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Menopausal symptoms in epithelial ovarian cancer survivors: a GINECO VIVROVAIRE2 study

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HIGHLIGHTS

- ≥3 years after treatment, more than half of epithelial ovarian cancer survivors EOCS had vasomotor symptoms.
- Two thirds of the EOCS reported a decrease in libido and, 1/3 sexually active EOCS complained of dyspareunia.
- EOCS with surgical menopause reported more vasomotor symptoms and sexual disorders than those with natural menopause.
- Very few patients received hormone replacement therapy after cancer treatment.

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ABSTRACT

Objective. We have previously shown that epithelial ovarian cancer (EOC) and its treatments have negative effects on long-term quality of life (QoL) and fatigue. The present multicenter study investigated the main menopausal symptoms and gynecological management of EOC survivors (EOCS).

Methods. 166 patients with relapse-free ≥3 years after the end of treatment attended a consultation with a gynecologist, including a questionnaire related to vasomotor symptoms (VMS) and sexuality, a clinical examination, a blood sample and an osteodensitometry. QoL, fatigue, insomnia and mood disorders were measured with validated questionnaires and correlated to VMS. VMS and QoL were assessed according to natural menopause (NM) or surgical menopause (SM).

Results. Mean age at the survey was 62 [21–83] years and stage III/IV (48%). Mean delay since the end of treatment was 6 years. Fifty-nine patients (36%) had SM. Half of patients reported VMS. Seventy-two percent of EOCS with SM had VMS compared to 41% with NM ($P < .001$). VMS were not associated with poor global QoL, fatigue, insomnia or mood disorders. Two-thirds of EOCS reported a decrease in libido. Patients with SM showed a greater

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decrease in libido than NM ($P < .02$). Fourteen percent of them had osteoporosis and 50% osteopenia. Among the 85 patients with VMS, 80 did not receive HRT after cancer treatment. At the time of the survey, only 7 (4%) patients were receiving hormone replacement therapy (HRT).

Conclusions. VMS and sexual disorders are frequently reported by EOCS, particularly among patients with SM. Most EOCS with menopausal symptoms could benefit from HRT to improve these symptoms.

1. Introduction

Epithelial ovarian cancer (EOC) is a gynecological malignancy with poor prognosis and high mortality [1]. However, in recent decades, greater surgical expertise and the use of multimodal therapies have improved the survival rate of women with EOC, with a 44% five-year survival rate [2]. Initial treatment includes wide abdominal and pelvic surgery with bilateral oophorectomy, followed in most of cases by a platinum-based chemotherapy, usually platinum-taxane combinations with maintenance therapy such as PARPi, avastin or a combination [3,4]. During periods of treatment, EOC patients experience a wide range of treatment-related symptoms that may persist after surgery and chemotherapy. Given the poor prognosis of EOC, the main goal until now has been to treat the primary cancer and relapses, whereas the identification and management of persistent treatment-induced side-effects were considered of secondary importance during the post-treatment follow-up. However, EOC survivors (EOCS) report persistent long-term side-effects [5]. Climacteric symptoms and sexual dysfunction induced by surgery are some of the most important complaints [6]. Studies of women who have undergone prophylactic oophorectomy have shown that most of them report moderate to severe menopausal symptoms, even 10 years after surgical menopause [7].

Several studies have demonstrated that hormone replacement therapy (HRT) is safe and beneficial for ovarian cancer patients with menopausal symptoms [8,9], and that HRT improved overall survival among EOCS; except for serous and endometrioid low-grade histologies with a putative hormonal link (theoretical contraindication (CI)), the authors concluded that there was no CI for HRT. The different guidelines promote their use in EOCS particularly in patients under 45 years old [10–12]. However, in practice, it is not sure whether gynecologists follow these guidelines, as demonstrated in a recent Swedish survey [13]. Few studies have explored menopausal symptoms, sexual function, and prescription of HRT among EOCS during the post-treatment period [14]. To our knowledge, no study has extensively explored menopausal complaints, gynecological symptoms, sexuality disorders and quality of life in long-term EOCS.

The aim of this multicenter VIVROVAIRE2 study was to report the main menopausal symptoms, sexual function and hormone replacement therapy (HRT) among EOCS who were relapse-free for at least three years after first-line treatment.

2. Materials and methods

2.1. Study design and participants

Eligible EOCS relapse-free ≥3 years after first-line treatment were identified from the GINECO case-control study "VIVROVAIRE_Step1" [15]. EOCS participating in the VIVROVAIRE1 study were given the opportunity to participate in step 2, which included a dedicated gynecological consultation with clinical examination, blood collection and osteodensitometry (ClinicalTrial.gov number, NCT02323568).

2.2. Recruitment and data collection

EOCS received information from their oncologists during the follow-up consultation. Among the 322 EOCS included in the VIVROVAIRE step 1, 166 accepted to participate in step 2 and attended a consultation by a gynecologist with additional examinations. EOCS medical data were collected from patient records. Patients filled in the different self-reported patient-reported outcomes (PROs) questionnaires. They included standardized and validated instruments assessing global quality of life (QoL), EOC-related symptoms, anxiety and depression, and sleep disturbances.

2.3. Questionnaires

QoL and fatigue were measured with the "functional assessment of cancer therapy scale" FATC-G, FACT-O (Ovarian subscale) and FACT Fatigue questionnaires [16,17]. Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS) [18]. Sleep disturbances were assessed using the 7-item Insomnia Severity Index (ISI) [19]. Socio-demographic parameters and economic status of participants were obtained with a specific questionnaire adapted from the "living conditions" questionnaire used in previous surveys [20].

2.4. Gynecological consultation

The consultation carried out by a gynecologist included a questionnaire related to menopausal symptoms and sexual disorders, a clinical examination, and osteodensitometry. This standardized consultation focused on long-term gynecological sequelae of cancer and its treatment: long-term side-effects of surgery and chemotherapy, climacteric symptoms (vasomotor symptoms, arthralgia, sleep and mood disorders) and sexual disorders (vaginal atrophy, vaginal narrowing, dyspareunia, libido). Vasomotor symptoms (VMS) included hot flushes and/or night sweats. Natural menopause (NM) was defined as the occurrence of spontaneous amenorrhea >12 months of menstruation before the diagnosis of cancer or by assessment of serum estradiol and FSH levels for women in the perimenopausal state at cancer diagnosis. Because menopause is associated with osteoporosis, a bone densitometry was performed in 145 of the EOCS. To define osteoporosis and osteopenia, we used the WHO's definition with respectively a bone mineral density T score ≤ −2.5 and T-score < −1 and >−2.5 on the lumbar spine or/and neck of the femur [21]. Average daily dietary intake of calcium was measured by asking the patient to declare the amount of food ingested the previous day. The target dietary calcium intake was set at 1200 mg/day in accordance with the recommendations for postmenopausal women [22]. A vitamin D assay was performed and presented according to the geographical area where the patient lived (divided into 2 parts by median, north and south latitude). Serum lipid levels and blood pressure assessment were also performed in the context of general health assessment in postmenopausal women.

2.5. Objectives of the study

The first objective was to report VMS in a large multicenter EOCS population. The other objectives were to report sexual disorders and osteoporosis, to compare VMS and QoL outcomes according to SM or NM and to identify patients who would benefit from receiving HRT according to the symptoms. We also described symptoms of women with premature ovarian insufficiency before the age of 45 years (POI), who are more at risk of deleterious outcomes.

2.6. Ethics statement

EOCS gave their written informed consent prior to their inclusion in the study. This study was approved by the Ethics Committee of the University Hospital of Caen (Normandy, France, Ref. CPP: 2014-30, N° ID RCB: 2014-A00768-39); by the French consultative committee for data processing concerning research and health (CCTIRS) and as well as by the National French Data Protection Authority (CNIL).

2.7. Statistical analysis

Descriptive analysis was performed using the Chi-square or Fisher's test for categorical variables on independent sample *t*-tests for continuous variables. We performed analyses of variance after checking for normal distribution using the Shapiro-Wilk test to compare QoL scores between EOCS with VMS and no VMS, adjusting for sociodemographic variables. Missing data for component items of QOL scores were processed according to published recommendations [16–18]. Statistical Analysis Software (version 9.4; SAS Institute Inc., Cary, NC) was used to analyze data.

3. Results

3.1. Sociodemographic, clinical and biological characteristics of EOCS

Sociodemographic, clinical and biological characteristics of the 166 EOCS are presented in Table 1. Their median age at the survey was 62.1 years [range 20.8–83.0; Q1:55.7, Q3:70.3]. All EOCS were postmenopausal and 59 EOCS (36%) had SM (28 of whom had POI). No statistically significant differences were observed between sociodemographic and clinical characteristics of women in VIVROVAIRE step 1 & 2 (data not shown). Half of them had advanced disease (FIGO stage III/IV) and 10% had BRCA 1 or 2 mutations. All the EOCS had surgery, and 97% received platinum and taxane chemotherapy. Median delay since treatment was 5.1 years [range 3.1–24.2; Q1:3.6, Q3:7.4].

Table 1
Socio-demographic, clinical and biological characteristics of Epithelial Ovarian Cancer Survivors.

	Total $N = 166$	Vasomotor Symptoms[a] $n = 85$ (52)	No Vasomotor Symptoms[a] $n = 79$ (48)	*p*-value[b]
Age at end of cancer treatment Mean ± sd (yrs) [Range]	55.8 ± 11.5 [16–79]	52 ± 11.5 [16–74]	60 ± 10.1 [16–79]	<0.0001
Time since end of treatment	5.8 ± 2.9	5.6 ± 2.5	6.1 ± 3.3	N.S.
Age at the survey Mean ± sd (yrs)	62 ± 11	58 ± 11	66 ± 9	<0.0001
High level of education n (%)[c]	97 (58)	46 (54)	51 (65)	<0.02
FIGO stages n (%)				
I / II	85(52)	45(54)	39 (51)	
III/IV	78 (48)	39 (46)	38 (49)	N.S.
Unknown	3	1	2	
Histology & grade n (%)[d]				
Serous	85 (52)	44(52)	41 (52)	
Low grade serous	*35 (22)*	*17*	18	
High grade serous	47 (28)	26	21	
unknown	3(2)	1	2	
Endometrioid	30 (18)	19 (22)	10 (13)	N.S.
Endometrioid G1	5(3)	3 (4)	2 (3)	
Endometrioid G2&3	25 (15)	16 (18)	8 (9)	
Clear cell	34(21)	17 (20)	17 (22)	
Mucinous	8(5)	3 (4)	5 (6)	
Undifferentiated	5(3)	1(1)	4(5)	
Other	3(2)	1 (1)	2 (3)	
Surgery with bilateral ovariectomy	166 (100)	85 (100)	79 (100)	N.S.
Chemotherapy	161 (97)	82 (96)	77(97)	N.S.
Surgical menopause	59 (36)32	41 (48)	18 (20)	<0.001
Body Mass Index at survey≥30^{kgm-2}	32(19)	15(17)	17 (22)	N.S.
Weight gain since cancer	79 (48)	48 (61)	31 (39)	0.03
Waist circumference (WC), cm[e]	86.2 ± 14.2	86.2 ± 14.8	86.2 ± 13,5	N.S.
Hip circumference (HC), cm[e]	102.3 ± 12.0	102.4 ± 12.8	102.3 ± 11.3	N.S.
WC/HC[e]	0.84 ± 0.8	0.84 ± 0.8	0.84 ± 0.8	N.S.
Waist circumference ≥ 88 cm[e]	63 (41)	33 (20)	30 (18)	N.S.
LDL-c, g/L[f]	1.3 ± 0.7	1.3 ± 0.7	1.4 ± 0.7	N.S.
Triglycerides, g/L[f]	1.1 ± 0.8	1.2 ± 0.8	1.1 ± 0.8	N.S.
Systolic blood pressure, mm Hg	131.2 ± 20.7	129.3 ± 19.3	133.0 ± 21.9	N.S.
Diastolic blood pressure, mm Hg	78.5 ± 10.3	78.3 ± 10.2	78.6 ± 10.5	N.S.
Hypertension[g]	51 (30)	22 (26)	29 (37)	N.S.
Tobacco use	46 (28)	22 (26)	24 (30)	N.S.
Physical activity (PA)	112 (67)	58 (68)	54 (68)	N.S.
PA following the WHO criteria[h]	83 (50)	42 (49)	41 (52)	N.S.

Abbreviations: EOCS: Epithelial Ovarian Cancer Survivors NS: not significant; sd: standard deviation; FIGO, International Federation of gynecology and Obstetrics; WHO: World Health Organization.

[a] Missing data (MD) among vasomotor symptoms(hot flashes or/and night sweat) = 2.
[b] p values are based on independent samples *t*-tests for continuous variables and χ^2 test or Fisher's exact tests for categorical variables.
[c] High level of education = baccalaureate degree, university or higher education.
[d] MD among Histology & grade = 1.
[e] MD among Waist/hip circumference = 12.
[f] MD among Serum lipid levels = 21.
[g] Hypertension = Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg or treatment for hypertension.
[h] At least 3 days of vigorous intensity physical activity for at least 25 min/day or 5 or more days of moderate intensity physical activity for at least 30 min/day.

Since the end of their cancer treatment, more than 2/3 of gynecological follow-ups have been conducted by oncologists, 30% by gynecologists and 3% by general practitioners.

3.2. Obesity, cardio-vascular risk factors

Concerning their metabolic profile, 63 women presented with abdominal obesity (Waist circumference > 88 cm) and none had received HRT after their cancer. Six patients (4%) had LDL values above the threshold for their category for cardio-vascular risk and 35 (21%) had triglyceride levels greater than 1.5 g/L (data not shown). Only twenty-six patients had a lipid-lowering treatment. Abdominal obesity was associated with elevated triglyceride levels ($p < .01$). Fifty-one patients had hypertension, 28 of whom were treated with antihypertensive medication. No statistically significant differences were observed between the type of menopause (NM, SM, POI) and serum lipid levels or blood pressure. Fifty two percent of the EOCS reported VMS with hot flushes in 47% or/and night sweats in 32% (Table 2).

3.3. Osteoporosis

Bone densitometry performed in 145 patients showed that 21 (14%) of them had osteoporosis and 73 (50%) osteopenia. Seven EOCS reported an osteoporotic fracture. Among the 20 EOCS under 50 years of age at the time of study who underwent bone densitometry, 2 (10%) had osteoporosis and 6 (30%) had osteopenia. Half of the EOCS had vitamin D deficiency, with a higher percentage for those living in the north of France (57% vs. 35% for those living in the south, $p = .01$). Eighty-eight percent of EOCS reported a calcium intake under the daily recommendations [22], 27% consumed less than 600 mg/day and the mean daily calcium intake was 841 mg/d (standard deviation (SD) =340). Nine percent of EOCS were receiving vitamin D supplementation and 4% ($n = 6$) were on bisphosphonates. If we include those 6 women, the percentage of women with osteoporosis is then 18%.

Table 2
Vasomotor symptoms and sexual functioning among EOCS according surgical menopause or natural menopause.

	Total n = 166	Surgical Menopause $n = 59$ (36)	Natural Menopause $n = 107$ (64)	p-value[a]
Vasomotor Symptoms[b]	85 (52)	41 (72)	44 (41)	**p < .001**
Hot flashes	78(47)	40 (70)	38 (35)	**p < .0001**
Night sweats	53 (32)	27 (47)	26 (24)	**p < .01**
Others Menopausal Symptoms				
Arthralgia	103 (62)	29 (51)	74 (69)	N.S.
Headache	43 (26)	26 (46)	17 (16)	**p < .0001**
Sexual Functioning				
Decreased sexual desire[c]	88 (65)	38 (78)	50 (57)	**<0.02**
Sexually active[d]	74 (45)	35 (60)	39 (36)	**<0.003**
Dyspareunia among 74 EOCS Sexually active	23 (32)	13 (37)	10 (26)	N.S.
Cancer-related reason among 88 EOCS no sexually active	39 (44)	15 (65)	24 (37)	**<0.02**
Vaginal atrophy	67 (40)	22 (37)	45 (42)	N.S.
Vaginal dryness	80 (63)	34 (71)	46 (57)	N.S.
Lubricating gel	35 (27)	18 (39)	17 (20)	**<0.02**
Vaginal ovules therapy	22 (17)	8 (17)	14 (17)	N.S.

Abbreviations: NS: not significant; EOCS: Epithelial Ovarian Cancer Survivors.
[a] p values are based on χ^2 test or Fisher's exact test.
[b] Missing data (MD) = 2.
[c] MD = 30.
[d] MD = 4.

3.4. Comparison between EOCS subgroups

3.4.1. EOCS with or without vasomotor symptoms

EOCS with VMS had a lower level of education and were younger than those without VMS ($p < .0001$, mean difference 8 years) (Table 1). We also observed a greater increase in weight gain since cancer in EOCS with VMS (61%) than in those without VMS (39%) ($P < .03$) (Table 1) but not according to the waist/hip ratio. Mean insomnia score was higher in EOCS with VMS than in those without VMS ($P < .03$). However, the difference no longer remained significant after adjustment for age and level of education. Forty percent ($n = 66$) of the EOCS in our series were anxious and 19% ($n = 31$) depressed. Neither anxiety nor depression was associated with VMS in either continuous or categorical forms. The different domains of QoL and emotional status were similar between the two groups (S1).

3.4.2. EOCS with surgical menopause (SM) or natural menopause (NM)

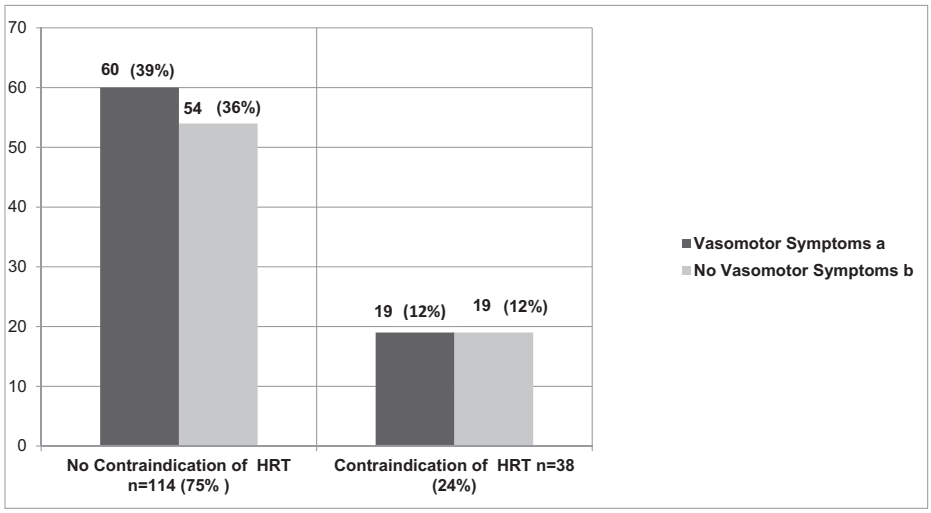
Table 2 presents VMS and sexual functioning in EOCS with SM or NM. Seventy-two percent of EOCS with SM had VMS compared to 41% with NM ($p < .001$). In particular, 70% of EOCS with SM complained about hot flushes vs. 35% of EOCS with NM ($p < .0001$). EOCS with SM were three times more likely to complain of headaches than those with NM ($p < .0001$). Women with POI complained more often of vasomotor symptoms (79% vs 46%, $p < .001$), hot flashes (75% vs 42%, $p < .001$) and headaches (61% vs 19%, $p < .001$) than other EOCS.

Two-thirds of EOCS had a decreased libido. EOCS with SM had a greater decrease in libido than EOCS with NM ($p < .02$). Women with POI complained of an even greater decrease in libido than other EOCS (88% vs 60% $p < .01$). At the time of the study, nearly half of the EOCS were sexually active. Among the sexually active (vaginal penetration) EOCS, 1/3 complained of dyspareunia. Among 88 EOCS without sexual activity, cancer history was the reason for the non-activity in 2/3 of them with SM and in fewer than 40% of those with NM ($p < .02$). While the majority of EOCS complained of vaginal dryness, few used topical treatments such as lubricating gel (27%) or vaginal ovules (17%). The use of topical treatments was similar regardless of the physician who performed the gynecological follow-up (oncologists, gynecologists, or general practitioners) (data not shown).

Among EOCS with SM, patients with VMS had poorer functional well-being than those without VMS, ($p < .001$). The other domains of QoL, insomnia and emotional status were similar between the two subgroups (S2).

3.5. Hormone replacement therapy (HRT)

Forty-two patients with NM received HRT before the cancer diagnosis (24 received a combined estrogen progestogen treatment (EPT), 10 an estrogen alone (ET), 4 a progestogen alone (PT) and 2 received unspecified treatment), 30 discontinued it before the cancer (12 with VMS) and 11 stopped it at diagnosis (5 with VMS). The other one discontinued it before the survey. Of these 42 patients, 17 (40%) reported VMS at the time of the survey. Nine patients with SM received a prescription for HRT after their diagnosis of cancer (4 EPT and 5 ET). Of these, 4 had theoretical CI associated with their histological type (hormone sensitive tumor). These patients were particularly young at end of their cancer treatment (15, 29, 33 and 38 years old). Of the 9 patients treated with HRT after cancer, 2 discontinued their treatment before the survey. At the time of the study, 7 EOC survivors were being treated with HRT and 3 reported VMS. Eight (6 NM and 2 SM) received HRT, but the start and end date of the treatment were unknown. In total, 107 patients have never been treated with HRT, including 59 who reported VMS and 48 who had SM. Among the 85 EOCS with VMS, 80 (94%) (38 SM and 42 NM) did not receive HRT after their cancer treatment and 76% had no contraindications for HRT. Fig. 1 shows that EOCS without HRT in the survey had no theoretical contraindications for it.



a :79 EOCS (51%) with Vasomotor Symptoms (hot flashes or/& night sweats) and no HRT at the survey; b: 73 EOCS (49%) without Vasomotor Symptoms (hot flashes or/& night sweats) and no HRT at the Survey.

Fig. 1. No theoretical Contraindication for Hormone Replacement Therapy among EOCS without HRT at the survey.

4. Discussion

More than half of the EOCS had vasomotor symptoms (VMS) more than three years after the end of their treatment. While VMS were more prevalent when menopause was surgically induced (72%), very few EOCS had access to HRT even when indicated. The main vasomotor symptoms (VMS) in EOCS were hot flushes (47%) and night sweats (32%), i.e. those most frequently reported in the general population. This rate is particularly high among young women with POI [6,7,23]. VMS were more prevalent in EOCS whose menopause was surgical than in those with a NM. In line with this finding, previous studies showed than SM was associated with more VMS and a higher negative impact on QoL [25,26].

Previous studies showed that abdominal obesity was promoted by the hormonal fall linked to menopause. While HRT had no negative effect on body weight, it decreased the accumulation of abdominal fat [27]. In our study, a majority of patients had a waist perimeter above normal. In a recent French cohort, of women with a wider range of age, the frequency of abdominal obesity measured by the waist diameter was much below, with a value of 42% [28]. Increase waist perimeter and W/H ratio are markers of insulinresistance and risk factors for cardio-vascular disease. Increased waist circumferences were already reported in POI patients and constitute a risk factor for cardio-vascular events [29]. This together with the abnormal values in lipid fractions in 24% of the patient highlighted the fact that those women need a thorough management of their cardio-vascular risk factors. EOCS with VMS were younger and had gained more weight since the end of their treatment. While our findings confirm the link between weight gain and VMS, the hypothetical association between VMS and high waist circumference was not confirmed. Those symptomatic young women could be even at higher risk of metabolic abnormalities and need stringent monitoring of their cardio-vascular risk factors.

Furthermore, in our study, 18% of EOCS had osteoporosis, i.e. prevalence similar to that of the general population with menopause [21]. However, two of the 20 young patients (<50 years) with SM had osteoporosis but were not treated for it. In addition, even if no association could be established with osteoporosis, half of the EOCS had vitamin D deficiency, notably those residing in northern France. The daily intake of calcium was far below the recommended 1000/1200 mg/day [22] and 27% of the EOCS consumed less than 600 mg/day. This is similar to a previous study conducted in France on the intake of calcium in the general population [30]. Very few patients ($n = 6$) were supplemented with calcium and vitamin D despite their deficiency. These findings demonstrate the need to strengthen preventive measures against osteoporosis during the long-term follow-up. Women with POI are at risk of osteoporosis at a younger age if they are not treated by HRT and should also be carefully monitored for their calcium intake and the level of vitamin D evaluated. Menopause was also associated with gynecological problems such as vaginal dryness and vaginal atrophy, which are caused by a decrease in estrogen and androgen levels [6,23]. However, only one-quarter of EOCS used lubricating gel and 17% used vaginal ovules. Two-thirds of the EOCS reported a decrease in their libido, particularly EOCS with SM. Among the non-sexually active women, half of them reported no longer having sexual activity because of their cancer, and patients with SM were more affected. One-third of sexually active EOCSs reported dyspareunia. Previous studies have also reported negative consequences on sexual function in women who have undergone oophorectomy without HRT, with decreased libido, a 3-fold increased risk of anorgasmia, and an increased risk of hypoactive sexual desire [25,26]. EOCS with SM complained more about headache and had a more disturbed sex life. Among these patients, those with VMS had poorer functional well-being than those without VMS ($p < .001$). A study in women with BRCA 1 and 2 mutations in breast cancer showed that SM was associated with moderate or severe VMS and impaired sexual function [7].

Few of our patients received HRT, even if they had severe VMS. HRT can decrease insulinresistance and prevent type2 diabetes as shown in randomized trials and observational studies [31,32] and in addition of improving climacteric symptoms can help to decrease cardio-vascular morbidity and mortality in women with POI [33]. HRT was also associated with a significant decrease in mortality in women treated between the age of 50 to 60 years old in randomized trials [34]. Several studies have demonstrated the safety of HRT in such patients without increase of risk of relapse [8,9,35,36]. In a randomized controlled trial with a median follow-up of 19 years, Eeles et al. observed an improvement in overall survival in EOCS with HRT vs. without [9]. These results were also replicated in a longitudinal Swedish study that found that HRT had a positive impact on 5-year survival in EOCS receiving it after diagnosis [35]. Furthermore, a recent metanalysis demonstrated the absence of an association between HRT use and an increased risk of death in EOCS [8]. It has even demonstrated a reduction in the incidence of cardio-vascular risk and bone demineralization [26]. This is in line with the increased risk in morbidity and mortality in particular from cardio-vascular diseases in women with POI especially after an oophorectomy [33].

Table 3
Summary of prevention and management of menopausal symptoms.

	Hormone replacement therapy (HRT)	Osteoporosis prevention and treatment	Cardio-vascular prevention
Epithelial ovarian cancer survivors with premature ovarian insufficiency (POI)	Highly recommended up until natural age of menopause and then according to climacteric symptoms excepted for hormone sensitive tumor (serous and endometrioid low-grade histologies)	Calcium intake over 1000/1500 mg/day Vitamin D measurement and substitution if necessary Bone densitometry (BMD) systematically Physical activity	Healthy nutrition Physical activity Maintaining a normal body mass index (BMI) Follow up of lipids fractions and glycemia Stop smoking Limiting alcohol consumption
Epithelial ovarian cancer survivors over 50 years	Indicated to treat the climacteric symptoms and osteoporosis in women up to 60 years or in the 10 years following a normal age at menopause (excepted for hormone sensitive tumor). In case of abstention to HRT, vaginal estrogens are not contraindicated and help to alleviate urogenital symptoms.	BMD recommended in case of risk factors for osteoporosis (family history of osteoporotic fracture, steroids treatment, smoking) In case of osteoporosis: Calcium intake over 1000/1500 mg/day Vitamin D measurement and substitution if necessary Physical activity	

Physical exercise can help to prevent cardio-vascular events and osteoporosis. In our series about 70% of the women declared at least any physical activity and half of them had an activity level according to WHO criteria. This fit with the results of a recent survey in France where 63% of the French at or over the age of 65 years reported a physical activity following the WHO criteria and 68% among the 45–65 years old [38].

HRT has also been found to improve VMS among EOCS and to help in managing sexual disorders [8]. HRT is recommended for EOCS with serous and endometrioid high-grade, mucinous and clear-cell adenocarcinomas [39]. In contrast, it is not recommended for hormone-linked serous and endometrioid low-grade, although this CI is entirely theoretical. For the latter, the benefit/risk of HRT prescription should be discussed. Indeed, in our series, 4 young patients with POI were receiving HRT despite this theoretical CI. Recent guidelines promote the prescription of HRT, particularly among patients with SM <45 years old [10,12]. Despite these guidelines, however, gynecologists are worried to prescribing HRT in EOCS [13,40]. In a Greek study based on an anonymous questionnaire, 52% of respondents declared that they did not prescribe HRT for ovarian cancer survivors for fear of promoting a recurrence [40]. This study is the first to evaluate long-term VMS in EOCS more than 3 years after the end of their treatment with a dedicated gynecological consultation (with standardized report with few missing data on sexuality and menopausal symptoms) and validated questionnaires. Nevertheless, it has some limitations since it is cross-sectional, did not include a pre-diagnosis work-up, and did not have any follow-up. Furthermore, the study did not include a specific self-assessment questionnaire for menopausal symptoms but a clinical assessment and an interview by a gynecologist.

In conclusion, VMS and sexual disorders in EOCS are underestimated. Long-term follow-up of EOCS should be reinforced, especially in young patients with SM who have more severe symptoms. The usual recommendation in women with POI (excepted for hormone sensitive tumor) is to prescribe an HRT up to the average age of menopause which is 51 years in US and France. For patients with NM with any CI to HRT and complaints VMS, benefits/risks should be discussed on the same base of that general women population. Despite its safety, HRT is still under-prescribed at the end of cancer treatment. EOCS should receive a long-term gynecological follow-up focusing on the persistent side-effect of their treatment, and more supportive care concerning oncosexuality, diet and physical activity should be made available to them. Oncologist, general practitioners and gynecologists need to be made more aware of the need to manage menopausal symptoms in EOCS. A summary of prevention and management menopausal symptoms is proposed in Table 3.

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Author contributions

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Appendix A. Supplementary data

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