 4-point scale. The HADS is considered a highly reliable and valid measurement of distress in Dutch somatically ill patients [10]. Anxiety and depressive symptoms were included as separate scales in the current analyses, as it is considered a more valid measurement if separate scales are used [10]. The total score on both scales was calculated by summing the item scores and ranged from 0 to 21 for both scales. Higher scores represent more anxiety or depressive symptoms. Anxiety and depression was only assessed in study 1 and the cancer-free population.

2.6. Statistical analyses

Sociodemographic and clinical factors were described by means in years with standard deviations, medians with minimum and maximum values or frequencies and percentages per category. Baseline characteristics were compared using independent samples *t*-tests for continuous variables and chi-square tests for categorical variables, comparing the sample of BOT survivors with the sample of early-stage ovarian cancer survivors and that of the cancer-free population separately.

Multivariable linear regression analyses were conducted to compare BOT survivors with survivors of early-stage ovarian cancer and the cancer-free population separately on HRQoL domains. All analyses were adjusted for pre-defined confounders: age at time of survey, education level, marital status and number of comorbidities [19]. Multivariable linear regression analyses to compare HRQoL between BOT survivors and early-stage ovarian cancer survivors were additionally adjusted for time since diagnosis. Cases with missing items on outcome measures were counted as "not applicable" and were not included in the analyses. Missing items on sociodemographic characteristics were imputed using multiple imputation methods.

Based on published guidelines for the EORTC QLQ-C30, clinically important differences (CID) were determined [35]. According to these guidelines, a large difference is defined as unequivocally clinically relevant, a medium difference as probably clinically relevant but to a lesser extent, a small difference as subtle but nevertheless clinically relevant, and a trivial difference as unlikely to have any clinical relevance [19]. No CID was available for emotional functioning, sexual functioning and both the anxiety and depression scales.

All analyses were performed in the statistical program R version 4.2.2 [36,37]. To assess whether the associations were significant, a two-sided p-value <0.05 was used.

3. Results

3.1. Participants

Of all eligible BOT ($n = 200$) and ovarian cancer ($n = 348$) survivors who were invited to participate in study 1, 83 BOT (42%) and 191 (55%) ovarian cancer survivors completed the questionnaire. In study 2, of all eligible Dutch ovarian cancer survivors invited ($n = 297$), 155 (52%) completed the questionnaire. Based on inclusion criteria, all survivors included in the current analysis were diagnosed with early-stage of the disease (stage I or II) and were only surgically treated. It is important to note that the NCR does not systematically register tumor stage for BOTs. All survivors of BOT were in stage I of the disease and were treated surgically only. Of the available ovarian cancer survivors in study 1, 58 survivors were in stage I of the disease and were treated surgically only. In study 2, this was the case for 32 ovarian cancer survivors. There were no ovarian cancer patients with stage II disease treated surgically alone.

The mean age at diagnosis of the BOT survivors was 52 years (SD = 13.6), and for the survivors of ovarian cancer, the mean age at diagnosis was 55 years ($SD = 13.6$). One-third of BOT survivors ($n = 27$; 33%) and one-fifth of ovarian cancer survivors ($n = 20$;23%) were younger than 52 years, indicating that these women were possibly premenopausal. In addition, most survivors of BOT (85.5%) and ovarian cancer (94.3%) had a unilateral tumor.

The mean age at the time of completing the survey of the 83 BOT survivors was 60 years ($SD = 14$) and they were diagnosed with a BOT on average 6.6 years ($SD = 3.0$) prior to completing the questionnaire. The 88 early-stage ovarian cancer survivors had a mean age of 61 years at the time of completing the survey ($SD = 14$) and were diagnosed on average 5.9 years ($SD = 2.9$) prior to completing the questionnaire. Due to one missing value on education level in the BOT sample, no matching could be done for this participant. Therefore, the education-, sex- and age-matched cancer-free population consisted of 82 participants with a mean age of 59 years ($SD = 14.4$) (Table 1).

BOT survivors were not statistically significantly different from early-stage ovarian cancer survivors and the cancer-free population in terms of baseline characteristics (Table 1).

3.2. HRQoL of BOT survivors compared with early-stage ovarian cancer survivors

In most subscales BOT survivors were not significantly different from early-stage ovarian cancer survivors. BOT survivors however, reported statistically significantly less insomnia than survivors of early-stage ovarian cancer (BOT survivors: $M = 18.5$, $SD = 27.2$; Early-stage ovarian cancer survivors: $M = 29.1$, $SD = 30.8$; $\beta = -9.6$, 95%CI [−18.0;-1.3]). This difference was of small clinical relevance. Although all other comparisons were statistically insignificant, BOT survivors tended to have better functioning outcome and less symptoms, but the clinical effect sizes were only trivial (Table 2).

3.3. HRQoL of BOT survivors compared with the cancer-free population

In most subscales BOT survivors were not significantly different from the cancer-free population. BOT survivors however, reported

Table 1
sociodemographic and clinical characteristics of BOT survivors, early-stage ovarian cancer survivors and the cancer-free population, N (%).

	BOT survivors ($n = 83$)	Early-stage ovarian cancer survivors ($n = 88$)	Matched cancer-free population[a] ($n = 82$)	P-value BOT vs. Ovarian cancer survivors*	P-value BOT survivors vs. cancer-free population*
Age at survey (years)					
Mean (SD)	59.5 (13.7)	60.6 (14.4)	58.5 (14.4)	0.606	NA
Median (Min, Max)	57.6 (26.9, 85.4)	60.6 (24.0, 91.3)	57.5 (23.0, 89.0)	NA	NA
Education level[b]					
Low	30 (36%)	28 (32%)	30 (37%)	0.517	NA
Medium	31 (37%)	29 (33%)	31 (38%)		
High	21 (25%)	29 (33%)	21 (26%)		
Missing	1 (1%)	2 (2%)	0 (0%)		
Marital status[c]					
Partner	57 (69%)	55 (63%)	61 (74%)	0.413	0.690
No partner	24 (29%)	32 (36%)	21 (26%)		
Missing	2 (2%)	1 (1%)	0 (0%)		
Number of comorbidities					
0	27 (33%)	27 (31%)	31 (38%)	0.884	0.801
1	19 (23%)	23 (26%)	17 (21%)		
≥2	36 (43%)	37 (42%)	34 (42%)		
Missing	1 (1%)	1 (1%)	0 (0%)		
Age at diagnosis (years)					
Mean (SD)	52.3 (13.6)	55.9 (13.9)	NA	0.237	NA
Median (Min, Max)	52.0 (22.0, 81.0)	55.0 (24.0, 82.0)	NA	NA	NA
Time since diagnosis (years)					
Mean (SD)	6.58 (2.95)	5.89 (2.88)	NA	0.126	NA
Median (Min, Max)	6.44 (1.75, 12.0)	5.37 (1.77, 12.1)	NA	NA	NA
Lateralization					
Unilateral	71 (85.5%)	83 (94.3%)	NA	0.053	NA
Bilateral	12 (14.5%)	4 (4.5%)	NA		
Missing	1 (1.1%)	0 (0%)	NA		

BOT = borderline ovarian tumor; SD = standard deviation; NA = not applicable.
* P-value indicates whether there are baseline differences between the sample of BOT survivors and early-stage ovarian cancer survivors and of BOT and the cancer-free population using independent samples t-tests and chi-square tests.
[a] The cancer-free population is matched to the BOT survivors on education, sex and age.
[b] Education level: low = primary or secondary education or less; middle = vocational training; high = university or higher.
[c] Partner = married/cohabitating; No partner = Single/ divorced/ widowed.

Table 2
The mean score (SD) on HRQoL domains of BOT survivors, early-stage ovarian cancer survivors and the cancer-free population. Unstandardized beta's with 95% confidence intervals (CI) of multivariable regression analysis with HRQoL domains as dependent variable and the diagnosis as independent variable, adjusted for pre-defined confounders. Clinically importance of the difference (CIDs) are reported.

	BOT survivors (n = 83)	Ovarian cancer survivors (n = 88)	Cancer-free population (n = 82)	BOT survivors vs. Ovarian cancer survivors		BOT survivors vs. Cancer-free population	
				β (95% CI)[1]	CID[a]	β (95% CI)[2]	CID[a]
Global health status	81.2 (17.0)	79.9 (17.5)	79.6 (16.7)	1.3 (−3.7;6.2)	Trivial	2.4 (−2.5;7.3)	Trivial
EORTC QLQ C-30 functioning scales							
Physical	84.9 (18.4)	80.9 (23.6)	87.6 (15.8)	3.6 (−1.6;8.7)	Trivial	−1.7 (−6.2;2.8)	Trivial
Role	81.3 (29.1)	80.9 (27.7)	87.8 (18.0)	0.9 (−6.8;8.6)	Trivial	−5.4 (−12.0;1.3)	Trivial
Emotional	85.6 (21.6)	84.2 (18.9)	85.7 (18.7)	1.1 (−5.1;7.3)	NA	0.4 (−5.7;6.5)	NA
Cognitive	90.6 (14.3)	88.3 (20.2)	93.3 (13.3)	2.3 (−3.0;7.6)	Trivial	−2.2 (−6.3;1.9)	Trivial
Social	92.2 (19.5)	92.0 (17.1)	94.5 (11.8)	0.1 (−5.4;5.6)	Trivial	−2.0 (−6.8;2.8)	Trivial
EORTC QLQ C-30 symptom scales							
Fatigue	18.1 (21.4)	20.9 (25.0)	19.8 (19.7)	−2.8 (−9.5;3.9)	Trivial	−2.4 (−8.4;3.6)	Trivial
Nausea/vomiting	2.8 (9.7)	5.1 (13.5)	3.0 (9.5)	−2.7 (−6.2;0.8)	Trivial	−0.3 (−3.2;2.7)	Trivial
Pain	16.3 (24.1)	18.4 (26.6)	19.1 (20.3)	−2.4 (−9.4;4.5)	Trivial	−3.8 (−10.1;2.5)	Trivial
Dyspnea	13.4 (26.6)	13.3 (25.0)	4.5 (12.6)	−0.6 (−8.0;6.7)	Trivial	**8.2 (2.1;14.4)**	**Small**
Insomnia	18.5 (27.2)	29.1 (30.8)	22.8 (28.1)	**−9.6 (−18.0;-1.3)**	**Small**	−4.9 (−13.1;3.3)	Small
Appetite loss	3.6 (13.8)	5.3 (18.1)	2.4 (10.2)	−1.5 (−6.3;3.2)	Trivial	0.9 (−2.8;4.6)	Trivial
Constipation	8.4 (20.7)	11.7 (23.2)	8.1 (17.8)	−4.4 (−10.9;2.2)	Trivial	−0.2 (−6.0;5.6)	Trivial
Diarrhea	2.0 (12.0)	3.4 (11.3)	4.9 (14.0)	−1.0 (−4.6;2.6)	Trivial	−3.1 (−7.1;0.9)	Small
Financial problems	3.3 (12.4)	5.7 (16.9)	2.4 (13.6)	−2.3 (−6.8;2.1)	Trivial	0.5 (−3.5;4.4)	Trivial
EORTC-OV28 functioning scale							
Sexual functioning	73.1 (27.3)	77.4 (25.8)	77.4 (25.8)	0.3 (−8.5;9.1)	NA	0.5 (−8.1;9.1)	NA
Hospital Anxiety and Depression scales							
Anxiety	4.6 (3.5)	4.6 (3.4)	4.3 (3.3)	0.3 (−0.9;1.5)	NA	0.2 (−0.8;1.2)	NA
Depression	3.4 (3.8)	3.8 (3.5)	3.1 (3.0)	−0.0 (−1.3;1.2)	NA	0.2 (−0.8;1.2)	NA

A higher score on global health status and functioning scales indicates better functioning, while a higher score on the symptom scales and anxiety and depressive symptoms indicates more symptoms.
[1] Adjusted for age, time since diagnosis, number of comorbidities, marital status and education level.
[2] Adjusted for age, number of comorbidities, marital status and education level.
[a] CID: small = a subtle but nevertheless clinically relevant difference; trivial = a difference unlikely to have any clinical relevance. Bold values indicate CID of small in combination with P-value <0.05. No CID is available for emotional functioning, sexual functioning and the anxiety and depression scales. BOT = borderline ovarian tumor; HRQoL = Health-related quality of life; NA = not available. The level of anxiety and depressive symptoms (HADS) was only assessed in study 1 and the cancer-free population, therefore no data were available for the 32 patients with ovarian cancer in study 2. BOT patients, ovarian cancer patients and the cancer-free population completed the same instruments to assess HRQoL.

statistically significantly more dyspnea than the cancer-free population (BOT survivors: $M = 13.4$, $SD = 26.6$; Cancer-free population: $M = 4.5$, $SD = 12.6$; $\beta = 8.2$, 95%CI [2.1;14.4]). This difference was of small clinical relevance. Although no other significant differences were found, BOT survivors tended to have poorer functioning outcome but better global health status, yet the clinical effect sizes were only trivial. BOT survivors tended to reported similar levels of symptom experience compared with the cancer-free population (Table 2).

Table explaining the included studies, populations and outcomes.

Study	Population	Outcome
BOT and OC (study 1)	**OC and BOT**	EORTC QLQ-C30, HADS
InCHARGE (study 2)	OC	EORTC QLQ-C30
CentERpanel	Cancer-free population	EORTC QLQ-C30, HADS

OC = ovarian cancer; BOT = borderline ovarian tumor; EORTC QLQ-C30 = The European Organization for Research and Treatment of Cancer QLQ-C30; HADS = Hospital Anxiety and Depression Scale.

4. Discussion

The current findings indicate that, as anticipated, the reported HRQoL of BOT survivors generally lies between that of early-stage ovarian cancer survivors and the cancer-free population. However, these differences were, except for two outcomes, not statistically significant and mostly of trivial clinical relevance. BOT survivors did experience less insomnia than early-stage ovarian cancer survivors and more dyspnea than the cancer-free population, both of which were of small clinical relevance.

To date, only one other study has evaluated HRQoL in BOT survivors, but it has not previously been assessed in comparison with (early-stage) ovarian cancer survivors or the cancer-free population. A German prospective cohort study that included 110 patients diagnosed with BOT assessed HRQoL using the EORTC QLQ-C30. In the study it was stated that these patients reported 'very good' quality of life and global health status ($M = 69.8$), although no comparison group was used [5]. In comparison with these results, BOT survivors in the current study reported on average a much higher score on global health status ($M = 81.2$), which was comparable with the score of both early-stage ovarian cancer survivors and the cancer-free population. One explanation is the population-based sampling of the current study and the more clinical-based approach in the previous study. A population-based sampling reflects a more diverse and representative sample of the general population, while the previous study focused more on a specific patient population, which may have led to different outcomes.

In line with the current findings, the German cohort study did also observe a relatively high score on dyspnea (Current study: $M = 13.4$ vs. German cohort study: $M = 20.2$) in BOT patients. The German cohort study also showed age differences, with younger patients having significantly less dyspnea than the older patients. The same high score on dyspnea is found in two other previous studies that included ovarian cancer patients. Van Walree et al. [19] included ovarian cancer survivors who received chemotherapy to evaluate age differences in HRQoL. They found a mean score of 25.4 among survivors <70 years old and a mean score of 29.7 among survivors ≥70, which was also a statistically significant difference. Bhugwandass et al. [22] evaluated differences in HRQoL between ovarian cancer patients who received chemotherapy and patient who did not, using partially the same data. The patients who did not receive chemotherapy reported a similarmean score on dyspnea as both the BOT and early-stage ovarian cancer survivors in the current study (Current study: M BOT survivors = 13.4; M early-stage ovarian cancer survivors = 13.3 vs. previous study:

$M = 15.6$). It is a consistent finding among patients, but no clinical or biological explanation was found for the high level of dyspnea observed in the current study and previous studies. The question now is whether dyspnea is a symptom that fits with another construct that has not been specifically measured, for example, anxiety or menopausal symptoms. Since the general population in the current study was matched on age to the BOT survivors, age differences do not seem to be an explanation for the difference found in the current study, although the age at which survivors entered (surgical) menopause is an important factor to consider. When women enter menopause, you often see an increase in weight and, in addition, iatrogenic menopause is associated with cardiovascular problems [38–41]. However, more research would need to be done, but it does seem to be relevant to this patient group.

It is suggested that BOT patients associate the malignant potential of their tumor with that of ovarian cancer, despite being informed of their more favorable prognosis [10]. A survey study in 60 women diagnosed with a BOT to assess their individual perception of BOTs and biological-behavior of the disease supported this statement [42]. Our results do not support this finding as we did not find a significant difference in emotional functioning, anxiety or depressive symptoms between survivors with a BOT or with early-stage ovarian cancer. However, given that dyspnea levels of BOT patients are worse than the cancer-free population and BOT generally lies in between HRQOL of ovarian cancer survivors and the cancer-free population, our results suggest an association with the malignant potential with cancer. Nevertheless, it remains uncertain whether the results of the current study conclusively support these previous findings, as the current study sought to investigate potential differences between groups, rather than testing for equivalency.

The finding of the current study regarding lower levels of insomnia among BOT survivors compared to ovarian cancer survivors has not been reported previously. However, another study evaluating the sleep outcomes in ovarian cancer patients, stated that 14–60% of ovarian cancer patients suffer from insomnia, which persists even years after diagnosis due to abdominal discomfort and high distress [43]. An explanation might be recurrence and, in particular, receiving chemotherapy as treatment in case of recurrence, as this has been shown to be associated with sleep disturbances [43]. However, in the current study, no information was available on recurrence and what treatment patients had to undergo in case of recurrence. In addition to diagnosis and treatment being associated with sleep disorders and insomnia, surgical menopause could be a possible explanation for the difference in insomnia [5,22,43]. It has been suggested that surgical menopause may have long-term consequences, which in addition could affect HRQoL [5,17,22]. Surgical menopause causes immediate and worse symptoms than the natural menopause, such as hot flashes, muscle and joints pain and loss of libido, and is also associated with sleep disturbances and insomnia [5,6,17,44–46]. Often, surgery for BOTs is less extensive (often unilateral) and invasive than the surgery required to treat ovarian cancer, which could possibly explain the difference between the two patient groups [19].

One strength of this study was the inclusion of a cancer-free population that was matched to the BOT survivors on age, education and sex. Another strength is the population-based sampling that increases the generalizability of the results, as there were few selection criteria and therefore minimal selection bias compared with clinical trials [19].

Despite these strengths, limitations must also be considered when interpreting the results. First, this is a cross-sectional study, meaning that no information is available on a potential change of HRQoL over time. Second, the current study faced a relatively low response rate, which increases the likelihood of selection bias and limits the generalizability. Participation was voluntary and, according to previous studies, non-respondents might experience poorer quality of life and health status [10,19,25]. The proportion respondents with poorer HRQoL could therefore be underestimated, which could affect the generalizability of the results. Given the lower 5-year survival rate compared with BOTs this selection is expected to occur primarily in ovarian cancer survivors, although the 5-year survival rate is significantly better for women diagnosed with early-stage ovarian cancer (75–100%) compared with ovarian cancer in general (38–46%) [10,22]. However, a previous study using the same data showed no differences in baseline characteristics between respondents and non-respondents [26]. In addition, data on sexual functioning, anxiety or depressive symptoms were not available for all survivors, resulting in a smaller sample size for these domains. Another limitation relates to possible information bias, as there is no detailed information on whether survivors were disease-free, were receiving any treatment at the time of completing the questionnaire, or on response to treatment, although all of these could affect HRQoL [19]. In addition, there is also no information on recurrence and whether there is still an ovary in situ. However, accurate clinical data on the initial treatment are available from the NCR and were used in the current study, something many studies also lack.

As some BOT patients do experience increased dyspnea, sufficient support to those in need should be provided. As mentioned earlier, early iatrogenic menopause may play a role in the increased dyspnea. To mitigate this effect, hormone replacement therapy (HRT) or lifestyle advice addressing weight gain and exercise could be considered [17,47]. It is important to note that comprehensive follow-up care is not solely the responsibility of gynecologists. Further research on the benefits and risks of HRT after surgery for BOT in premenopausal women is needed.

Also, we were not able to do a sub analysis among the younger BOT population who may also be in need of more support [5]. Future research could investigate what explanatory mechanisms might underlie the higher dyspnea symptom burden, considering age differences and the impact of immediate surgical menopause. Especially in premenopausal women due to the removal of one or both ovaries in BOT surgery. Surgery for BOT may lead to long-term hormonal changes and menopause-related issues, affecting quality of life, weight and cardiovascular problems [5,17,38–41,48]. In fact, the patients' long-term patient survival may be directly compromised as overall mortality increases [49]. HRQoL differences between pre- and postmenopausal women should be investigated in larger studies, possibly using longitudinal designs to examine HRQoL changes over time.

In conclusion, the HRQoL of BOT survivors generally lies in between that of early-stage ovarian cancer survivors and the cancer-free population. However, functioning does not significantly nor clinically differ from these two groups. However, BOT survivors experienced less insomnia than early-stage ovarian cancer survivors and more dyspnea than the cancer-free population. Future research is warranted into the impact of surgical menopause on HRQoL and could provide insights into the higher dyspnea burden after having a BOT.

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Author contributions

All authors contributed to the study conceptualization and design. Data collection was performed by BHR, MCV, DB, DH, NPME. Material preparation was done by BE, BHR and NPME. Formal analyses were conducted by BE. The first draft of the manuscript was written by BE, BHR, NPME and all authors commented on previous versions of the manuscript. Supervision was given by BHR and NPME. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Babette van der Eerden: Writing – original draft. **Belle H. de Rooij:** Writing – review & editing, Supervision. **Leo J. Schouten:** Writing – review & editing, Supervision. **Dorry Boll:** Writing – review & editing. **Dennis van Hamont:** Writing – review & editing. **M. Caroline Vos:** Writing – review & editing. **Nicole P.M. Ezendam:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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