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Hormone replacement in premenopausal women treated with bilateral oophorectomy for ovarian cancer – a nationwide population-based study

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HIGHLIGHTS

- HRT prescription pick-up is low in women with premature menopause and ovarian cancer.
- <50% of premenopausal women with ovarian cancer were dispensed HRT after surgical menopause.
- Young age and borderline ovarian tumors were factors that led to a significant dispensing of HRT.

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ABSTRACT

Objective. To study the extent of hormone replacement therapy (HRT) dispensing in premenopausal women after being treated with bilateral salpingo-oophorectomy (BSOE) for ovarian cancer (OC).

Methods. Nationwide population- and register-based cohort study including women 18–50 years old, registered in The Swedish Quality Register for Gynecological Cancer (SQRGC), where BSOE was performed due to epithelial (EOC) and non-epithelial ovarian cancers (NEOC) or borderline ovarian tumor (BOT) between 2008 and 2014. Data on HRT dispensing was obtained from the National Prescribed Drug Register analyzed at semi-annual intervals from surgery until end of follow-up December 2015, including a logistic regression analysis.

Results. A cohort of 664 women were identified with OC, whereas 396 women had an EOC, 61 a NEOC and 207 a BOT. At surgery 49% of the women were ≤44 years. HRT dispensed to the total cohort varied between 32% and 41% the first five years after surgery. During follow-up at first 0.5–1 year 51% of the women <40 years were dispensed HRT compared to 25% of women ≥40 years. Of women with EOC, 21% dispensed HRT at first 0.5–1 year. In the multivariable regression analysis; age <40 (OR6.17, $p < 0.001$) and age 40–44 (OR2.95, $p < 0.001$) as well as BOT histology (OR3.84, $p < 0.001$) were found significant variables for dispensing of HRT.

Conclusion. A majority of premenopausal women undergoing BSOE for OC did not use HRT postoperatively. Our study shows that there is a need to address HRT use after OC treatment in young women to prevent from morbidity and a poorer quality of life.

1. Introduction

Premenopausal women undergoing bilateral salpingo-oophorectomy (BSOE) because of epithelial ovarian cancer (EOC), non-epithelial ovarian cancer (NEOC) or borderline ovarian tumor

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(BOT) will experience a premature (<40 years of age) or early menopause (40–45 years of age). Without HRT they have an increased risk for cardiovascular disease, osteoporosis, impaired cognition, mood, sexual health and increased overall mortality [1–3]. To decrease morbidity and mortality associated with premature or early menopause women are recommended hormone replacement therapy (HRT) until age of natural menopause [2,4]. Some women with OC will be cured from the disease and others will become long-term cancer survivors. Managing menopausal symptoms improve quality of life for these women [5]. Furthermore, for women with BOT, NEOC and early stages of EOC survival rates are high and thus long-term negative health-effects of surgical menopause is an important issue [6]. For women with advanced stages of EOC, where the disease is more life-limiting, an optimal quality of life is desirable [7].

Several studies have evaluated the safety of HRT after EOC suggesting that postoperative HRT does not have a negative effect on overall survival (OS) or risk for recurrence, on the contrary HRT improved OS [8–14]. Among EOCs there have been concerns regarding the safety of HRT use in low-grade serous carcinomas with estrogen receptors (ERs) and in potentially estrogen sensitive endometroid cancers, however data is limited [15]. Regarding NEOC HRT can be recommended after treatment for germ cell and sex-cord stromal tumors except granulosa cell tumors [5,16]. Since granulosa cell tumors are likely to be hormone-sensitive, and safety data is lacking, HRT is not recommended (theoretical contraindication) [4,15,17,18].

Around 20% of women diagnosed with OC are premenopausal [19]. International and Swedish guidelines recommend HRT to these women. The last two decades HRT decreased dramatically and the discussions about its benefits and risks are ongoing [20,21]. In addition, physicians may be cautious in prescribing HRT to an extent when cancer survivors do not receive an adequate treatment leading to unnecessary morbidity and mortality [3,5,22,23] . Studies exploring the prescription of HRT after ovarian cancer treatment have shown a use of HRT varying between 4%- 47% [8,12,23,24]. As far as we know there are scarce national data on HRT use in ovarian cancer survivors.

The aim of our study was to examine the extent of HRT dispensing in premenopausal women with surgical menopause due to BSOE for EOC, NEOC or BOT in a nationwide population-based cohort.

2. Method

2.1. Study design and population

This is a nationwide population- and register-based cohort study of all women diagnosed with EOC, NEOC or BOT at 18–50 years of age from January 1st, 2008 to December 31th, 2014. The Swedish Quality Register for Gynecological Cancer (SQRGC) was used for identification of women whom all had a BSOE performed as part of OC treatment and finally use of HRT after surgery was assessed in this defined cohort.

Exclusion criteria were former or current breast cancer or endometrial cancer. Women who died within 0.5 year after surgery were excluded from the analysis. All women were followed from date of surgery until turning 52 years of age, breast cancer diagnose, death or end of the study period (December 31th, 2015), whichever came first.

Information on tumor location and classification was obtained from the SQRGC and defined according to the World Health Organization criteria [25]. Borderline tumors were classified as mucinous or serous since more specific details were missing in 2008. Serous epithelial ovarian cancer was not divided into high-grade or low-grade since this classification was introduced during the study period and missing during 2008–2010. Since Fallopian tube cancer and EOC are considered similar cancers and are treated likewise they were grouped together and referred to as EOC. Tumor stage was classified according to the FIGO 2014 classification system [26].

We focused on HRT dispensing every half year period (half-year analysis) after surgery but also assessed dispensing during a full 1-year period 0–12 months after surgery (one-year analysis, 365d instead of 182d) to allow for carry-over effects of dispensing between periods. In case some patients dispensed HRT irregularly during the half-year periods the one- year analysis is a method to cover up for that situation. In the half-year analysis, the cohort was divided in two age groups; <40 and ≥40 due to HRT being most important for women with premature menopause. To further explore if dispensing was associated with age a second age group categorization was made in the one-year analysis as well as the uni- and multivariable logistic regression. For these analyses the cohort was divided in three age groups: <40, 40–44 years and ≥ 45. During our study period in 2012, the Swedish national guidelines added recommendations regarding HRT after OC treatment. To evaluate if the recommendations affected dispensing, the total study cohort was also divided in two calendar periods, 2008–2011 and 2012–2014, for subgroup analysis.

The regional Ethics Committee of Stockholm approved the study (Dnr 2016/1161–31/2, and amendments Dnr 2016/ 2189–32, Dnr 2017/1199–32).

2.2. Data sources

All citizens in Sweden are assigned with a 12-digit personal identification number (PIN). This number was used to obtain further data on the individuals in the study cohort from the Swedish National Cancer Register (NCR), the National Cause of Death Register and the National Prescribed Drug Register. All three registers are maintained by the National Board of Health and Welfare.

The SQRGC, established in 2008, consequently and prospectively collects data on clinical, surgical, oncological variables, pathology reviews as well as mortality data. In Sweden, all cancers are mandatory to be reported to NCR, and it covers over 96% of all malignant cancers in the population [27]. The register contains information of date of diagnose as well as information on cancers including tumor site and histology according to the International Classification on Diseases (ICD). The SQRGC has a 94% coverage rate towards the NCR and has been validated with 72–98% agreement to core variables described in previous studies [28,29]. The National Cause of Death Register, with data from 1961 and onwards, was used to ensure follow-up and date of death.

2.3. Hormone replacement therapy

Data on HRT dispensing was obtained from the National Prescribed Drug Register [30]. This register was established in July 2005 records all drug dispensing in Sweden. Hormonal Drugs are often prescribed for 1 year at a time with one dispensation every third month. HRT can only be obtained through prescription by a doctor. Codes from the Anatomical Therapeutic Classification system (ATC-codes) were used to define hormone therapy-codes. Data for systemic hormone therapy, defining HRT dispensing, was obtained for contraceptives (G03A), oral and transdermal estrogen (G03C), and progesterone and estrogen in combination (G03F). HRT was also defined as type of formulation and route of administration; contraceptives, estrogen in tablets, transdermal estrogen (patch or gel), estrogen and progesterone in combination (tablets or patch). Products for vaginal estrogen treatment were excluded from the analyses.

2.4. Statistical analysis

In the half-year analysis HRT dispensing was analyzed as half-year intervals from surgery until end of follow-up. We also included dispensing 30 days before BSOE if doctors prescribed HRT before surgery and some women wanted to be prepared and retrieved HRT before surgery. Women were defined as users or non-users during each half-year based on whether they had at least *one* dispensing of HRT during each period or not and proportion of HRT dispensing per half-year could then be calculated. When calculating the proportion of HRT dispensing the

denominator was the number of women <52 years at the midpoint of the 6-months periods. In the one-year analysis we further focused specifically on HRT dispensing during the period of 0–12 months after surgery to allow for carry-over effects of dispensing between periods. In this analysis women were defined as users if they had at least *one* dispensing of HRT during the first 12 month after surgery, non-users had no dispensing.

Uni- and multivariable logistic regression were used to analyze the association of HRT dispensing 0–12 months after surgery and the following covariables; age at surgery, calendar period of diagnosis, FIGO stage, histologic subtype and complete cytoreduction at surgery were chosen as variables. Proportions with 95% confidence intervals of HRT users were estimated by logistic regression divided in three groups; <40 years, 40–44 years and ≥ 45 years and by the following variables, respectively; FIGO stage, subtype histology, calendar period and complete cytoreduction. A p-value <0.05 was considered as statistically significant. STATA 17.0 was used for analysis (StataCorp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC).

3. Results

In the SQRGC, we identified a total of 693 women treated with BSOE for OC from January 1st, 2008 to December 31th, 2014. After exclusion of women with previous breast cancer ($n = 13$), endometrial cancer ($n = 7$) or death within 6 months after surgery ($n = 9$), 664 women remained in the study cohort. Baseline characteristics at surgery are presented in Table 1. Of the excluded women, who died within the first six months after surgery, 8 women were diagnosed with EOC and one with BOT.

In the total study cohort, 396 (59.6%) women were diagnosed with EOC, 61 (9.2%) with NEOC and 207 (31.2%) with BOT. At time of surgery 169 (25.5%) women were <40 years, 156 (23.5%) women were 40–44 years and 339 (51%) 45–50 years. Median follow-up in the cohort was 2.8 years IQR (1.7–4.8). Number of deaths within 5 years were 121 and 5-year overall survival 81% (95% CI 0.78–0.84).

The first year after surgery (including 30 days before surgery) a total of 913 dispensations of HRT were made by 38.4% of the women (255 of 664). The type of HRT dispensed were mainly oral estrogen 54% (493 of 913) or transdermal estrogen therapy 38% (384 of 913). 1% (9 of 913) dispensed contraceptives and 7% (63 of 913) estrogen- progesterone therapy in combination.

3.1. HRT dispensing per half-year interval after surgery; total cohort and subgroups

During the first five years of the follow-up the HRT dispensing per half-year interval varied between 32% (0.5–1 years) and 41% (3–3.5 years) in the total cohort (Fig. 1). Separate analysis of women with dispensing of HRT per half year intervals were made for age at surgery, subtype histology and FIGO stage during 5 years from surgery (Fig. 2A, B and C). During the follow-up at 0.5–1 years 51% women <40 years dispensed HRT compared to 25% of the women ≥40 (Fig. 2A). In the analysis for subtype histology at 0.5–1 year 53% of women with BOT dispensed HRT compared to 31% with NEOC and 21% with EOC (Fig. 2B). Finally, in the analysis for FIGO stage, 37% of women with FIGO I dispensed HRT compared to 25% of women with FIGO II-IV during the follow-up at 0.5–1 year (Fig. 2C). A separate analysis was made for women diagnosed with endometrioid EOC ($n = 74$) where follow-up at 0.5–1 year showed that 20.3% of the women had dispensing of HRT. During the first five years of follow-up dispensing in this group varied between 14.3% and 25.0% (Data not shown).

3.2. HRT dispensing 0–12 months after surgery; total cohort and subgroups

When HRT dispensing was analyzed at 0–12 months, the proportion was 38% in the total cohort (Table 2). Within the first year 62% of women <40 years, 46% of women 40–44 years and 23% of women 45–50 years had dispensing of HRT. When analyzed for subtype histology 59% of women with BOT, 36% of NEOC and 28% of EOC were dispensed HRT. The highest proportion of HRT dispensing (88%) was seen for women <40 years diagnosed with BOT. Of women diagnosed with FIGO stage I, 43% had HRT dispensation within the first year, compared with 31% for FIGO II-IV. There was no difference seen in the proportion of HRT dispensing between the two calendar periods 2008–2011 and 2012–2014, 38% and 39% respectively.

Table 1
Patient characteristics in women with ovarian cancer ≤50 years at date of BSOE in Sweden 2008–2014.

	Total	EOC	NEOC	BOT
	$N = 664$	$N = 396$	$N = 61$	$N = 207$
Age at surgery				
18–29	43 (6.5)	17 (4.3)	14 (23.0)	12 (5.8)
30–34	36 (5.4)	15 (3.8)	11 (18.0)	10 (4.8)
35–39	90 (13.6)	49 (12.4)	6 (9.8)	35 (16.9)
40–44	156 (23.5)	92 (23.2)	14 (23.0)	50 (24.2)
45–50	339 (51.1)	223 (56.3)	16 (26.2)	100 (48.3)
Year of surgery				
2008	80 (12.0)	51 (12.9)	5 (8.2)	24 (11.6)
2009	97 (14.6)	58 (14.6)	8 (13.1)	31 (15.0)
2010	116 (17.5)	67 (16.9)	13 (21.3)	36 (17.4)
2011	91 (13.7)	50 (12.6)	9 (14.8)	32 (15.5)
2012	64 (9.6)	30 (7.6)	5 (8.2)	29 (14.0)
2013	101 (15.2)	68 (17.2)	10 (16.4)	23 (11.1)
2014	115 (17.3)	72 (18.2)	11 (18.0)	32 (15.5)
FIGO stage				
I	391 (58.9)	161 (40.7)	55 (90.2)	175 (84.5)
II	62 (9.3)	49 (12.4)	3 (4.9)	10 (4.8)
III	171 (25.8)	147 (37.1)	2 (3.3)	22 (10.6)
IV	40 (6.0)	39 (9.8)	1 (1.6)	0 (0.0)
Subtype histology				
EOC Serous	213 (32.1)	213 (53.8)	–	–
EOC Mucinous	55 (8.3)	55 (13.9)	–	–
EOC Endometroid	74 (11.1)	74 (18.7)	–	–
EOC Clear Cell	42 (6.3)	42 (10.6)	–	–
EOC Other/Undefined	12 (1.8)	12 (3.0)	–	–
NEOC Germ Cell	17 (2.6)	–	17 (27.9)	–
NEOC Sex cord-stromal Cell	44 (6.6)	–	44 (72.1)	–
BOT Serous	49 (7.4)	–	–	49 (23.7)
BOT Mucinous	55 (8.3)	–	–	55 (26.6)
BOT Other/Undefined	103 (15.5)	–	–	103 (49.8)
Type of surgery				
Primary debulking surgery	516 (77.7)	324 (81.8)	35 (57.4)	157 (75.8)
Re-staging	123 (18.5)	56 (14.1)	23 (37.7)	44 (21.3)
Interval debulking surgery	7 (1.1)	6 (1.5)	0 (0.0)	1 (0.5)
Undefined/missing	18 (2.7)	10 (2.5)	3 (4.9)	5 (2.4)
Complete cytoreduction				
Yes	571 (86.0)	319 (80.6)	56 (91.8)	196 (94.7)
No	79 (11.9)	72 (18.2)	3 (4.9)	4 (1.9)
Undefined/missing	14 (2.1)	5 (1.3)	2 (3.3)	7 (3.4)
Hysterectomy				
Yes	589 (88.7)	365 (92.2)	38 (62.3)	186 (89.9)
No	74 (11.1)	30 (7.6)	23 (37.7)	21 (10.1)
Undefined/missing	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)
Adjuvant chemotherapy				
Yes	246 (37.0)	227 (57.3)	14 (23.0)	5 (2.4)
No	4 (0.6)	3 (0.8)	0 (0.0)	1 (0.5)
Undefined/missing	414 (62.3)	166 (41.9)	47 (77.0)	201 (97.1)

Abbreviations: BSOE: bilateral salpingo-oophorectomy; EOC: Epithelial ovarian cancer; NEOC: Non-epithelial ovarian cancer; BOT: Borderline ovarian tumor; FIGO: International Federation of Gynecology and Obstetrics.
Data are presented as *n* (%).

3.3. Logistical regression analysis

In univariable logistical regression analysis age at surgery, subtype histology, FIGO stage and complete cytoreduction were associated with HRT dispensing at 0–12 months (Table 3). In the multivariable analysis age < 40 years (OR 6.17, 95% CI 3.90–9.53, $p < 0.001$) and age 40–44 years (OR 2.95, 95% CI 1.93–4.53, $p < 0.001$) as well as subtype

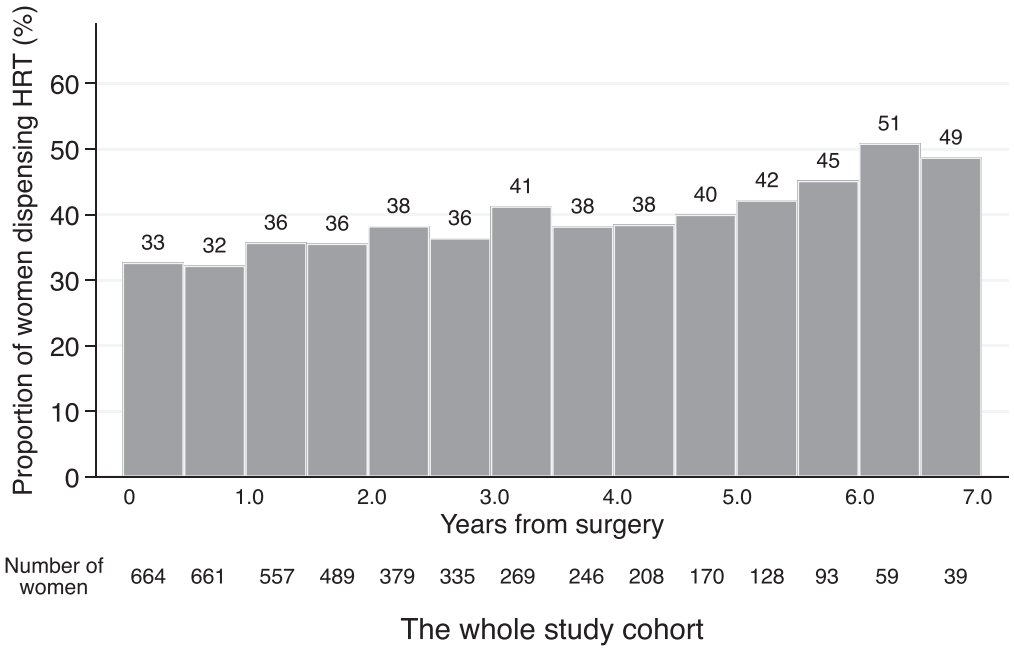

Fig. 1. Proportion of women, age 50 years or younger, with bilateral salpingo-oophorectomy performed due to epithelial ovarian cancer, non-epithelial ovarian cancer or borderline ovarian tumor in Sweden (from 2008 to 2014) with at least one dispensing of hormone replacement therapy (HRT) per half-year during 7-year follow-up after surgery.

histology BOT (OR 3.84, 95% CI 2.65–5.57, $p < 0.001$) remained significant variables for dispensing of HRT.

4. Discussion

In this large nationwide population-based study, including premenopausal women with BSOE performed as part of an ovarian cancer treatment, <50% of the complete study cohort dispensed HRT after surgery within the first five years. In the half-year interval analysis over 1/3 of women younger than 40 years at surgery were not dispensed HRT during the follow-up. Women who were older, had more advanced stages and diagnosed with EOC were less likely to be dispensed HRT. The proportion of HRT dispensing was fairly stable over time for different groups analyzed.

Current guidelines recommend HRT after surgical menopause up to average of natural menopause and therefore the women were followed until turning 52 years of age [4,15,18,19]. Today there are some studies that have explored the prevalence of HRT use after ovarian cancer treatment. Eels et al. found that 20.9% of women aged 50 or younger ($n = 373$) and diagnosed with EOC were users of HRT after diagnose [24]. Furthermore, Mascarenas et al. studied HRT use before and after ovarian cancer treatment in women aged 50–74 ($n = 799$) and reported that women with EOC only 23% and 51% of the BOTs were users [8]. However, their results are not totally comparable to ours since they included an older age group than our cohort. In one recently published French study by Gernier et al. only 4% of women with EOC (median age 62.1 years, $n = 166$) received HRT after surgery [23]. Moreover, Power et al. evaluated HRT use after treatment for non-serous epithelial ovarian cancer and found that as many as 47% of women <55 years used HRT ($n = 158$) [12]. To our knowledge there are no previous studies on the extent of HRT use after treatment for NEOC.

We do not know the reason why over half of the study population did not dispense HRT. However, we speculate about whether it could be fear of recurrence and/or progression of disease or fear of negative health effects of HRT such as breast cancer. Additionally, there may be a fear and ambivalence within the profession in prescribing HRT after ovarian cancer treatment [31]. There may also be concerns regarding thromboembolism in ovarian cancer survivors. Importantly, no studies have shown negative effects of HRT use in ovarian cancer survivors even though larger prospective studies are warranted [5,14]. International guidelines do not recommended HRT in women with granulosa cell tumors since they may be hormone dependent [4,16]. In our cohort only 44 patients out of 664 were diagnosed with Sex Cord Stromal tumors and they cannot explain why so many women did not dispense HRT in our study population. There have been extra concerns regarding endometroid cancers as well as LGSOC which are potentially estrogen sensitive. In our cohort women diagnosed with endometroid EOC generally had a slightly lower dispensation of HRT compared with all women diagnosed with EOC. Among the EOCs we did not separate LGSOC and HGSOC since this grading was not registered and thereby missing in 2008–2010. During our study period in 2012, the Swedish national guidelines added recommendations regarding HRT after OC treatment. To evaluate if the recommendations affected dispensing we analyzed HRT dispensing for two calendar periods 2008–2011 and 2012–2014 but no significant difference was seen.

The discussion of negative health effects with HRT is not applicable for women with premature or early menopause. In contrary, HRT in these women is not associated with increased risk for breast cancer [17,32]. Furthermore, there are studies indicating low HRT use after surgical early menopause for benign indications as well as natural early menopause and also discontinuation of HRT use [33,34]. Maybe women in general are afraid of using HRT due to previous alarm reports on adverse health effects after HRT use.

Younger women with surgical menopause often report more intense and prolonged menopausal symptoms such as vasomotor symptoms and sexual disorders than those after natural menopause [32]. In our cohort, women <40 years had a higher proportion of HRT dispensing compared with women ≥40 years at all half-year intervals. This may indicate that the question of premature menopause and HRT is more likely to be addressed to them. Nevertheless, in our study as much as 38% of women <40 years and 56% of women <44 years at surgery were not dispensed any HRT during the first year after surgery. For those women HRT can prevent the long-term negative heath consequences such as bone loss, negative cardiovascular effects as well as estrogen deficiency symptoms.

Interestingly, women with FIGO stage I had a higher proportion of HRT dispensing compared to women diagnosed with FIGO II-IV.

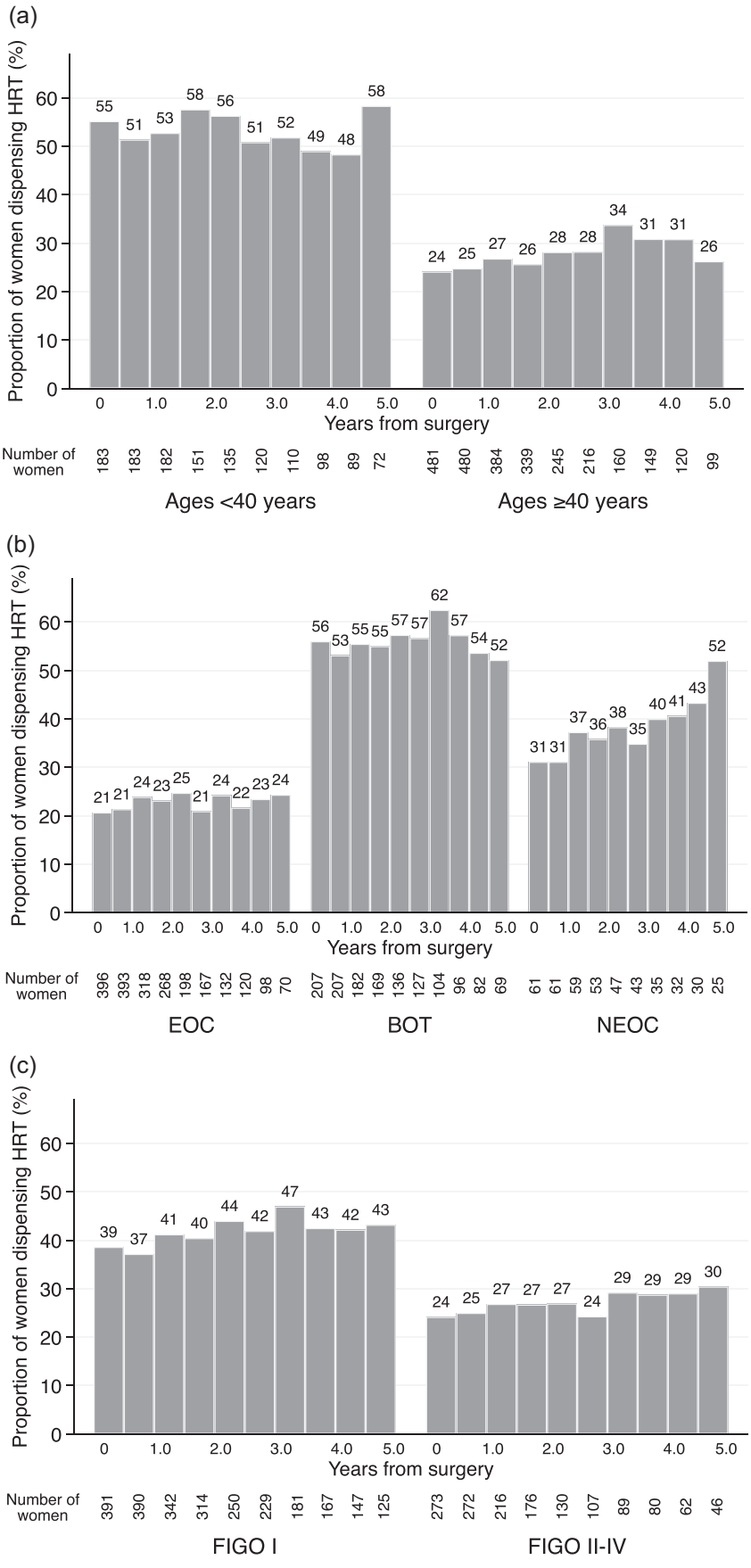
(a)
Proportion of women dispensing HRT (%)
0
10
20
30
40
50
60
55 51 53 58 56 51 52 49 48 58
24 25 27 26 28 28 34 31 31 26
0 1.0 2.0 3.0 4.0 5.0 0 1.0 2.0 3.0 4.0 5.0
Years from surgery
Number of women
183 183 182 151 135 120 110 98 89 72
481 480 384 339 245 216 160 149 120 99
Ages <40 years
Ages ≥40 years
(b)
Proportion of women dispensing HRT (%)
0
10
20
30
40
50
60
21 21 24 23 25 21 24 22 23 24
56 53 55 55 57 57 62 57 54 52
31 31 37 36 38 35 40 41 43 52
0 1.0 2.0 3.0 4.0 5.0 0 1.0 2.0 3.0 4.0 5.0 0 1.0 2.0 3.0 4.0 5.0
Years from surgery
Number of women
396 393 318 268 198 167 132 120 98 70
207 207 182 169 136 127 104 96 82 69
61 61 59 53 47 43 35 32 30 25
EOC
BOT
NEOC
(c)
Proportion of women dispensing HRT (%)
0
10
20
30
40
50
60
39 37 41 40 44 42 47 43 42 43
24 25 27 27 27 24 29 29 29 30
0 1.0 2.0 3.0 4.0 5.0 0 1.0 2.0 3.0 4.0 5.0
Years from surgery
Number of women
391 390 342 314 250 229 181 167 147 125
273 272 216 176 130 107 89 80 62 46
FIGO I
FIGO II-IV

Table 2
Number and proportion with HRT 0–12 months after BSOE in women with ovarian cancer.

Variable	Number of women and proportion with HRT							
	0–12 months after surgery, % (95%CI), by age group							
	<40 years		40–44 years		45–50 years		Total	
	n	Proportion (95% CI)	*n*	Proportion (95% CI)	*n*	Proportion (95% CI)	*n*	Proportion (95% CI)
Calendar period								
2008–2011	94	59 (49–68)	92	43 (33–54)	198	25 (19–31)	384	38 (33–43)
2012–2014	75	67 (56–77)	64	48 (36–61)	141	21 (14–27)	280	39 (34–45)
Subtype histology								
EOC	81	49 (38–60)	92	37 (27–47)	223	16 (11−21)	396	28 (23−32)
NEOC	31	48 (31–66)	14	36 (11–61)	16	13 (0–29)	61	36 (24–48)
BOT	57	88 (70–96)	50	64 (51–77)	100	41 (31–51)	207	59 (53–66)
FIGO stage								
I	109	61 (52–71)	90	53 (43–64)	192	29 (22–35)	391	43 (39–48)
II-IV	60	63 (51–76)	66	35 (23–46)	197	16 (10−22)	273	31 (26–37)
Complete cytoreduction								
Yes	149	64 (56–71)	134	49 (40–57)	288	25 (20−30)	571	41 (37–45)
No	16	44 (19–68)	18	17 (0–34)	45	16 (5–26)	79	22 (12−31)
Total	169	62 (55–69)	156	46 (38–53)	339	23 (19–28)	664	38 (35–42)

Abbreviations: BSOE: bilateral salpingo-oophorectomy; HRT; hormone replacement therapy; EOC: Epithelial ovarian cancer; NEOC: Non-epithelial ovarian cancer; BOT: Borderline ovarian tumor; FIGO: International Federation of Gynecology and Obstetrics, CI: confidence interval.

Women with BOT had a higher proportion of HRT dispensing compared to women diagnosed with EOC as well as NEOC. We speculate that physicians may be more comfortable in prescribing HRT focusing on quality-of-life questions in women with FIGO stage I where OS is high and risk of recurrence of disease lower. Probably the situation can be the same for women diagnosed with subtype histology BOT and NEOC where OS is also high. Of the same reasons the women diagnosed with FIGO I, BOT and NEOC may feel safer using HRT. For some women in our cohort with higher stages and less favorable histology the seriousness of the diagnosis and disease may take focus away from quality-of-life issues. Physicians may focus on cancer treatment forgetting to address the need for HRT. However, we highlight that among women diagnosed with FIGO I, where OS is favorable regardless of histology type, only 43% were dispensed HRT within the first year. We were are unaware of who prescribed the HRT; the gynecologist, the gynecologic oncologist or the general practitioner. In the study by Halldorsdottir et al. they showed that gynecological oncologists were more positive towards prescribing HRT to ovarian cancer survivors than the general gynecologists [31].

One strength with our study is the large size where all data is registry based including data on HRT dispensing. It excludes selection and recall biases. Furthermore, that is a nationwide study. A limitation of the study is that we do not know if the women used the dispensed medication, meaning that actual use could be even lower than presented in our data. Nor did we calculate designated daily dose (DDD) as previously described in an article by Everhov et al. [22]. Here HRT use among cervical cancer survivors in Sweden were examined. They found that <50% the women used HRT at or close to the recommended dose. Another limitation is that some women could have contraindications to HRT such as ongoing thromboembolic disease, current arterial vascular disease or advanced bile duct or liver disease that are unknown to us. On the other hand in women with premature or early menopause there are only a few absolute contraindications for HRT since the positive effects of HRT outweighs the negative effects [35]. In our cohort, the first year

Table 3
HRT dispensing 0–12 months after BSOE in women with ovarian cancer.

Variable	Univariable		Multivariable	
	Logistic regression		Logistic regression	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age at surgery				
<40	5.40 (3.62–8.06)	<0.001	6.17 (3.90–9.53)	<0.001
40–44	2.75 (1.84–4.11)	<0.001	2.95 (1.93–4.53)	<0.001
45–50	1		1	
Calendar period				
2008–2011	1			
2012–2014	1.07 (0.78–1.46)	0.698		
FIGO stage				
I	1.70 (1.23–2.35)	0.001		
II-IV	1			
Subtype histology				
EOC	1		1	
NEOC	1.47 (0.83–2.59)	0.186	0.93 (0.50–1.71)	0.811
BOT	3.81 (2.67–5.42)	<0.001	3.84 (2.65–5.57)	<0.001
Complete cytoreduction				
Yes	1.89 (1.23–2.91)	0.004		
No	1			

Abbriviations: BSOE:bilateral salpingo-oophorectomy; HRT; hormone replacement therapy; FIGO: International Federation of Gynegology and Obstetrics; EOC: Epithelial ovarian cancer; NEOC: Non-epithelial ovarian cancer; BOT: Borderline ovarian tumor.
OR = Odds Ratio.
p-values: 2-tailed p-value used in testing the null hypothesis that the coefficient (parameter) is 0 based on the z-value of the parameter (the quote of the parameter estimate and its standard error).
CI: confidence interval.

Fig. 2. A. Proportion of women, age 50 years or younger, with bilateral salpingo-oophorectomy performed due to EOC, NEOC or BOT in Sweden (in 2008–2014) with at least one dispensing of HRT per half-year during 5-year follow-up after surgery grouped as age group: <40 years and ≥40 years.
B. Proportion of women, age 50 years or younger, with bilateral salpingo-oophorectomy performed due to EOC, NEOC or BOT in Sweden (in 2008–2014) with at least one dispensing of HRT per half-year during 5-year follow-up after surgery grouped as subtype histology: EOC, BOT and NEOC.
C. Proportion of women, age 50 years or younger, with bilateral salpingo-oophorectomy performed due to EOC, NEOC or BOT in Sweden (in 2008–2014) with at least one dispensing of HRT per half-year during 5-year follow-up after surgery grouped as FIGO stage group: FIGO I and FIGO II-IV.
2A. Abbreviations: EOC: Epithelial ovarian cancer; NEOC: Non-epithelial ovarian cancer; BOT: Borderline ovarian tumor; HRT: hormone replacement therapy.
2B. Abbreviations: EOC: Epithelial ovarian cancer; NEOC: Non-epithelial ovarian cancer; BOT: Borderline ovarian tumor; HRT: hormone replacement therapy.
2C. Abbreviations: EOC: Epithelial ovarian cancer; NEOC: Non-epithelial ovarian cancer; BOT: Borderline ovarian tumor; HRT: hormone replacement therapy; FIGO: International Federation of Gynecology and Obstetrics.

after surgery, 38% of the dispensations of HRT were transdermal estrogen, which is the recommended route of estrogen administration for women with a high risk of venous thromboembolism [4,7]. Another limitation is that we did not separate LGSOC and HGSOC since this grading was missing in earlier years 2008–2010. In the follow-up year 6 and 7 must be interpreted with caution due to fewer patients.

In conclusion, far too few premenopausal women receive HRT after BSOE for ovarian cancer. To avoid morbidity and improve quality of life, HRT can be recommended up to average age of menopause. Our findings address the need to increase and follow-up the use of HRT especially in younger women since they are at risk of developing significant morbidity and having a poorer quality of life.

Author contributions

All authors designed the study and analyzed the results. EH extracted data and performed the statistical analyzes. AFR, PD-K and ÅEK wrote the manuscript. All authors critically revised the manuscript, approved the final version and are accountable for all aspects of the work.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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