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Lifestyle and Personal Factors Associated with Having Macroscopic Residual Disease after Ovarian Cancer Primary Cytoreductive Surgery

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Abstract

Objective—The presence of macroscopic residual disease after primary cytoreductive surgery (PCS) is an important factor influencing survival for patients with high-grade serous ovarian cancer (HGSC). More research is needed to identify factors associated with having macroscopic residual disease. We analyzed 12 lifestyle and personal exposures known to be related to ovarian cancer risk or inflammation to identify those associated with having residual disease after surgery.

Methods—This analysis used data on 2,054 patients with advanced stage HGSC from the Ovarian Cancer Association Consortium. The exposures were body mass index, breastfeeding, oral contraceptive use, depot-medroxyprogesterone acetate use, endometriosis, first-degree family history of ovarian cancer, incomplete pregnancy, menopausal hormone therapy use, menopausal status, parity, smoking, and tubal ligation. Logistic regression models were fit to assess the association between these exposures and having residual disease following PCS.

Results—Menopausal estrogen-only therapy (ET) use was associated with 33% lower odds of having macroscopic residual disease compared to never use (OR=0.67, 95%CI 0.46–0.97, p=0.033). Compared to nulliparous women, parous women who did not breastfeed had 36% lower odds of having residual disease (OR=0.64, 95%CI 0.43–0.94, p=0.022), while there was no association among parous women who breastfed (OR=0.90, 95%CI 0.65–1.25, p=0.53).

Conclusions—The association between ET and having no macroscopic residual disease is plausible given a strong underlying biologic hypothesis between this exposure and diagnosis with HGSC. If this or the parity finding is replicated, these factors could be included in risk stratification models to determine whether HGSC patients should receive PCS or neoadjuvant chemotherapy.

Keywords

ovarian cancer; residual disease; primary cytoreductive surgery; lifestyle

Introduction

Ovarian carcinoma is the deadliest gynecologic cancer with about 20,000 new cases and more than 13,000 deaths in the US in 2022[1]. High-grade serous cancer (HGSC) is the most common histotype, comprising ~70% of all epithelial ovarian cancers[2]. About 80% of HGSCs are diagnosed at an advanced stage[3] and the five-year survival rate is very low (~32%)[4]. An important factor influencing survival for HGSC patients is whether no macroscopic residual disease is achieved during primary cytoreductive surgery (PCS)[5, 6].

Factors known to be associated with residual disease following ovarian cancer PCS include disease stage and age[7–9]. Significant efforts have been made to identify additional factors, including personal and lifestyle exposures. We have previously reported that use of menopausal hormone therapy for five or more years before diagnosis was associated with 29% lower odds of having residual disease compared to never use (odds ratio OR=0.71, 95% confidence interval CI 0.54–0.93)[10]. Other studies have suggested that having a family history of cancer[11], a personal history of endometriosis[11], or use of combined oral contraceptives (COCs)[12] are associated with a higher likelihood of achieving no macroscopic residual disease or cytoreduction to residual disease ≤1 cm. Conversely, post-menopausal status[11–13], higher parity[12, 14], higher body mass index (BMI)[12, 13, 15], and ever smoking[12] have been associated with a lower likelihood of achieving no macroscopic residual disease or cytoreduction to residual disease ≤1 cm.

However, previous studies have significant limitations. Most findings of associations with the presence of residual disease are difficult to interpret because there was no adjustment for potential confounders, small sample sizes, and heterogeneity in outcome definitions. Less rigorous definitions of residual disease following PCS has been used, e.g., ‘optimal’ cytoreduction (residual disease ≤1 cm) versus ‘suboptimal’ cytoreduction (residual disease >1 cm)[8, 11]. There is evidence that factors associated with achieving no macroscopic residual disease after PCS may not mirror factors associated with cytoreduction to ≤1 cm residual disease[15].

To address these limitations, we comprehensively examined the association between 12 lifestyle and personal factors and the likelihood of having macroscopic residual disease after PCS in 2,054 patients with advanced-stage HGSC. Data from seven studies from the international Ovarian Cancer Association Consortium (OCAC; https://ocac.ccge.medschl.cam.ac.uk/) were used. We were able to adjust for important confounders and to consider temporal changes in clinical practice.

Materials and Methods

Study population

All OCAC studies obtained institutional review board approval and all participants provided written consent. Studies that had information on residual disease following PCS and data on at least eight of the 12 exposures of interest (see below) were included. Two studies from Australia and five from the United States (US) met these criteria (Table 1). Figure 1 presents the flow chart of patients considered for this analysis. People who were diagnosed with

advanced stage (i.e., distant stage) invasive HGSC (tubal, peritoneal or ovarian), had no prior cancer (except non-melanoma skin cancer), underwent PCS, and had information on residual disease following PCS were included in the analysis. Women undergoing neoadjuvant chemotherapy (NACT; N=544), those who were missing information on whether they had PCS or NACT (N=913), and those without residual disease information (N=398) were excluded. This left 2,054 participants available for this analysis (Figure 1).

Outcome and Exposure Variables

The outcome of interest was macroscopic residual disease after ovarian cancer PCS. The exposures we considered for this analysis were those that are known to be associated with ovarian cancer risk or inflammation. The 12 self-reported pre-diagnosis exposures of interest are: BMI (<18.5, 18.5–24.99, 25–29.99, 30+ kg/m^2); combined oral contraceptive (COC) duration of use (<1 year, 1–4.99, 5–9.99, 10+ years); depot-medroxyprogesterone acetate (DMPA) use for contraception (yes, no); personal history of endometriosis (yes, no); first-degree family history of ovarian cancer (yes, no); incomplete pregnancy (yes, no); menopausal hormone therapy use (never use, estrogen-only therapy [ET] use, combined estrogen-progestin therapy [EPT] use, other [use of both ET and EPT or type unknown]); menopausal status (pre-, post-menopausal); parity/breastfeeding (nulliparous, parous/never breastfed, parous/breastfed); smoking (never, former, current); and tubal ligation (yes, no). Results were similar when conducting analyses on finer categories of parity (0, 1, 2, 3+), incomplete pregnancy (0, 1, 2+), breastfeeding duration (never breastfed, breastfed <12, 12–23, 24+ months), and menopausal hormone therapy duration of use (never use, use for <5 years and 5+ years) separately for ET and EPT use. We considered other exposures but did not include them in the final analysis due to a high proportion of missing values, i.e., >50% (history of polycystic ovary syndrome and pelvic inflammatory disease, alcohol consumption, exposure to environmental smoking, use of talcum powder, and use of non-steroidal anti-inflammatory drugs, aspirin, or acetaminophen).

Multiple imputation

The proportion of missingness for the 12 exposures ranged from 5% for menopausal status to 33% for parity/breastfeeding among the 2,054 participants included in this analysis. Multiple imputation was carried out using the *mice* package in R to generate 20 imputed datasets. All variables were imputed, except for the outcome (residual disease). All variables were included in the imputation models, except for those with 70% of missingness or higher. All studies were imputed together; OCAC study site (n=7) and country (Australia and US) were included as predictors in the imputation models. Results were pooled from 20 imputed datasets using Rubin's rule[16].

Statistical analyses

Patients included in this analysis were diagnosed between 1986 and 2015, a time period over which surgical techniques and treatment approach changed. The value of achieving no macroscopic residual disease became more evident, thus over time patients have generally undergone longer and more extensive and aggressive surgeries[17]. We adjusted for this by including a linear term for year of surgery in the model. However, the frequency of NACT followed by interval debulking surgery increased over time beginning around 2007; prior to

2007 about 10% of patients in the US received NACT whereas by 2018 that number was around 40%, according to the National Cancer Database[18]. Notably, following the clinical trials[19–22] showing non-inferiority of NACT compared to PCS, the number of patients receiving NACT increased across most regions. PCS has increasingly been used in patients most likely to be able to be cytoreduced to no macroscopic residual disease, a decision which is institution-/surgeon-specific. Since our analysis was restricted to patients who did not receive NACT, the proportion of patients cytoreduced to no macroscopic residual disease would therefore be anticipated to be higher in the later calendar periods compared to the earlier periods. We studied the effect of this by estimating the associations separately for year of diagnosis before 2007 versus 2007 and later and carrying out a meta-analysis for the exposures for the two time periods. I^2 are provided for each exposure across the two time periods.

Logistic regression models in the two time periods were fit regressing the presence of macroscopic residual disease on the 12 exposures of interest, adjusted for age at diagnosis (per five years); race/ethnicity (non-Hispanic White, Black, Asian, other); education level (<high school, high school, some college, college or above); year of diagnosis (continuous); Federation of Gynecology and Obstetrics (FIGO) stage (IIIA, IIIB, IIIC, III NOS, and IV); grade (moderately differentiated and poorly differentiated/undifferentiated); CA125 within one month of PCS; and OCAC study site.

Sensitivity analyses

We conducted a sensitivity analysis to assess the appropriateness of pooling the data from the OCAC studies. Meta-analysis results among patients diagnosed before 2007 showed little evidence of heterogeneity in the associations between the exposures and having macroscopic residual disease across the OCAC studies: I^2=0.0% for 16 of the total 19 comparisons (i.e., the number of categories of all exposures excluding the reference groups), except for COC use for 14.99 years (I^2=26%) and 10+ years (I^2=61%), and tubal ligation (I^2=28%). Heterogeneity across OCAC study sites among patients diagnosed in 2007 or later could not be assessed due to the smaller sample size. Thus, given the limited evidence of heterogeneity, the OCAC studies were pooled and analyzed as described above.

Statistical significance was defined as $p \leq 0.05$ using a 2-sided test. Analyses were conducted using R version 4.2.0.

Data availability

The data generated in this study are not publicly available due to limitations imposed by the original studies in which these data were collected. The corresponding author will facilitate access through existing data request processes for the OCAC.

Results

Of the total 2,054 advanced stage HGSC patients included in the analysis, 1,359 (66.2%) were diagnosed before 2007 and 695 (33.8%) in 2007 or later (Table 1). The proportion of participants with macroscopic residual disease following PCS was higher among patients before 2007 compared to those who were diagnosed in 2007 or later (72.7% and 54.7%,

respectively; Table 1). Participant characteristics are shown in Table 2. In both calendar periods, patients with FIGO Stage IIIC and IV disease were more likely to have residual disease compared with those with FIGO stage IIIA/B (Table 3); stage IIIA and IIIB accounted for only 13% of the study population.

Meta-analysis across the two calendar periods (patients diagnosed in 2007 or later compared to those diagnosed before 2007) showed no evidence of heterogeneity, with the exception of first-degree family history of ovarian cancer. First-degree family history of ovarian cancer was statistically significantly inversely associated with macroscopic residual disease in patients diagnosed before 2007 (OR=0.47, 95% CI 0.27–0.80; p=0.005), however in patients diagnosed in 2007 or later, the association was positive, but not statistically significant (OR=1.28, 95% CI 0.64–2.56, p=0.48; Table 4).

ET use was statistically significantly associated with 33% lower odds of having macroscopic residual disease compared to never use (OR=0.67, 95% CI 0.46–0.97, p-value=0.033; Table 4). Compared to nulliparous women, parous women who did not breastfeed had 36% lower odds of having residual disease (OR=0.64, 95% CI 0.43–0.94, p=0.022), while there was no association among parous women who breastfed (OR=0.90, 95% CI 0.65–1.25, p=0.53). There was some suggestion that smoking was associated with having residual disease, but this relationship was only of borderline statistical significance. Compared to never smoking, current smoking was associated with increased odds of having macroscopic residual disease whereas former smoking was associated with reduced odds (OR=1.44, p=0.053, and OR=0.81, p=0.100; Table 4). None of the other exposures was associated with macroscopic residual disease following PCS (Table 4).

Discussion

We comprehensively examined the association between 12 lifestyle and personal factors and the presence of macroscopic residual disease after PCS for advanced stage HGSC. We found evidence for a role of ET and parity in residual disease after PCS. Previously, using data from OCAC we found that people who used menopausal hormone therapy for 5+ years were more likely to have no macroscopic residual disease after ovarian cancer surgery[10], but we did not evaluate ET and EPT use separately. In the current analysis, we did not find an association between EPT use and having macroscopic residual disease.

The mechanism for the association between ET use and having macroscopic residual disease after PCS is unknown. This is unlikely due to access to care, since the majority of our patients were diagnosed at stage IIIC or IV (85.7%; Table 2). We have previously hypothesized that exposure to estrogen makes the tumor less adhesive to their neighbor tissues and thus easier to resect[10]. Estrogen promotes the epithelial-mesenchymal transition process, through which the tumor detaches from nearby tissues. Estrogen also promotes tumor mobility by regulating estrogen responsive genes that are related to survivin, cyclin D1, cyclin E and cathepsin D[23]. Additionally, estrogen may alter the anatomic distribution of disease within a given stage and thus improve resectability. Another possibility is ET might be related to resectability through inflammation. Inflammation may be associated with resectability because the cytokines secreted by immune cells during inflammatory reactions

such as IL-6, TNF-α and CXCR2 promote angiogenesis and tumor growth[24]. Estrogen at high concentrations promotes an anti-inflammatory environment[25, 26] and this milieu may make it easier to achieve no macroscopic residual disease. However, further studies are warranted to elucidate the precise mechanisms through which menopausal estrogen use is associated with resectability.

We found that parity was inversely associated with having macroscopic residual disease among people who did not breastfeed. Contrary to our results, two previous studies found that ovarian cancer patients who had residual disease (>1cm) after PCS had more births than women who were optimally debulked (residual disease ≤1cm)[12, 14]. However, the results from these studies were not adjusted for potential confounders, had a different outcome definition, and did not take breastfeeding into account. Parity is associated with high exposure to both estrogen and progesterone and it is possible that exposure of the pelvis and upper abdomen to these hormones creates an environment that ultimately makes HGSC easier to resect. It is also possible that the association between parity and the presence of residual disease after PCS among women who did not breastfeed was due to chance, given the lack of a clear underlying biologic mechanism and the number of hypotheses we tested. More studies are needed to explore the role of hormones in risk of residual disease after ovarian cancer PCS.

The observation that current smokers have higher odds of having macroscopic residual disease after PCS compared to never smokers could also be related to inflammation given that smoking leads to a pro-inflammatory environment. Former smokers had lower odds of having macroscopic residual disease after PCS compared to never smokers. This may be because people who quit smoking adopt healthier lifestyles, including diets[27], which are associated with less inflammation. However, the associations between smoking and having residual disease following PCS were only of borderline statistical significance.

We found that a first-degree family history of ovarian cancer was statistically significantly associated with lower odds of having residual disease among patients diagnosed before 2007, but was associated with a higher odds among patients diagnosed in 2007 or later although this result was not statistically significant. This could be due to the smaller sample size among patients diagnosed in the later period. It is also possible that the proportion of *BRCA* mutation carriers is different among patients in the two calendar periods in our study. There is suggestive evidence that ovarian cancer patients with *BRCA* mutations are more likely to have cytoreduction to ≤1 cm residual disease compared to noncarriers[28]. However, we did not have information on who carried a pathogenic *BRCA* variant in our study population.

Strengths of the current study include the large sample size and the ability to adjust for confounders. However, we did not have information on surgical expertise, effort, complexity, or comorbidities which may impact surgical outcome. Most of the data in the OCAC studies came from patients who received care at large treatment centers where surgical expertise would be expected to be high. In addition, we adjusted for tumor stage in the analysis which could serve as a proxy for surgical complexity. However, we acknowledge that OCAC study site and tumor stage may not fully capture surgical expertise, effort, and

complexity. Surgical expertise and effort could be effect modifiers. Our analysis included seven study sites, some of which are made up of multiple hospitals and surgeons. Further, the proportion of patients undergoing PCS as well as the proportion of patients with no macroscopic residual disease varies somewhat across study site (Table 1). However, our meta-analysis found no heterogeneity in the effect of menopausal hormone therapy, parity/breastfeeding, or smoking on the presence of macroscopic residual disease across study site. This suggests that the associations observed in this study are independent of surgical expertise or effort, primary cytoreductive surgery rate, and debulking rate, thus enhancing the generalizability of our findings. Also, because of the increase in the use of NACT over time, the participants who were recruited in early calendar years were likely materially different from those enrolled in later years. To address this issue, we stratified our analyses on calendar period and meta-analyzed the results across the two calendar periods. Lastly, a quarter of participants were excluded due to missing information on treatment sequence (PCS vs NACT). We did not impute this information because there was heterogeneity across the OCAC study sites in year, which could affect the treatment sequence selection.

In conclusion, our results suggest that parity among women who did not breastfeed and ET use are associated with lower odds of having macroscopic residual disease after ovarian cancer PCS. The association between ET use and having no macroscopic residual disease is plausible given a strong underlying biologic hypothesis between this exposure and diagnosis with ovarian cancer. If this finding or the parity association is replicated, these factors may be able to be included in prospective risk stratification models to determine whether HGSC patients should be managed with PCS or NACT. Future studies on the mechanisms of these associations are warranted.

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Highlights

- Menopausal estrogen-only therapy use was associated with 33% lower odds of having macroscopic residual disease following PCS.
- Being a current smoker may be associated with higher odds of having macroscopic residual disease following PCS.
- These factors could be included in models to determine if patients should receive PCS or neoadjuvant chemotherapy.

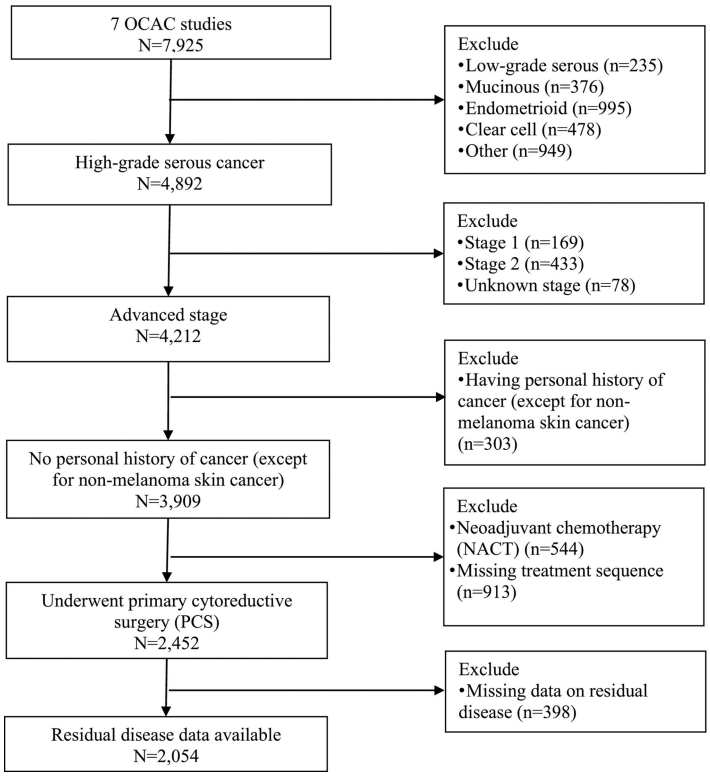

Figure 1:
Flowchart of participants included in the analysis

Table 1:

Characteristics of studies included in the analysis

Study abbreviation	Study full name	Study location	Year of diagnosis	Total of participants included in the main analysis	Diagnosed before 2007 N=1,359 (66.2%)		Diagnosed in 2007 or later N=695 (33.8%)	
					Macroscopic residual disease n (%)	No macroscopic residual disease n (%)	Macroscopic residual disease n (%)	No macroscopic residual disease n (%)
AUS[29]	Australian Ovarian Cancer Study	Australia	2001-2006	544	424 (77.9%)	120 (22.1%)	0	0
OPL[30]	Ovarian Cancer Prognosis and Lifestyle Study	Australia	2012-2015	245	0	0	148 (60.4%)	97 (39.6%)
HAW[31]	Hawaii Ovarian Cancer Case-Control Study	Hawai'i, US	1994-2006	65	47 (72.3%)	18 (27.7%)	0	0
HOP[32]	Hormones and Ovarian Cancer Prediction	Western Pennsylvania, Northeast Ohio, Western New York, US	2003-2008	289	148 (76.7%)	45 (23.3%)	64 (66.7%)	32 (33.3%)
LAX	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	California, US	1986-2008	134	51 (45.9%)	60 (54.1%)	13 (56.5%)	10 (43.5%)
MAYO[33, 34]	Mayo Clinic Ovarian Cancer Study	Minnesota, US	1993-2014	569	177 (70.0%)	76 (30.0%)	144 (45.6%)	172 (54.4%)
NEC[35]	New England Case Control Study	New Hampshire and Eastern Massachusetts, US	1992-2008	208	141 (73.1%)	52 (26.9%)	11 (73.3%)	4 (26.7%)
				2,054	988 (72.7%)	371 (27.3%)	380 (54.7%)	315 (45.3%)

Table 2:

Characteristics of participants included in the main analysis based on the unimputed dataset

	Diagnosed before 2007		Diagnosed in 2007 or later	
	Macroscopic residual disease n=988	**No macroscopic residual disease n=371**	**Macroscopic residual disease n=380**	**No macroscopic residual disease n=315**
Age at diagnosis				
Mean [SD]	60.7 [10.3]	59.3 [11.2]	62.0 [10.6]	60.6 [11.1]
Median [IQR]	61.0 [14.0]	60.0 [16.5]	62.5 [15.0]	60.0 [15.5]
FIGO stage				
IIIA and IIIB	39 (3.9%)	60 (16.2%)	13 (3.4%)	41 (13.0%)
III (NOS)	133 (13.5%)	52 (14.0%)	11 (2.9%)	4 (1.3%)
IIIC	657 (66.5%)	229 (61.7%)	289 (76.1%)	241 (76.5%)
IV	159 (16.1%)	30 (8.1%)	67 (17.6%)	29 (9.2%)
Grade				
Moderately differentiated	147 (14.9%)	50 (13.5%)	23 (6.1%)	21 (6.7%)
Poorly differentiated or undifferentiated	841 (85.1%)	321 (86.5%)	357 (93.9%)	294 (93.3%)
CA125				
Mean [SD]	2680 [7,370]	1080 [1,960]	1,990 [3,160]	1480 [8,900]
Median [IQR]	904 [1,740]	433 [915]	920 [1,970]	386 [962]
Missing	337 (34.1%)	131 (35.3%)	98 (25.8%)	84 (26.7%)
Education				
< high school	159 (16.1%)	50 (13.5%)	68 (17.9%)	37 (11.7%)
High school	247 (25.0%)	82 (22.1%)	90 (23.7%)	80 (25.4%)
Some college	238 (24.1%)	73 (19.7%)	84 (22.1%)	85 (27.0%)
College or above	202 (20.4%)	80 (21.6%)	112 (29.5%)	92 (29.2%)
Missing	142 (14.4%)	86 (23.2%)	26 (6.8%)	21 (6.7%)
Race/ethnicity				
Non-Hispanic White	904 (91.5%)	327 (88.1%)	352 (92.6%)	285 (90.5%)
Black	12 (1.2%)	3 (0.8%)	1 (0.3%)	2 (0.6%)
Asian	20 (2.0%)	18 (4.9%)	13 (3.4%)	13 (4.1%)
Other	23 (2.3%)	14 (3.8%)	12 (3.2%)	12 (3.8%)
Missing	29 (2.9%)	9 (2.4%)	2 (0.5%)	3 (1.0%)
BMI (kg/m2)				
<18.5	20 (2.0%)	5 (1.3%)	3 (0.8%)	4 (1.3%)
18.5–24.99	364 (36.8%)	137 (36.9%)	159 (41.8%)	123 (39.0%)
25–29.99	293 (29.7%)	108 (29.1%)	115 (30.3%)	85 (27.0%)
30+	225 (22.8%)	79 (21.3%)	84 (22.1%)	83 (26.3%)
Missing	86 (8.7%)	42 (11.3%)	19 (5.0%)	20 (6.3%)
COC use (years)				
<1	475 (48.1%)	160 (43.1%)	136 (35.8%)	99 (31.4%)
1–4.99	190 (19.2%)	63 (17.0%)	82 (21.6%)	81 (25.7%)

	Diagnosed before 2007		Diagnosed in 2007 or later	
	Macroscopic residual disease n=988	No macroscopic residual disease n=371	Macroscopic residual disease n=380	No macroscopic residual disease n=315
5–9.99	109 (11.0%)	42 (11.3%)	69 (18.2%)	51 (16.2%)
10+	115 (11.6%)	31 (8.4%)	62 (16.3%)	58 (18.4%)
Missing	99 (10.0%)	75 (20.2%)	31 (8.2%)	26 (8.3%)
DMPA use				
Never	709 (71.8%)	220 (59.3%)	218 (57.4%)	133 (42.2%)
Ever	5 (0.5%)	3 (0.8%)	88 (23.2%)	117 (37.1%)
Missing	274 (27.7%)	148 (39.9%)	74 (19.5%)	65 (20.6%)
Endometriosis				
No	769 (77.8%)	253 (68.2%)	336 (88.4%)	264 (83.8%)
Yes	51 (5.2%)	19 (5.1%)	18 (4.7%)	25 (7.9%)
Missing	168 (17.0%)	99 (26.7%)	26 (6.8%)	26 (8.3%)
Family history of ovarian cancer				
No	785 (79.5%)	276 (74.4%)	326 (85.8%)	271 (86.0%)
Yes	37 (3.7%)	30 (8.1%)	24 (6.3%)	20 (6.3%)
Missing	166 (16.8%)	65 (17.5%)	30 (7.9%)	24 (7.6%)
Incomplete pregnancy				
No	605 (61.2%)	231 (62.3%)	246 (64.7%)	200 (63.5%)
Yes	320 (32.4%)	110 (29.6%)	118 (31.1%)	100 (31.7%)
Missing	63 (6.4%)	30 (8.1%)	16 (4.2%)	15 (4.8%)
Menopausal status				
Pre-menopause	184 (18.6%)	82 (22.1%)	65 (17.1%)	65 (20.6%)
Post-menopause	757 (76.6%)	262 (70.6%)	303 (79.7%)	236 (74.9%)
Missing	47 (4.8%)	27 (7.3%)	12 (3.2%)	14 (4.4%)
Menopausal hormone use				
Never use	486 (49.2%)	159 (42.9%)	225 (59.2%)	187 (59.4%)
ET use	93 (9.4%)	42 (11.3%)	29 (7.6%)	25 (7.9%)
EPT use	155 (15.7%)	51 (13.7%)	67 (17.6%)	55 (17.5%)
Other	38 (3.8%)	13 (3.5%)	27 (7.1%)	16 (5.1%)
Missing	216 (21.9%)	106 (28.6%)	32 (8.4%)	32 (10.2%)
Parity/Breastfeeding				
Nulliparous	145 (14.7%)	47 (12.7%)	56 (14.7%)	46 (14.6%)
Parous/never breastfed	189 (19.1%)	86 (23.2%)	57 (15.0%)	35 (11.1%)
Parous/breastfed	405 (41.0%)	108 (29.1%)	124 (32.6%)	74 (23.5%)
Missing	249 (25.2%)	130 (35.0%)	143 (37.6%)	160 (50.8%)
Smoking				
Never	499 (50.5%)	168 (45.3%)	179 (47.1%)	154 (48.9%)
Current	134 (13.6%)	30 (8.1%)	44 (11.6%)	26 (8.3%)
Former	247 (25.0%)	106 (28.6%)	118 (31.1%)	111 (35.2%)
Missing	108 (10.9%)	67 (18.1%)	39 (10.3%)	24 (7.6%)

	Diagnosed before 2007		Diagnosed in 2007 or later	
	Macroscopic residual disease n=988	**No macroscopic residual disease n=371**	**Macroscopic residual disease n=380**	**No macroscopic residual disease n=315**
Tubal ligation				
No	629 (63.7%)	234 (63.1%)	208 (54.7%)	156 (49.5%)
Yes	192 (19.4%)	71 (19.1%)	70 (18.4%)	52 (16.5%)
Missing	167 (16.9%)	66 (17.8%)	102 (26.8%)	107 (34.0%)

Abbreviations: BMI: body mass index; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; FIGO: International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; SD: standard deviation

Table 3:

Association between clinical factors and year at diagnosis and having macroscopic residual disease after ovarian cancer primary cytoreductive surgery by calendar period of diagnosis (before 2007 vs 2007 or later)

	Diagnosed before 2007 N=1,359		Diagnosed in 2007 or later N=695	
	OR (95% CI)*	p-value	OR (95% CI)*	p-value
Age at diagnosis				
Every 5 years	1.05 (0.96–1.16)	0.30	1.06 (0.94–1.18)	0.34
Year at diagnosis				
Every calendar year	1.00 (0.94–1.05)	0.92	0.93 (0.83–1.04)	0.18
CA125				
Every 200 units	1.02 (1.00–1.03)	0.063	1.00 (0.99–1.01)	0.72
FIGO stage				
IIIA+IIIB	1.0		1.0	
III (NOS)	5.75 (1.94–16.99)	0.002	10.24 (0.89–117.77)	0.062
IIIC	5.52 (3.45–8.84)	<0.001	4.96 (2.46–9.97)	<0.001
IV	10.50 (5.63–19.59)	<0.001	11.40 (4.94–26.32)	<0.001
Grade				
Moderately differentiated	1.0		1.0	
Poorly differentiated or undifferentiated	0.94 (0.63–1.39)	0.74	1.38 (0.69–2.77)	0.36

*Pooled results using the 20 imputed datasets.

Abbreviations: CI: confidence interval; FIGO: International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; OR: odds ratio

Table 4:

Association between the exposures of interest and having macroscopic residual disease after ovarian cancer primary cytoreductive surgery by calendar period of diagnosis (before 2007 vs 2007 or later)

	Diagnosed before 2007 N=1,359		Diagnosed in 2007 or later N=695		Meta-analysis**		
	OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)	p-value	I^2
BMI (kg/m^2)							
18.5–24.99	1.0		1.0		1.0		
25–29.99	0.99 (0.71-1.38)	0.95	1.04 (0.69-1.55)	0.86	1.01 (0.78-1.30)	0.95	0%
30+	0.98 (0.68-1.41)	0.91	0.78 (0.51-1.18)	0.24	0.89 (0.67-1.17)	0.39	0%
COC use (years)							
<1	1.0		1.0		1.0		
1–4.99	1.06 (0.73-1.55)	0.75	0.97 (0.61-1.54)	0.89	1.02 (0.76-1.37)	0.88	0%
5–9.99	0.91 (0.58-1.44)	0.70	1.02 (0.62-1.67)	0.95	0.96 (0.69-1.34)	0.81	0%
10+	1.14 (0.69-1.89)	0.60	0.89 (0.54-1.46)	0.64	1.01 (0.71-1.43)	0.97	0%
DMPA use							
No	1.0		1.0		1.0		
Yes	0.65 (0.14-2.92)	0.57	0.92 (0.29-2.94)	0.89	0.81 (0.33-2.00)	0.64	0%
Endometriosis							
No	1.0		1.0		1.0		
Yes	1.03 (0.55-1.95)	0.92	0.73 (0.36-1.47)	0.38	0.88 (0.55-1.41)	0.61	0%
First-degree family history of ovarian cancer							
No	1.0		1.0		1.0		
Yes	0.47 (0.27-0.80)	0.005	1.28 (0.64-2.56)	0.48	0.68 (0.45-1.04)	0.075	80.5 %
Incomplete pregnancy							
No	1.0		1.0		1.0		
Yes	1.12 (0.84-1.50)	0.44	1.00 (0.69-1.44)	0.99	1.07 (0.85-1.35)	0.55	0%
Menopausal status							
Pre-menopausal	0.84 (0.52-1.33)	0.45	0.87 (0.48-1.56)	0.64	0.85 (0.59-1.22)	0.38	0%
Post-menopausal	1.0		1.0		1.0		
Menopausal hormone therapy use							
Never	1.0		1.0		1.0		
EPT use only	0.62 (0.39-0.98)	0.42	0.77 (0.40-1.46)	0.42	0.67 (0.46-0.97)	0.033	0%
EPT use only	0.92 (0.61-1.37)	0.67	1.10 (0.69-1.76)	0.69	0.99 (0.73-1.34)	0.95	0%
Other	0.99 (0.48-2.03)	0.97	1.07 (0.51-2.24)	0.86	1.02 (0.61-1.72)	0.93	0%
Parity/Breastfeeding							
Nulliparous	1.0		1.0		1.0		
Parous/never breastfed	0.53 (0.33-0.87)	0.013	0.85 (0.45-1.59)	0.60	0.64 (0.43-0.94)	0.022	21.9%
Parous/breastfed	0.84 (0.55-1.31)	0.45	0.98 (0.59-1.64)	0.94	0.90 (0.65-1.25)	0.53	0%
Smoking							

	Diagnosed before 2007 N=1,359		Diagnosed in 2007 or later N=695		Meta-analysis**		
	OR (95% CI)*	p-value	OR (95% CI)*	p-value	OR (95% CI)	p-value	I^2
Never	1.0		1.0		1.0		
Current	1.50 (0.93-2.41)	0.094	1.36 (0.74-2.48)	0.32	1.44 (0.99-2.09)	0.053	0%
Former	0.78 (0.57-1.08)	0.13	0.86 (0.59-1.26)	0.44	0.81 (0.64-1.04)	0.100	0%
Tubal ligation							
No	1.0		1.0		1.0		
Yes	0.93 (0.65-1.32)	0.67	0.98 (0.61-1.59)	0.94	0.95 (0.71-1.26)	0.70	0%

*Models adjusted for age at diagnosis, race/ethnicity, education level, year of diagnosis, FIGO stage, grade, CA125, and OCAC study site.

**Fixed odds ratios, 95% confidence intervals and p-values from meta-analyses across calendar period of diagnosis (before 2007 vs 2007 or later). ND=not done.

Abbreviations: BMI: body mass index; CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; EPT: estrogen plus progestin therapy; ET: estrogen therapy; FIGO: International Federation of Gynecology and Obstetrics; OCAC: Ovarian Cancer Association Consortium; OR: odds ratio