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Older ovarian cancer survivors report lower long-term health-related quality of life than younger survivors: A study from the population-based profiles registry

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HIGHLIGHTS

- The number of older ovarian cancer survivors is growing but data on long-term HRQoL are lacking.
- Compared to an age-matched normative population, older ovarian cancer survivors report lower HRQoL than younger survivors.
- Most clinically affected items were physical and cognitive functioning and among older survivors also dyspnea and fatigue.
- Age appeared to moderate the effect of chemotherapy on HRQoL.

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ABSTRACT

Objective. To assess long-term differences in health-related quality of life (HRQoL) of older ovarian cancer survivors compared to both an age-matched normative population and to younger survivors. In addition, the differential effect of chemotherapy on HRQoL between older and younger survivors was compared.

Methods. Ovarian cancer survivors (n = 348) diagnosed between 2000 and 2010, as registered by the Dutch population-based Eindhoven Cancer Registry, were invited to complete the EORTC QLQ-C30 HRQoL questionnaire in 2012. HRQoL outcomes of survivors were compared with an age-matched normative population and older survivors (≥70 years) were compared with younger survivors.

Results. The questionnaire was returned by 191 ovarian cancer survivors (55%), 31% were aged ≥70 years (n = 59). Compared to the normative population, survivors ≥70 years scored lower on global health status and all functioning subscales except emotional functioning, and they reported more symptoms. Survivors aged <70 years only reported worse physical and cognitive functioning in comparison with the normative population. Most differences were of medium to small clinical relevance. Age appeared to moderate the effect of chemotherapy on HRQoL. Older survivors who had received chemotherapy experienced better physical functioning and less pain and insomnia while the opposite was found in younger survivors.

Conclusion. In comparison with an age-matched normative population, older ovarian cancer survivors report lower HRQoL scores than younger survivors. As this represents a selection of long-term survivors, future research should focus on the trajectory of HRQoL from diagnosis throughout treatment and follow-up to identify which factors are related to worse HRQoL in the entire older ovarian cancer population and whether timely interventions are able to improve HRQoL.

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1. Introduction

Ovarian cancer is primarily a disease of the elderly and in the Netherlands, more than one third of ovarian cancer patients are aged 70 years or older at diagnosis [1], and this proportion is growing [2]. Most patients present with advanced-stage disease and have a poor prognosis, with five-year survival rates of <15% in patients aged 75 years or older [3].

The majority of patients with ovarian cancer are treated with cytoreductive surgery and combination chemotherapy [4], which is an extensive treatment. In early stage disease, treatment consists of surgery; adjuvant chemotherapy is offered when there are unfavorable tumor characteristics [4] and to patients in whom the staging procedure was suboptimal, which occurs more often in elderly patients [5].

Health-related quality of life (HRQoL) of women with ovarian cancer is seriously impaired by both the diagnosis as well as the extensive treatment [6,7]. With the growing number of older ovarian cancer survivors, data on long-term HRQoL are highly relevant. Multiple organizations have recommended the use of HRQoL as a primary outcome measure in studies on patients with (ovarian) cancer [8–11] but long-term data on these outcomes are largely missing for older patients. Answers to questions such as "How long can I keep living in my own house?" and "Will my cognitive functioning be maintained after treatment?" may be at least as important to older cancer patients as actual long-term survival [12,13]. The scarce research on age and HRQoL in ovarian cancer shows inconsistent results [6,14–18] and in all these studies, the relation between age and HRQoL was not the primary study outcome.

One of the most characteristic aspects of ageing is the failure to maintain homeostasis when challenged by stressors such as disease or treatment, due to diminished physiological reserves [19]. In addition, because of age-related changes in pharmacokinetics and pharmacodynamics [20] and thus a risk of larger lingering side-effects in older women, chemotherapy may disproportionately affect HRQoL of older survivors. Only one prospective study evaluated older patients' chemotherapy tolerance and found that both functioning and quality of life were associated with completion of 4 cycles of chemotherapy [21]. However, the moderating effect of age on the impact of chemotherapy on HRQoL of older and younger ovarian cancer survivors has not been investigated yet. In addition, studies that assessed long-term functioning and symptoms in older ovarian cancer survivors compared to an age-matched general population are currently lacking, while this comparison may be more relevant than comparisons with their younger counterpart.

Therefore, the aims of the present study were to assess long-term differences in HRQoL of older ovarian cancer survivors compared to both an age-matched normative population and to younger ovarian cancer survivors. In addition, the effect of chemotherapy on HRQoL of older and younger ovarian cancer survivors was compared. We hypothesized older survivors' HRQoL to be worse than that of both the normative population and younger survivors and that older survivors' HRQoL is more negatively affected by chemotherapy than HRQoL of younger survivors.

2. Methods

2.1. Setting, participants and data collection

For this study, data of a cross-sectional, population-based survey among ovarian cancer survivors were used. Details of the data collection have been reported previously [22]. In short, all women diagnosed with ovarian cancer between 2000 and 2010, as registered in the Southern region of the Netherlands Cancer Registry (NCR), were eligible for participation (n = 1147). Patients were excluded if they died prior to the start of the study or if their address was unverifiable. Of the 348 eligible ovarian cancer survivors, 191 completed the questionnaire (55%). Respondents and non-respondents did not differ on baseline characteristics (age, years since diagnosis, tumor stage, treatment and socio-economic status) [22].

Patient-reported outcomes were collected in 2012. Ovarian cancer survivors received a letter from their (ex)-attending specialist and a paper questionnaire. Data collection was performed within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship), which is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a population-based cohort of cancer survivors [23]. Ethical approval for the study was obtained from the Medical Ethics Committee of the St. Elisabeth Hospital, Tilburg, the Netherlands.

2.2. Normative population

Socio-demographic and HRQoL data of the normative population were obtained from CentERpanel; an online household panel representative of the Dutch population in the Netherlands [24]. Details of the annual data collection are described elsewhere [25]. In total, data of 1883 cancer-free respondents ≥18 years were available. Of this sample, a random 5-years age-matched normative sample was selected, reflecting the distribution of the ovarian cancer survivors in this study, resulting in 264 respondents.

2.3. Clinical and sociodemographic characteristics

Clinical and sociodemographic information was obtained from the NCR (i.e., date of birth, date of diagnosis, tumor stage, tumor grade, primary treatment and socio-economic status) [26]. Comorbidity at the time of the study was assessed with the adapted Self-administered Comorbidity Questionnaire [27].

2.4. Health-related quality of life

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) was used to assess HRQoL [28]. This questionnaire contains five functional scales regarding physical, role, cognitive, emotional and social functioning and a global health status scale. In addition, it comprises symptom scales on fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial problems. Each item is scored on a 4-point Likert scale ranging from 1: *not at all*, to 4: *very much*. All scale scores were linearly transformed to a 0–100 score [29]. Higher scores on the functioning scales and global health status/QoL represent better HRQoL, while higher scores on the symptom scales indicate worse HRQoL.

2.5. Statistical analyses

Ovarian cancer survivors and the normative population were divided into groups according to age: <70 years and ≥70 years of age at time of the survey. To describe sociodemographics and clinical characteristics, stratified according to age group, we used independent samples *t*-tests for continuous and chi-square tests for categorical variables.

To compare differences in HRQoL levels between ovarian cancer survivors and the normative population (similar age groups), multivariable linear regression analyses were performed. These analyses were adjusted for the following a priori defined confounders: number of comorbidities (as continuous variable), educational level (high = university or higher education; medium = vocational training; low = primary or secondary education or less) and partner status (partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited). In addition, multivariable linear regression analyses were conducted to compare HRQoL of both age groups of ovarian cancer survivors adjusted for the time since diagnosis, number of comorbidities, educational level, partner status and treatment received (chemotherapy yes/no; all but one of the survivors received surgery). Due to

missing values on one or more dependent or independent variables across the different regression analyses, between four to twelve patients were not included in each regression analysis.

Linear regression analysis was performed to assess the moderating effect of age on the association between chemotherapy and HRQoL outcomes. To assess the moderating effect of age, an interaction term of chemotherapy and age was included, and all a priori-selected covariates (i.e. time since diagnosis, number of comorbidities, educational level, partner status and treatment received) were added to the model. Dependent variables were the HRQoL functioning and symptom scales of the QLQ-C30. For outcome scales where the interaction term of chemotherapy and age was statistically significant, stratified analyses for the two age groups were carried out.

Clinically important differences (CID) were determined based upon published guidelines for the EORTC QLQ-C30 [30]. A large difference is defined as one representing unequivocal clinical relevance, a medium difference as likely to be clinically relevant but to a lesser extent, a small difference to be subtle but nevertheless clinically relevant and a trivial difference as circumstances unlikely to have any clinical relevance. For emotional functioning there is no CID available, and therefor Norman's rule of thumb was used to assess clinical relevance. Norman's rule of thumb states that a difference between groups of half a SD or more can be regarded clinically relevant [31].

All analyses were performed using IBM SPSS Statistics version 23.0. A two-sided P-value <0.05 was considered significant, while for the moderation analysis a P-value <0.1 was considered significant [32].

3. Results

3.1. Sample characteristics

The mean age of the 191 ovarian cancer survivors who responded to the questionnaire was 64 years; 59 were aged ≥70 years at the time of the survey (31%, Table 1). Women were diagnosed with ovarian cancer on average 6 years before completing the questionnaire (range 2–12 years). Two-thirds were diagnosed with early-stage disease (64%). All but one received surgery, while 131 (69%) received chemotherapy. The normative population consisted of 264 controls.

3.2. Comparison of baseline characteristics among ovarian cancer survivors and the normative population

Older ovarian cancer survivors more often did not have a partner (56% versus 27% respectively; P < 0.01; Table 1) and had lower educational levels (64% versus 37% respectively low educational level; P < 0.01) compared to younger survivors.

The normative population had a higher educational level compared to the ovarian cancer survivors (P < 0.01).

3.3. Comparison of HRQoL between ovarian cancer survivors and the normative population

Ovarian cancer survivors aged <70 years reported significantly worse physical and cognitive functioning compared to the normative population (Table 2; Fig. 1A). These differences were of small clinical relevance. Emotional and social functioning were not significantly different compared to the normative population, nor were the QLQ-C30 symptom scales (Table 2; Fig. 2A).

Considering women aged ≥70 years, compared to the normative population, ovarian cancer survivors reported significantly lower levels on global health status as well as all functioning subscales except emotional functioning (Table 2; Fig. 1B). The differences in cognitive and role functioning were of medium clinical relevance, while the others were of small clinical relevance. Among the QLQ-C30 symptom scales, the following were scored significantly worse in the ovarian cancer survivors: fatigue, nausea/vomiting, dyspnea, and appetite loss (Table 2; Fig. 2B). There was a trend towards statistical significance for insomnia and diarrhea which were both reported more often in the ovarian cancer survivors. The clinical relevance of the differences was large for dyspnea, medium for fatigue and small for other symptoms.

Table 1
Sociodemographic and clinical characteristics of the study population, N (%).

	Survivors <70 (n = 132)	Norm <70 (n = 181)	P-value*	Survivors ≥70 (n = 59)	Norm ≥70 (n = 83)	P-value*	P-value survivors*
Age at time of survey (mean, SD)	58.5 (8.4)	58.2 (8.1)	0.75	77.3 (5.3)	76.0 (4.4)	0.10	
Educational level[a]							
High	29 (22)	64 (35)		5 (9)	27 (33)		
Medium	53 (41)	20 (11)	<**0.01**	15 (27)	3 (4)	<**0.01**	<**0.01**
Low	48 (37)	97 (54)		35 (64)	53 (64)		
Missing	2	0		4	0		
Marital status[b]							
Partner	95 (73)	134 (74)	0.85	25 (44)	42 (51)	0.43	<**0.01**
No partner	35 (27)	47 (26)		32 (56)	41 (49)		
Missing	2	0		2	0		
Number of comorbidities							
0	37 (29)	48 (27)		10 (17)	6 (7)		
1	34 (26)	43 (24)	0.78	18 (31)	19 (23)	0.07	0.24
≥2	59 (45)	89 (49)		31 (53)	58 (70)		
Missing	2	1		0	0		
Years since diagnosis (mean, SD)	6.1 (3.2)			6.4 (3.2)			0.48
FIGO stage at diagnosis							
I	83 (63)			32 (54)			0.72
II	13 (10)			9 (15)			
III	30 (23)			14 (24)			
IV	5 (3)			3 (5)			
Missing	0			0			
Treatment							0.78
Chemotherapy only	1 (1)			0 (0)			
Surgery only	42 (32)			18 (31)			
Chemotherapy + surgery	89 (67)			41 (70)			
Missing	0			0			

* Bold data indicate P-value <0.05.
[a] Educational level: high = university or higher education; medium = vocational training; low = primary or secondary education or less.
[b] Marital status: partner = married or cohabiting; no partner = divorced, widowed, never married or never cohabited.

Table 2
Mean score (SD) on the EORTC QLQ-C30 functioning and symptom scales of ovarian cancer survivors and the normative population according to age. Multivariable regression analysis with HRQoL as dependent variable and age as independent variable.

EORTC QLQ-C30 scales	Survivors <70 (n = 132)	Survivors ≥70 (n = 59)	Norm <70 (n = 181)	Norm ≥70 (n = 83)	Survivors vs norm <70 β (95% CI)	P-value	CID[a]	Survivors vs norm ≥70 β (95% CI)	P-value	CID[a]	Survivors <70 vs survivors ≥70 β (95% CI)	P-value	CID[a]
Physical functioning	83.3 (20.4)	70.2 (23.5)	88.5 (15.8)	75.7 (20.8)	−5.6 (−9.0; −2.2)	<0.01	**Small**	−11.1 (−18.1; −4.1)	<0.01	**Small**	−11.0 (−17.6; −4.5)	<0.01	**Small**
Role functioning	81.2 (24.8)	68.8 (33.3)	86.4 (22.3)	80.3 (24.3)	−5.5 (−10.1; −0.9)	0.02	Trivial	−19.4 (−28.5; −10.2)	<0.01	**Medium**	−12.4 (−21.2; −3.5)	<0.01	**Small**
Emotional functioning	83.1 (20.6)	82.4 (20.0)	84.5 (17.6)	86.9 (15.8)	−1.0 (−5.1; −3.0)	0.62	No	−6.6 (−12.9; −0.2)	0.04	No	−2.0 (−8.7; 4.9)	0.57	No
Cognitive functioning	84.9 (20.0)	84.2 (22.6)	90.3 (15.9)	91.0 (13.6)	−5.5 (−9.3; −1.6)	<0.01	**Small**	−9.1 (−15.5; −2.8)	<0.01	**Medium**	0.7 (−6.4; 7.9)	0.84	Trivial
Social functioning	87.5 (19.7)	86.1 (22.9)	91.1 (17.8)	92.0 (14.3)	−3.3 (−7.3; 0.8)	0.11	Trivial	−10.4 (−16.6; −4.3)	<0.01	**Small**	−2.9 (−9.9; 4.3)	0.44	Trivial
Global health status	77.8 (16.8)	70.5 (21.9)	76.7 (16.8)	72.7 (17.3)	1.4 (−1.9; 4.8)	0.39	Trivial	−6.9 (−12.8; −0.9)	0.02	**Small**	−7.2 (−12.8; −1.7)	0.01	**Small**
Fatigue	22.1 (23.2)	31.1 (28.5)	19.4 (20.3)	24.1 (21.4)	2.7 (−1.7; 7.0)	0.23	Trivial	13.6 (5.7; 21.4)	<0.01	**Medium**	8.9 (1.0; 16.8)	0.03	**Small**
Nausea/vomiting	4.3 (12.1)	8.5 (20.5)	4.4 (12.4)	3.8 (13.4)	−0.4 (−3.0; 2.3)	0.78	Trivial	6.1 (0.3; 11.9)	0.04	**Small**	3.0 (−2.1; 8.1)	0.25	Small
Pain	19.4 (26.1)	25.4 (30.7)	20.3 (24.2)	27.5 (28.6)	−1.1 (−5.6; 3.5)	0.65	Trivial	5.8 (−3.3; 14.9)	0.21	Trivial	5.5 (−2.9; 13.9)	0.20	Trivial
Dyspnoea	10.4 (21.9)	21.0 (31.3)	8.3 (17.2)	11.3 (21.0)	1.8 (−2.4; 5.9)	0.40	Trivial	15.8 (7.0; 24.6)	<0.01	**Large**	10.9 (2.6; 19.2)	0.01	**Medium**
Insomnia	25.4 (29.0)	29.7 (34.4)	22.4 (27.9)	21.3 (26.8)	3.2 (−2.8; 9.1)	0.30	Trivial	9.7 (−0.7; 20.1)	0.07	Small	0.6 (−9.7; 10.9)	0.91	Trivial
Appetite loss	15.2 (3.8 (10.6)	16.4 (30.6)	3.2 (13.0)	3.2 (9.9)	0.37 (−2.3; 3.0)	0.79	Trivial	13.4 (6.5; 20.4)	<0.01	**Small**	9.8 (3.7; 15.9)	<0.01	**Small**
Constipation	11.4 (21.3)	6.9 (24.7)	6.9 (17.2)	12.1 (18.5)	3.8 (−0.3; 7.8)	0.07	Trivial	7.0 (−0.7; 14.7)	0.07	Small	6.4 (−1.0; 13.9)	0.09	Small
Diarrhea	6.3 (18.0)	6.0 (19.2)	3.5 (11.4)	3.2 (11.2)	2.4 (−0.6; 5.3)	0.11	Trivial	3.7 (−1.7; 9.1)	0.17	Trivial	−1.6 (−7.3; 4.3)	0.61	Trivial
Financial problems	7.4 (19.5)	6.1 (15.8)	4.3 (15.8)	3.6 (13.8)	3.3 (−0.6; 7.2)	0.11	Small	4.1 (−1.3; 9.5)	0.14	Small	−1.6 (−8.2; 5.0)	0.63	Trivial

2nd - 5th column show crude means and standard deviations (SD). From the 6th column to the end: multivariable regression analysis with EORTC-QLQ-C30 functioning domains or symptoms as dependent variable and age as dichotomous independent variable, adjusted for covariates. A higher score on the functioning scales and global health status means better functioning and quality of life, whereas a higher score on the symptom scales means more complaints. Unstandardized betas (β), confidence intervals (95% CI) and P-values are reported.

[a] Legend for clinically important difference (CID): large = a difference representing unequivocal clinical relevance; medium = a difference likely to be clinically relevant but to a lesser extent; small = a subtle but nevertheless clinically relevant difference; trivial = a difference unlikely to have any clinical relevance. For emotional functioning, no CID is available and Norman's rule of thumb was used to assess clinical relevance. Norman's rule of thumb states that a difference between groups of half a SD or more can be regarded clinically relevant. Bold value indicate CID of small or higher in combination with P-value ≤0.05.CID = clinically important difference; HRQoL = health-related quality of life; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

3.4. Comparison of HRQoL between younger and older ovarian cancer survivors

In comparison with younger survivors, older survivors reported significantly poorer physical and role functioning and a lower global health status (Table 2; Fig. 1C). These three differences were of small clinical relevance. Emotional, social and cognitive functioning were comparable between both groups. Considering the symptom scales, older survivors scored worse on fatigue, dyspnea and appetite loss (Table 2; Fig. 2C). The clinical relevance of these differences was medium for dyspnea and small for fatigue and appetite loss.

3.5. Differential association between chemotherapy treatment and HRQoL between younger and older ovarian cancer survivors

There was a significant interaction between chemotherapy and age for physical functioning, pain and insomnia, while the other scales did not differ between women who received chemotherapy and those who did not (data not shown). Stratified multilevel linear regression analyses subsequently showed that older survivors who had received chemotherapy (n = 41) experienced better physical functioning and less pain and insomnia compared to older survivors who had not received chemotherapy (n = 18; Fig. 3A–C). The clinical relevance for differences in physical functioning and pain were small and for insomnia medium. In younger survivors who had received chemotherapy (n = 90), physical functioning and pain were scored slightly worse compared to those who had not received chemotherapy (n = 42) and those that had received chemotherapy experienced more insomnia (Fig. 3A–C). The clinical relevance for differences in physical functioning and pain were trivial and was small for insomnia.

4. Discussion

We analyzed HRQoL in 191 ovarian cancer survivors at an average of six years after diagnosis and found that compared to a normative population, older survivors scored worse on global health status and all functioning domains except emotional functioning, and they reported more symptoms. Younger survivors only scored worse on physical and cognitive functioning. In addition, compared to their younger counterparts, physical and role functioning were rated poorer by older survivors and they reported a lower global health status and more symptoms. The majority of these differences were of medium to small clinical relevance. Lastly, although the number of patients was small, age appeared to moderate the effect of chemotherapy on HRQoL; in contrast to our hypothesis, older survivors who had received chemotherapy experienced better physical functioning and less pain and insomnia while the opposite was seen for younger survivors who had received chemotherapy.

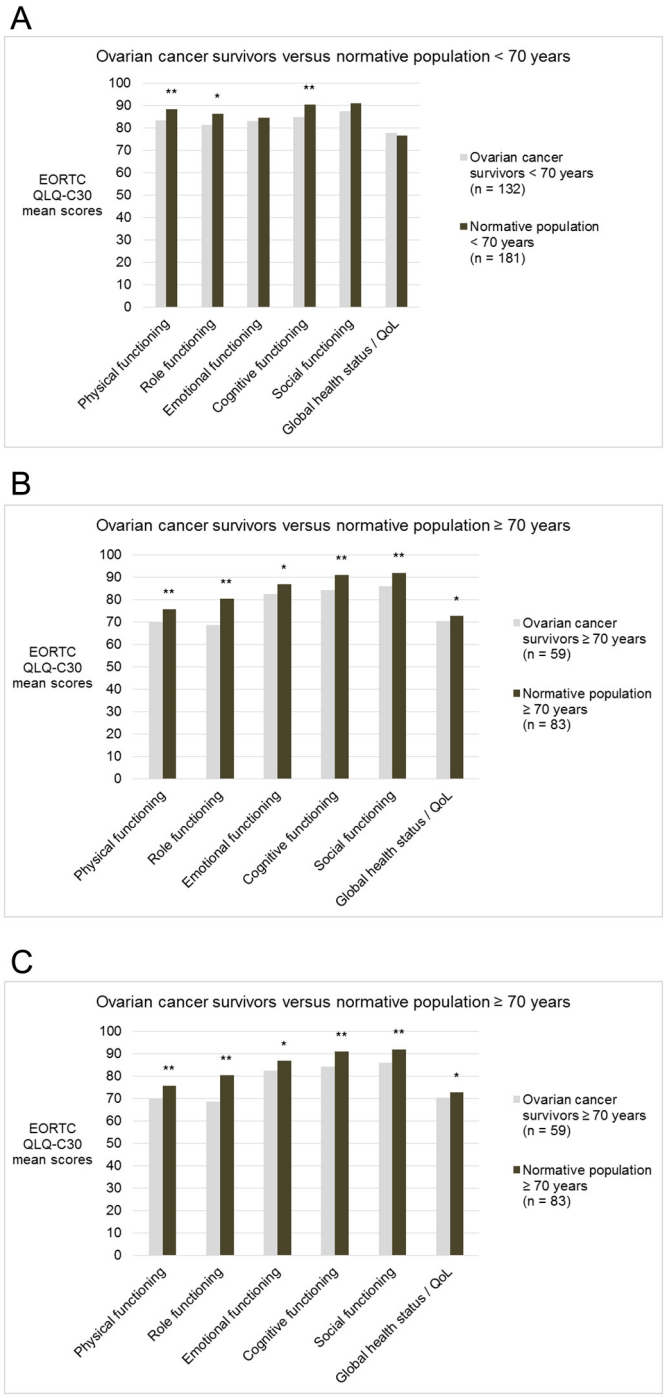

Fig. 1. Differences in EORTC QLQ-C30 mean functioning and global health scores between A. ovarian cancer survivors and the normative population <70 years; B. ovarian cancer survivors and the normative population ≥70 years; C. ovarian cancer survivors aged <70 years and ≥70 years.

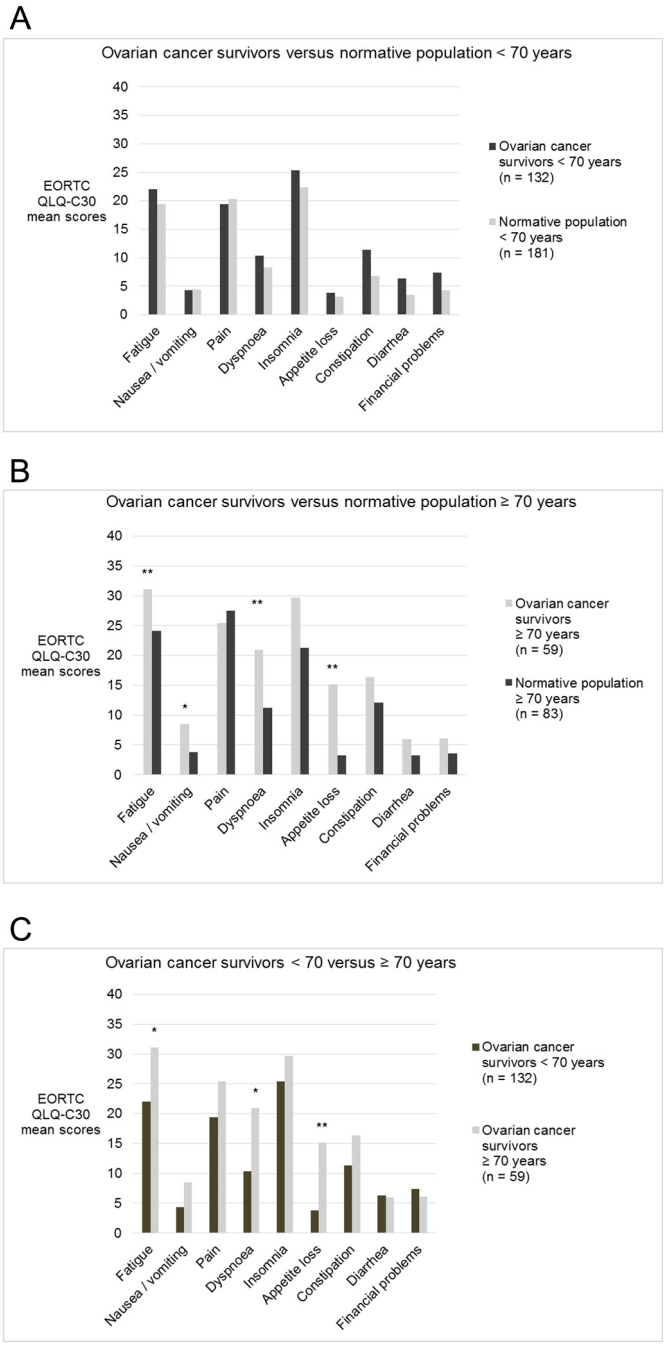

Fig. 2. Differences in EORTC QLQ-C30 mean symptom scores between A. ovarian cancer survivors and the normative population <70 years; B. ovarian cancer survivors and the normative population ≥70 years; C. ovarian cancer survivors aged <70 years and ≥70 years.

Earlier studies evaluating HRQoL in ovarian cancer survivors - without age-specific analyses -yielded conflicting results [7,33–36]. Most observed rather good post-treatment HRQoL, showing similar or better mental and physical HRQoL scores in comparison with norms for the general population [33–35]. However, poor HRQoL in ovarian cancer survivors has also been reported, with observations of persistent mental and somatic morbidity in this population [6,7]. Survivors suffered from cognitive and social impairments and reported lingering symptoms of fatigue, pain and neuropathy [6,7]. None but one of these studies [7] used an age-matched normative control population for comparison.

Studies in different types of malignancies did compare HRQoL outcomes of cancer survivors with an age-matched normative population [37–39]. Similar to our results, older survivors experienced more functional limitations compared to a normative population. However, while in our study the difference in HRQoL compared to the normative population was greater for older survivors than for younger survivors, most of these studies reported an opposite effect. It was suggested that this greater impact of the disease and its treatment for younger patients was due to higher work-related and social demands. On the other hand, it is also possible that older patients received less aggressive treatment than younger patients, and that this explains the difference in impact. There is no clear explanation for the higher impact for older than

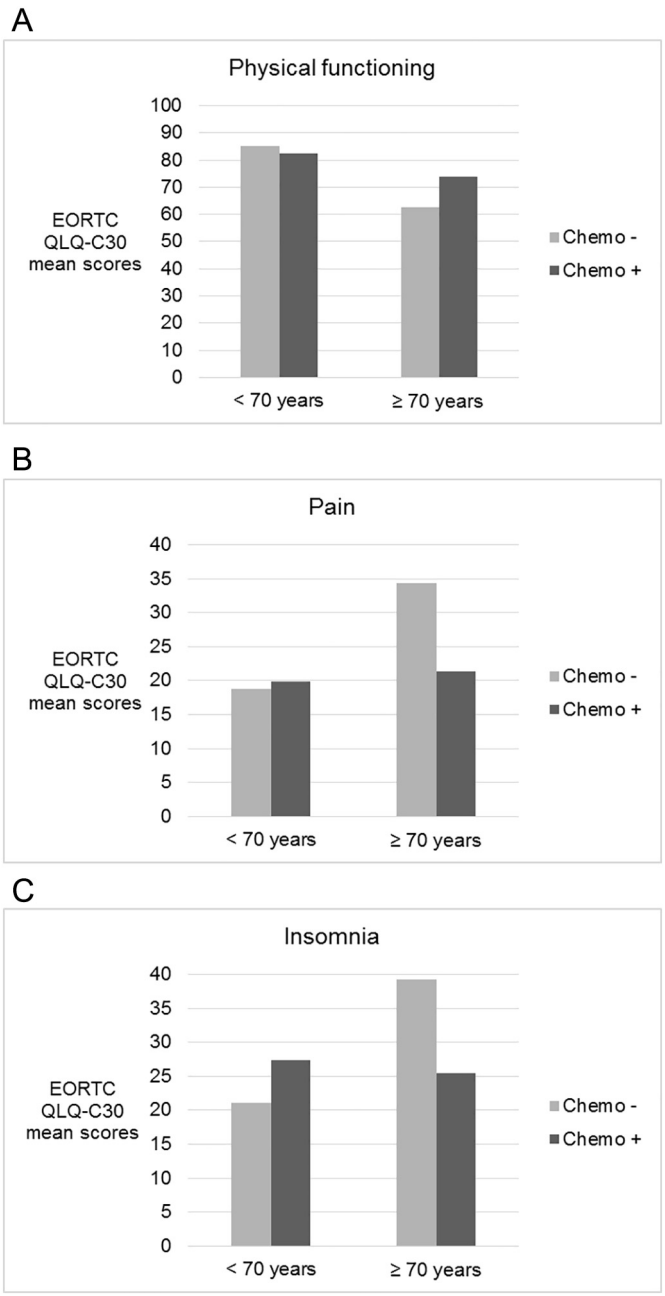

Fig. 3. Moderation of the association between chemotherapy and HRQoL by age for A. physical functioning; B. pain; C. insomnia.

for younger patients in our study compared to prior studies. As we do not have detailed information on the treatment regimens the patients received, we cannot assess whether this may explain differences in the impact of HRQoL.

Only a handful of prior studies assessed whether cancer and its treatment have different consequences for older than for younger ovarian cancer survivors. None of these studies primarily assessed the association of age with HRQoL outcomes, nor did they use an age-matched normative population. Furthermore, these studies differed from our study in that they used a lower age cutoff and mostly other questionnaires to assess HRQoL, such as the SF-36 and the FACT-O, and survivors were generally more recently diagnosed with ovarian cancer. On the one hand, they found that older age was associated with poorer physical functioning one-year post-diagnosis [14] and that older survivors reported worse symptoms of fatigue on average 16 months post-treatment [6]. However, others did not find age to be predictive of HRQoL or symptoms [16,18] or reported that older age predicted better physical and emotional wellbeing during chemotherapy [17].

Although many studies have investigated HRQoL in cancer survivors, we were – to the best of our knowledge – the first to compare the HRQoL of older and younger ovarian cancer survivors with an age-matched normative population. As hypothesized, we found that older ovarian cancer survivors experienced poorer HRQoL than their younger counterparts. Effect sizes were clinically relevant, albeit of medium to small difference, except for a difference of large clinical relevance for dyspnea in older survivors compared to the normative population. An explanation for our findings may be the decreased physiological reserve of older ovarian cancer survivors. Ageing in general is associated with a decrease in physiological reserve and deconditioning due to a gradual deterioration of organ function [19]. Although many age-related changes might not be relevant under normal conditions, they may become apparent when the individual is faced with stressors, such as the diagnosis and treatment of ovarian cancer. HRQoL of older ovarian cancer survivors thus might be more affected by this disease and its lingering treatment sequelae than HRQoL of younger survivors.

Contrary to what we expected, HRQoL of our older survivors seemed not to be negatively affected by chemotherapy. These findings need to be interpreted with caution due to a risk of selection bias. The older survivors participating in our study reflect a selected population of healthier older women; they were considered to be fit enough to receive a burdensome treatment and they were still alive six years (range 2–12 years) after treatment. Unfit older patients may have received less aggressive chemotherapy regimens or best supportive care only and detriments in HRQoL are presumably underestimated as those patients who deceased before the start of the study will tend to have poorer HRQoL and more symptoms than those surviving longer. Other studies demonstrated that long-term side effects of chemotherapy negatively affect HRQoL [40]. The most important contributing factors to deterioration of HRQoL among patients receiving chemotherapy were peripheral neuropathy, a more negative attitude towards sickness and a poorer financial situation [40].

One of the strengths of this study is that it is the first to report on the association of age with long-term HRQoL in ovarian cancer survivors using an age-matched norm population for the comparisons. Also, this study was performed in a population-based setting instead of a hospital-based setting and this improves the generalizability of our results. Limitations include that our findings apply to long-term survivors only and are therefore not representative of the entire population of older ovarian cancer patients. Indeed, most of our patients had early-stage disease while ovarian cancer is normally diagnosed at advanced stage disease. In addition, as the mean age of our cohort was 64 years, we have no information on HRQoL in the oldest old and our results cannot be extrapolated to them. Because of this age composition, we chose to use the somewhat arbitrary cut-off of 70 years rather than a higher cut-off, as this would result in too few older patients to make valid comparisons between groups. In addition, there is a risk of selection bias of both ovarian cancer survivors and normative respondents as it has been demonstrated that non-respondents have poorer HRQoL [41]. Lastly, we lack detailed information on the exact primary treatment and the response to this treatment, and whether the survivors were disease free or received any treatment at the time of the questionnaire, although these treatment and disease characteristics may have influenced HRQoL outcomes.

We found that long-lasting deficits in functioning and symptoms are prevalent particularly in older ovarian cancer survivors. Accordingly, patients should receive information regarding HRQoL outcomes to manage their expectations. The items most clinically affected were physical and cognitive functioning and, among older survivors also, dyspnea and fatigue. This is important as these are areas that may be amenable to targeted interventions, such as counseling, psychosocial support, physical therapy and symptom management, with the aim of stabilizing or improving HRQoL. Ovarian cancer survivors with lingering sequelae

may benefit from supportive care. Future research should identify which predictors are related to worse HRQoL in older survivors and whether targeted interventions are able to improve their HRQoL.

In conclusion, in comparison with an age-matched normative population, older ovarian cancer survivors report lower long-term HRQoL scores than younger survivors. Future research could focus on patients with advanced-stage disease as well and should identify which predictors are related to worse HRQoL in older survivors and whether timely interventions are able to improve their HRQoL.

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Conflict of interest

None.

This manuscript has been prepared in accordance with the style of the journal, and all authors have approved of its contents. This manuscript is not being considered for publication elsewhere and the findings of this manuscript have not been previously published or presented.

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Author contributions statement

IW: study design, data analysis, writing, figures.

MH: study design, writing, figures, approval of final document.

LP: data collection, study design, writing, approval of final document.

MV: writing, approval of final document.

DB: writing, approval of final document.

LH: writing, approval of final document.

NE: study design, data analysis, writing, figures, approval of final document.

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