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Impact of Chemotherapy Dosing on Ovarian Cancer Survival According to Body Mass Index

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Abstract

IMPORTANCE—Optimal chemotherapy dosing in obese patients remains uncertain, with variation in practice. Dose reduction strategies are often used to avoid chemotoxicity, but recent American Society of Clinical Oncology guidelines recommend full dose.

OBJECTIVE—To evaluate the impact of body mass index (BMI) on chemotherapy dosing and of dose reduction on ovarian cancer survival.

DESIGN, SETTING, AND PARTICIPANTS—Cohort study in Kaiser Permanente Northern California (KPNC) health care setting of patients with primary invasive epithelial ovarian cancers diagnosed from January 2000 through March 2013. Analyses focused on 806 patients receiving adjuvant first-line therapy of carboplatin and paclitaxel with curative intent.

MAIN OUTCOMES AND MEASURES—Overall and ovarian cancer–specific mortality. Deaths were identified through the KPNC Mortality Linkage System, with median follow-up of 52.5 months. Hazard ratios (HRs) and 95% CIs were estimated from proportional hazards regression, accounting for prognostic variables including age at diagnosis, race, stage, grade, histologic type, chemotoxic effects, comorbidities, cancer antigen 125 levels, and BMI at diagnosis.

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RESULTS—The strongest predictor of dose reduction was a high BMI. Compared with normal-weight women, obese class III women received 38% and 45% lower doses in milligrams per kilogram of body weight of paclitaxel and carboplatin, respectively ($P < .001$ for each agent). They also received lower relative dose intensity (RDI) for each agent and the combined regimen, calculated as average RDI (ARDI). Mean ARDI was 73.7% for obese class III women and 88.2% for normal-weight women ($P < .001$). Lower ARDI (<70%) was associated with worse overall (HR, 1.62 [95% CI, 1.10–2.37]) and ovarian cancer–specific survival (HR, 1.69 [95% CI, 1.12–2.55]). Women who were obese at diagnosis appeared to have better survival. In multivariable-adjusted analyses considering joint effects by BMI and ARDI, compared with women with normal weight and no dose reduction, normal-weight women with dose reduction (ARDI < 85%) experienced worse survival (HR, 1.50 [95% CI, 1.02–2.21]). For each BMI category, those with ARDI less than 85% had worse survival than those without dose reduction. The improved survival among obese women was no longer apparent with dose reduction.

CONCLUSIONS AND RELEVANCE—Lower RDI was an independent predictor of ovarian cancer mortality. This finding was strongest among normal-weight women but seen at all levels of BMI. Our results suggest that body size should not be a major factor influencing dose reduction decisions in women with ovarian cancer.

Ovarian cancer is the second most common gynecologic cancer and the leading cause of death from gynecologic malignant neoplasm in the United States.[1] Standard treatment for epithelial ovarian cancer (EOC) consists of surgical cytoreduction followed by platinum and taxane–based chemotherapy,[2] with the primary adjuvant chemotherapy regimen being combination therapy with carboplatin and paclitaxel.[3] However, there is considerable variation in practice and uncertainty regarding optimal chemotherapy dosing of overweight and obese patients, mainly based on concerns that using full dose based on actual weight may lead to increased toxicity.[4,5]

Body surface area (BSA) has been used for calculation of chemotherapy dose for some agents for more than 40 years. The use of BSA was based on the notion that it is proportionate to metabolism, a theory first proposed by Rubner in 1883, with the most common formula currently used for estimating BSA developed more than 100 years ago and based on a few subjects.[6] Because dosing of some chemotherapy drugs, such as paclitaxel, is based on BSA, concerns that use of high doses of drugs in obese patients may result in excess toxicity has resulted in various strategies for dose reduction. For example, dose may be capped at a BSA of 2 m^2 or calculated on the basis of ideal rather than actual weight.[7] In contrast, carboplatin dosing is based on renal function, measured as glomerular filtration rate, and estimated by calculating creatinine clearance.[8,9] Several formulas are used in clinical practice to calculate creatinine clearance, with the commonly used Cockcroft-Gault equation[8] also a function of weight. There is uncertainty regarding the use of ideal or actual weight in the formula, with concern that using actual bodyweight may overestimate glomerular filtration rate and, consequently, carboplatin dosing.[8,9]

Although there is growing evidence that dose reduction decreases cancer survival, several surveys have estimated that up to 40% of obese patients receive reduced doses.[5] An expert panel convened by the American Society of Clinical Oncology recommended full dose

based on actual weight to treat the obese patient and found no evidence of associated increased short- or long-term toxicity.[5] However, these conclusions were mostly based on breast cancer studies. Optimal chemotherapy dosing in overweight and obese patients with ovarian cancer remains uncertain.

This study evaluated the association of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and chemotherapy dosing, predictors of dose reduction, and chemotherapy efficacy in improving survival and related toxic effects according to BMI in a large population-based cohort study of patients with ovarian cancer.

Methods

Study Population

The Kaiser Permanente Research on Ovarian Cancer Study (KP-ROCS) is a cohort study of EOC based in the Kaiser Permanente Northern California (KPNC) integrated health care setting. A flowchart describing the KP-ROCS cohort is shown in Figure 1. Primary invasive EOC cases were identified through the KPNC Cancer Registry and were eligible for inclusion if age at diagnosis was 21 years or older, with date of diagnosis between January 2000 and March 2013. Women who were not KPNC members at diagnosis or who disenrolled from the KPNC health plan before full standard chemotherapy treatment could have been completed were also excluded. This resulted in a cohort of 2299 patients with EOC.

Kaiser Permanente Northern California began to include BMI or weight and height data in electronic records in 2002. We defined BMI at diagnosis as the measurement closest to the diagnosis date and within 6 months before diagnosis. If BMI was not available during that period, then the closest measurement to the diagnosis date within 2 months after diagnosis and before treatment was selected. Body mass index was categorized according to World Health Organization classification, as shown in Table 1. As illustrated in Figure 1, 453 cases were excluded because they did not have data on BMI at diagnosis, resulting in a cohort of 1846 EOC cases. Cases without data on BMI were those occurring early in the case identification period (ie, occurring prior to inclusion of BMI in electronic health records). Distributions by major demographic and clinical characteristics for women with and without BMI at diagnosis were similar (data not shown).

We included patients who started a standard regimen (surgery followed by chemotherapy administration every 3 weeks) of intravenous adjuvant first-line therapy of carboplatin and paclitaxel within 6 months of diagnosis with curative intent. This regimen was used in approximately 79% of patients receiving chemotherapy. Selecting patients with the same regimen and route of administration minimized variation in dosing parameters and possible adverse effects that may result in dose reduction and delay, thereby facilitating focus on the effects of body size on dose received. Exclusion of an additional 35 women missing dosing variables resulted in an analytic subcohort of 806 patients with EOC (Figure 1).

Data Obtained for Analysis

Data on demographic characteristics (age, race, ethnicity), tumor characteristics (stage, grade, histologic type), treatment information, toxic effects, and comorbidities were obtained from KPNC electronic databases, including its Virtual Data Warehouse (VDW).[10,11] Information on race/ethnicity came from the VDW's Tumor File, which is based on the KPNC Cancer Registry, and was considered as potential covariates. The VDW extracts data into a standardized data model that facilitates research conducted at KPNC and other integrated health care settings that participate in the National Cancer Institute (NCI)–supported Cancer Research Network (http://crn.cancer.gov). Variables for chemotherapy dosing analyses, described in eTable 1 in the Supplement, included actual dose, relative dose intensity (RDI) (actual dose administered per week/expected dose per week), early discontinuation, and treatment delay. The RDI was computed for paclitaxel and carboplatin separately, and for the combination regimen by computing the average RDI (ARDI), as described by others.[9,12,13] Expected doses were based on National Comprehensive Cancer Network Guidelines (http://www.nccn.org) and are presented in eTable 1 in the Supplement. Actual weight was used when calculating BSA and creatine clearance to compute expected doses. The area under the curve (AUC) value used for carboplatin dosing was that indicated in the medical record for the first course of therapy and was 6 in 75% and 5 in 21% of the women. Serum creatinine to estimate creatinine clearance was also the value associated with the first course of therapy. Chemotherapy reduction was defined as an RDI for the full regimen of less than either 85%[14–16] or 70%.[17] Early discontinuation was defined as not completing the full 6 scheduled treatments[18] or alternatively, 4 scheduled treatments. Treatment delay was defined as a delay in receiving scheduled chemotherapy treatment of more than 7 days.

Chemotoxic effects considered as potential predictors of chemotherapy dose reduction included myelosuppression (severe neutropenia or thrombocytopenia) and neuropathy before chemotherapy (within 1 month prior to first cycle for neutropenia and thrombocytopenia and within 1 month prior to diagnosis to first cycle for neuropathy) or during chemotherapy (between first and last cycle). The *National Cancer Institute's Common Terminology Criteria for Adverse Events* (NCI CTCAE), version 3.0, was used to identify chemotherapy-related toxicity grade 3/4. Use of granulocyte colony-stimulating factor (G-CSF) for prophylaxis or treatment of neutropenia was also obtained from the VDW.

Comorbidities considered were those known to be related to obesity, to impair chemotherapy dosing or survival,[19] or to occur commonly among patients with ovarian cancer.[20] These included diabetes mellitus, hypertension, cardiovascular disease, and renal disease comprising acute kidney disease during chemotherapy or chronic renal insufficiency occurring at least 1 year before diagnosis throughout the end of follow-up. On the basis of our inclusion criteria, all patients underwent surgery before chemotherapy; cancer antigen 125 (CA125) level after treatment was used as a marker of residual disease.[21,22]

Outcomes were total and ovarian cancer–specific deaths through December 31, 2013, identified through the KPNC Mortality Linkage System, which includes date of death and

International Classification of Diseases, Ninth Revision, Clinical Modification coded underlying cause of death. Through that date, 334 deaths, 291 due to ovarian cancer, were identified in the chemotherapy subcohort, with median (SD) follow-up of 52.5 (38.4) months. The study was approved by the institutional review boards of Kaiser Permanente Northern California, which waived the requirement for informed consent due to the retrospective nature of the study and high fatality rate for this type of cancer, and Rutgers Biomedical and Health Sciences at Rutgers University.

Statistical Analyses

Distributions for demographic and clinical characteristics were compared across categories of BMI using χ^2 tests. χ^2 Goodness-of-fit tests were used to compare distributions in the overall cohort and the chemotherapy subcohort. Mean values of RDI and ARDI, actual dose of paclitaxel and carboplatin, number of cycles, and treatment duration across BMI categories were compared using analysis of variance. The proportions of women with dose reduction, early discontinuation, and treatment delay across BMI groups were also compared using χ^2 tests. Predictors of dose reduction (RDI < 85%) were evaluated by logistic regression analysis with dose reduction as a dichotomous outcome.

The impact of dose reduction on survival was evaluated by comparing survival curves using the Kaplan-Meier method and log-rank test and by estimating HRs and 95% CIs for all-cause and ovarian cancer–specific mortality using Cox proportional hazards regression analysis. Type 3 Wald χ^2 tests were conducted to evaluate whether there were significant differences in mortality among exposure categories.*P* values for trend were computed by including the median in each category as a continuous variable in regression models. Covariates included age at diagnosis, race, American Joint Committee on Cancer stage, grade, histologic type, chemotherapy-related toxic effects, BMI at diagnosis, comorbidities (diabetes, hypertension, cardiovascular disease, and renal disease), and CA125 levels after treatment. All *P* values were 2 sided, and $P < .05$ was defined as statistically significant. SAS, version 9.2 (SAS Institute), was used for analyses.

Results

Demographic and clinical characteristics were generally similar in our chemotherapy subcohort and the overall KP-ROCS cohort, with the exception, as expected, of the chemotherapy subcohort having a smaller proportion of women older than 70 years or with advanced disease (Table 1). Approximately 30% of patients were obese and another 31% overweight, whereas fewer than 3% were underweight.

BMI and Chemotherapy Dosing

Dose reduction (RDI < 85%) was significantly more common among obese women, particularly those with BMI at least 35, for both paclitaxel ($P = .01$) and carboplatin ($P < .001$) (eTable 2 in the Supplement). There was a significant inverse association between BMI and RDI for each agent and for ARDI, for both the first cycle and all cycles combined. Mean ARDI for the regimen for all cycles was 73.7% for obese class 3 women and 88.2% for normal-weight women ($P < .001$). We also found a significant inverse association between

BMI and actual total dose of paclitaxel and carboplatin administered per kilogram of body weight. Compared with normal-weight women, obese class 3 women received 38% and 45% lower doses in milligrams per kilogram of bodyweight of paclitaxel and carboplatin, respectively ($P < .001$ for both agents).

Toxic Effects and Comorbidities by BMI at Diagnosis

Aside from cardiovascular disease, comorbidities were more common among obese than normal-weight women (eTable 3 in the Supplement). Neutropenia during chemotherapy and G-CSF use were less common among obese than normal-weight women. Chemotherapy-related neuropathy was unrelated to BMI. Chemotoxic effects were more common among those receiving lower RDI for all categories of BMI (data not shown).

Predictors of Dose Reduction

Body mass index at diagnosis was the strongest predictor of dose reduction (RDI < 85%), with a stronger association for carboplatin than paclitaxel (eTable 4 in the Supplement). Compared with normal-weight women, obese women were substantially more likely (for ARDI, odds ratio, 2.85 [95% CI, 1.79–4.55] for obese class 1, and odds ratio, 19.85 [95% CI, 7.21–54.65] for obese class 3) to have received dose reduction. Advanced stage, chemotoxic effects, and cardiovascular disease were also associated with dose reduction.

Dose Reduction and Overall and Ovarian Cancer–Specific Survival

There was a suggestion that obesity at diagnosis was associated with better survival after adjusting for prognostic factors (Table 2). As shown in Table 2 and Table 3, compared with those with an ARDI of 85% to 100%, lower ARDI (<70%) was a strong predictor of overall (HR, 1.62 [95% CI, 1.10–2.37]) and ovarian cancer–specific mortality (HR, 1.69 [95% CI, 1.12–2.55]). Similar findings are shown in eFigure 1 in the Supplement. Similar associations were observed for paclitaxel RDI and carboplatin RDI, although there was not a clear dose-response association for carboplatin RDI (Table 3).

Joint Effects of BMI and Dose Reduction on Survival

Compared with normal-weight women receiving ARDI of at least 85%, women of normal weight receiving dose reduction had worse survival (HR, 1.50 [95% CI, 1.02–2.21]) (Figure 2A). For the 3 body size categories, those with dose reduction had poorer survival; the possible survival advantage for obese women disappeared with dose reduction. The interaction between body size and dose reduction was not statistically significant ($P = .36$). Similar findings were seen for ovarian cancer–specific survival (Figure 2B).

Discussion

In this study we found that obese patients with ovarian cancer received considerably less paclitaxel and carboplatin per kilogram of body weight and lower RDI for each chemotherapy agent and for the combined regimen. We also found that the strongest predictor of dose reduction, defined as an RDI below 85%, was a high BMI. Dose reduction was associated with reduced survival time, particularly for normal weight women. This association was apparent even after accounting for diagnostic and prognostic factors such as

stage of disease, comorbid conditions, or posttreatment CA125 levels, a marker of residual disease.

Only a few studies have evaluated dose reduction in patients with ovarian cancer. Barrett et al,[23] using data from the SCOTROC I clinical trial based in Scotland, in which taxane (docetaxel or paclitaxel) dose was calculated on the basis of BSA with no dose capping, reported no statistical difference in taxane dose intensity among BMI categories—unsurprising because the study used no dose capping. Wright et al,[24] using Gynecologic Oncology Group clinical trial data, evaluated the impact of bodyweight on carboplatin-related toxic effects and survival inpatients (n = 387) treated with carboplatin and dosed on the basis of the Jelliffe formula, which includes age and creatinine clearance but does not account for weight. They found that, compared with normal-weight patients, obese patients were less likely to have dose reduction and treatment delay and experienced fewer toxic effects. Dose reduction was defined as at least a 30% decrease in dose after the first cycle. An additional study of ovarian cancer[25] (n = 198) found that obese patients were less likely to have dose reduction or treatment delay compared with underweight or normal-weight patients, but the difference was not statistically significant (P = .11).

Chemotherapy dosing decisions in obese women tend to occur at the first cycle (eg, to cap dose at a BSA of 2.0 m^2 or to use ideal weight rather than actual weight), and thus dose reduction during the course of chemotherapy may be less common for such women.[26] For this reason, using RDI is a better method to evaluate dose reduction. In a recent Australian study,[16] there were no differences in dose reduction across BMI categories, but a significantly higher proportion of obese patients received an ARDI less than 85% for carboplatin and paclitaxel, in agreement with our study. Body mass index was also a major predictor of RDI less than 85% in another study.[15]

In agreement with others,[24] we found that obese women were less likely to experience toxic effects, in particular neutropenia. Decreased occurrence of toxic effects may be a consequence of differences in metabolism that are not well understood, such as binding of chemotherapy agents in adipose tissue, or in clearance of these drugs in obese women.[26] Regardless of BMI, women who received dose reduction had a higher prevalence of chemotoxic effects. This is likely a reflection of chemotoxic effects resulting in decisions to reduce dose.

Few studies have evaluated the impact of RDI on ovarian cancer survival. Unadjusted analyses in a small study based on participants in clinical trials revealed no impact on survival among those receiving RDI less than 75%.[27] In contrast, another small study (n = 138) using retrospective medical record review in an Alabama hospital reported decreased survival for patients with ovarian cancer receiving RDI less than 70%, but no multivariable analyses were conducted. Only 2 studies have presented results adjusted for prognostic variables, with conflicting conclusions, both based on retrospective medical record review and including fewer than 350 patients, and both evaluating an RDI less than 85%.[15,16] Hanna et al,[15] in a study in North Carolina, found decreased overall survival, similar to our findings. The other study, conducted in Australia,[16] found no association with overall

survival. Although both studies adjusted for several prognostic factors, neither took into account chemotoxic effects or comorbidities.

To our knowledge, our study is the first to evaluate the impact of reduced RDI on survival across BMI categories. Our findings are in agreement with those of Barrett et al,[23] who found that obese women with ovarian cancer participating in the SCOTROC I trial who received dosing based on full weight did not experience worse survival than normal-weight women. Oncologists are often reticent to use full doses in obese women because of concern for toxicity and thus cap the dose. Our study showed that neither survival nor toxicity is worse in obese women given full drug doses of chemotherapy.

In our study, the impact of dose reduction on survival was more apparent for paclitaxel than for carboplatin, for which we did not find a clear dose-response relationship with mortality. Whereas this may be attributed to differences in metabolism and mechanism of action between the 2 drugs, it may also be driven by expected dose calculations. Carboplatin dosing requires selection of an AUC value, most commonly 5 or 6, which may reflect clinical judgment incorporating decisions to decrease dose in those who are obese or have more advanced disease or preexisting conditions. This would result in a lower calculated expected dose and higher RDI among those who tend to have worse survival. To evaluate this possibility, we compared these characteristics by AUC used. Whereas obesity did not appear to be a deciding factor, those with AUC of 5 were more likely to have received a diagnosis at stage IV or to have diabetes, renal disease, or hypertension, with differences in presence of diabetes statistically significant ($P = .02$). Nevertheless, survival analysis results for carboplatin remained essentially unchanged when analyses were limited to women with AUC of 6. Furthermore, the optimal weight for use in the Cockcroft-Gault formula to calculate expected dose for carboplatin remains uncertain. Studies have shown that in obese women, using ideal body weight underestimates creatinine clearance whereas actual body weight overestimates it.[28] Because we used actual weight rather than ideal bodyweight, expected carboplatin dose may have been overestimated in obese women, which would result in underestimation of RDI (ie, the ratio of observed to expected doses).

Our data show that overweight and obesity are nearly as common among patients with ovarian cancer as in the general population.[29] Previous studies were based mostly on data from clinical trials, which typically exclude women with obesity-related comorbidities, or observational studies in volunteers that include only patients who were healthy enough and interested in participating. In contrast, we included all cases diagnosed in an integrated health care system that provides a substantial proportion of care in a large geographical area and who received standard treatment with carboplatin-paclitaxel. Cancers were identified from the KPNC Cancer Registry, which follows data quality and reporting standards of the North American Association of Centralized Cancer Registries and the NCI Surveillance, Epidemiology, and End Results (SEER) Program, and contains information on all patients who receive a diagnosis or treatment at a KPNC facility. The distributions of stage at diagnosis[30,31(p33)] and 5-year relative survival rate by stage[31(p35)] are similar to SEER estimates, suggesting generalizability of our findings.

Conclusions

Dose reduction for paclitaxel and carboplatin was associated with poorer survival in women with ovarian cancer, and body size was the strongest predictor of dose reduction. This association with poorer survival was apparent regardless of body size, with the effect strongest among patients with normal weight. Our results suggest that BMI should not be a major factor influencing dose reduction decisions in women with ovarian cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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At a Glance

- The impact of body mass index (BMI) on chemotherapy dosing and dose reduction and ovarian cancer survival was assessed in 806 women in a cohort study.
- Body mass index was the strongest predictor of dose reduction, with obese women receiving less paclitaxel and carboplatin per kilogram of body weight, and lower relative dose intensity (RDI) for each agent and the combined regimen.
- Lower average RDI for the regimen was associated with worse overall and ovarian cancer–specific survival (HR, 1.62 [95% CI, 1.10–2.37] and HR, 1.69 [95% CI, 1.12–2.55], respectively).
- For each BMI category, those with average RDI less than 85% had worse survival than those without dose reduction.

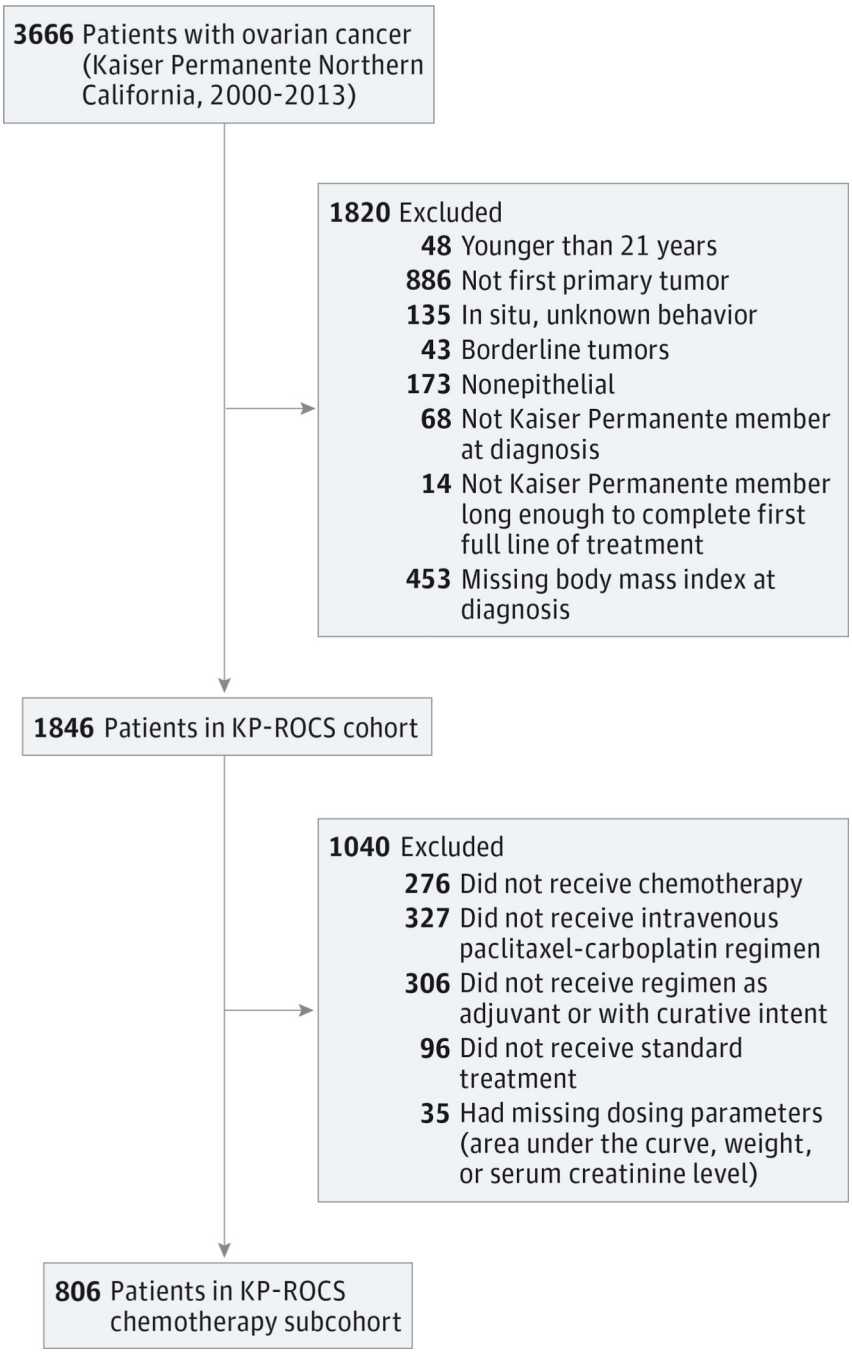
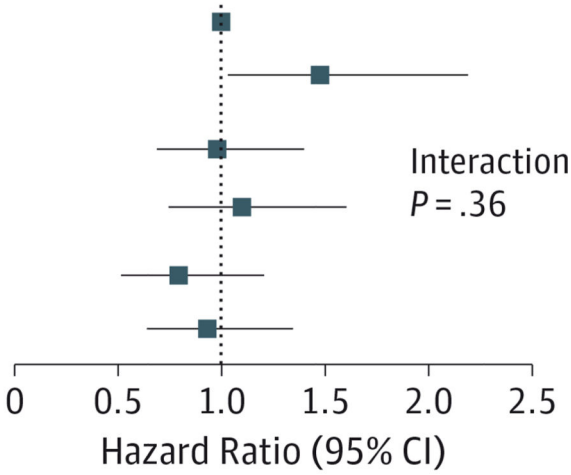


Figure 1.
Flowchart for Patient Selection in the Kaiser Permanente Research on Ovarian Cancer Study (KP-ROCS) Cohort and the Chemotherapy Subcohort

A Overall mortality

BMI at Diagnosis	ARDI	Hazard Ratio (95% CI)
Normal	≥0.85	1 [Reference]
	<0.85	1.50 (1.02-2.21)
Overweight	≥0.85	0.98 (0.69-1.39)
	<0.85	1.10 (0.75-1.61)
Obese	≥0.85	0.79 (0.51-1.21)
	<0.85	0.93 (0.65-1.33)



B Ovarian cancer-specific mortality

BMI at Diagnosis	ARDI	Hazard Ratio (95% CI)
Normal	≥0.85	1 [Reference]
	<0.85	1.62 (1.07-2.45)
Overweight	≥0.85	1.02 (0.70-1.50)
	<0.85	1.18 (0.79-1.78)
Obese	≥0.85	0.73 (0.45-1.17)
	<0.85	0.95 (0.64-1.40)

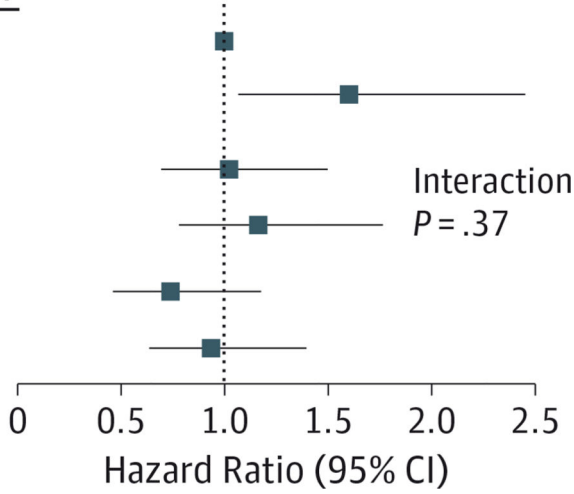


Figure 2. Hazard Ratios for Overall and Ovarian Cancer–Specific Survival According to Body Mass Index (BMI) Category and Average Relative Dose Intensity (ARDI)

Hazard ratios and 95% CIs are adjusted for age at diagnosis, race, BMI at diagnosis, stage, grade, histologic type, toxic effects during chemotherapy, granulocyte colony-stimulating factor use, diabetes mellitus, hypertension, cardiovascular disease, renal disease, and cancer antigen 125 (CA125) levels after treatment.

Table 1

Select Demographic and Clinical Characteristics, Kaiser Permanente Research on Ovarian Cancer Study Cohort and Chemotherapy Subcohort

Characteristic	No. (%)		*P* Value[a]
	Overall Cohort (n = 1846)	Chemotherapy Subcohort (n = 806)	
Age at diagnosis, y			
21–39	86 (4.7)	39 (4.8)	<.001
40–49	254 (13.8)	117 (14.5)	
50–69	983 (53.2)	503 (62.4)	
>70	523 (28.3)	147 (18.2)	
Race			
White	1474 (79.9)	651 (80.8)	.87
African American	106 (5.7)	42 (5.2)	
Asian	219 (11.9)	95 (11.8)	
Other	46 (2.5)	18 (2.2)	
Ethnicity			
Hispanic	168 (9.1)	82 (10.2)	.57
Not Hispanic	1655 (89.6)	714 (88.6)	
AJCC stage			
I	404 (21.9)	219 (27.2)	<.001
II	171 (9.3)	98 (12.2)	
III	769 (41.7)	342 (42.4)	
IV	476 (25.8)	140 (17.4)	
Unknown	26 (1.4)	7 (0.9)	
Grade, SEER definition			
Well differentiated	125 (6.8)	50 (6.2)	<.001
Moderately differentiated	237 (12.8)	133 (16.5)	
Poorly differentiated	663 (35.9)	318 (39.4)	
Undifferentiated	311 (16.8)	133 (16.5)	
Unknown	510 (27.6)	172 (21.3)	
Histologic type			
Serous	963 (52.2)	432 (53.6)	<.001
Mucinous	94 (5.1)	39 (4.8)	
Endometrioid	190 (10.3)	107 (13.3)	
Clear cell	133 (7.2)	76 (9.4)	
Other	466 (25.2)	152 (18.9)	
BMI at diagnosis			
Underweight, <18.50	48 (2.6)	20 (2.5)	.69
Normal, 18.50–24.99	685 (37.1)	297 (36.8)	

Characteristic	No. (%)		*P* Value[a]
	Overall Cohort (n = 1846)	Chemotherapy Subcohort (n = 806)	
Overweight, 25.00–29.99	566 (30.7)	248 (30.8)	
Obese 1, 30.00–34.99	289 (15.7)	134 (16.6)	
Obese 2, 35.00–39.99	150 (8.1)	70 (8.7)	
Obese 3, ≥40.00	108 (5.8)	37 (4.6)	

Abbreviations: American Joint Committee on Cancer; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SEER, Surveillance, Epidemiology, and End Results.

[a]Based on χ^2 goodness-of-fit test.

Table 2

Association of Selected Factors With Mortality After Ovarian Cancer Diagnosis

		Overall Ovarian Cancer Mortality			Ovarian Cancer–Specific Mortality		
Factor	**No.**	**Events**	**HR[a] (95% CI)**	**Type 3 *P* Value[b]**	**Events**	**HR[a] (95% CI)**	**Type 3 *P* Value[b]**
Age, continuous	806	334	1.03 (1.02–1.04)	…	291	1.03 (1.02–1.04)	…
Race							
White	651	272	1 [Reference]	.18	238	1 [Reference]	.29
Black	42	23	1.61 (1.03–2.52)		19	1.52 (0.93–2.49)	
Asian	95	32	0.91 (0.61–1.36)		27	0.90 (0.58–1.39)	
Other	18	7	1.28 (0.57–2.87)		7	1.41 (0.62–3.21)	
Stage							
I/II	317	50	1 [Reference]	<.001	39	1 [Reference]	<.001
III	342	177	4.12 (2.85–5.96)		158	4.48 (2.97–6.76)	
IV	140	103	7.45 (4.96–11.19)		90	7.80 (4.98–12.22)	
Grade							
Well differentiated	50	5	1 [Reference]	.20	4	1 [Reference]	.29
Moderately differentiated	133	39	1.91 (0.73–4.99)		34	2.10 (0.72–6.08)	
Poorly differentiated	318	153	2.41 (0.96–6.09)		134	2.61 (0.93–7.32)	
Undifferentiated	133	52	2.67 (1.02–6.98)		45	2.80 (0.96–8.16)	
Histologic type							
Serous	432	214	1 [Reference]	.05	191	1 [Reference]	.02
Mucinous	39	10	2.63 (1.30–5.31)		10	3.16 (1.54–6.47)	
Endometrioid	107	23	0.88 (0.56–1.39)		18	0.81 (0.48–1.34)	
Clear cell	76	21	1.38 (0.82–2.33)		16	1.25 (0.69–2.24)	
Other	152	66	1.11 (0.83–1.49)		56	1.03 (0.75–1.42)	
Toxic effects[c]	309	137	1.15 (0.90–1.45)	.27	119	1.08 (0.83–1.41)	.55
G-CSF use[c]	182	72	0.79 (0.59–1.05)	.11	64	0.81 (0.60–1.10)	.18
Diabetes mellitus[c]	142	62	0.98 (0.72–1.35)	.92	53	0.96 (0.69–1.36)	.84

Factor	No.	Overall Ovarian Cancer Mortality			Ovarian Cancer–Specific Mortality		
		Events	HR[a] (95% CI)	Type 3 *P* Value[b]	Events	HR[a] (95% CI)	Type 3 *P* Value[b]
Hypertension[c]	435	187	0.74 (0.57–0.96)	.02	160	0.73 (0.55–0.97)	.03
Cardiovascular disease[c]	392	168	0.77 (0.59–0.99)	.05	144	0.72 (0.55–0.95)	.02
Renal disease[c]	243	132	1.53 (1.19–1.96)	<.001	115	1.49 (1.14–1.95)	.003
CA125							
<35	678	239	1 [Reference]	<.001	21	1 [Reference]	<.001
35–70	37	25	2.18 (1.41–3.38)		21	2.06 (1.28–3.32)	
>70	69	53	2.94 (2.07–4.17)		51	3.16 (2.19–4.54)	
Unknown	22	17	6.44 (3.76–11.02)		13	5.54 (3.02–10.16)	
BMI							
Underweight	20	10	0.66 (0.33–1.32)	.20	10	0.78 (0.39–1.56)	.16
Normal	297	127	1 [Reference]		110	1 [Reference]	
Overweight	248	101	0.86 (0.65–1.13)		90	0.88 (0.65–1.18)	
Obese class 1	134	54	0.75 (0.53–1.06)		43	0.67 (0.46–0.99)	
Obese class 2	70	23	0.55 (0.34–0.91)		19	0.53 (0.31–0.91)	
Obese class 3	37	19	0.76 (0.42–1.36)		19	0.82 (0.45–1.49)	
Average RDI, %							
>100	79	35	0.84 (0.57–1.25)	.05	29	0.78 (0.51–1.20)	.03
100–85	386	142	1 [Reference]		122	1 [Reference]	
<85–70	253	113	1.16 (0.88–1.52)		101	1.21 (0.90–1.62)	
<70	88	44	1.62 (1.10–2.37)		39	1.69 (1.12–2.55)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CA125, cancer antigen 125; ellipses, not applicable; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; RDI, relative dose intensity.

[a] HR and CI mutually adjusted for all other factors in the Table.

[b] Based on type 3 Wald χ^2 tests.

[c] Reference category is not having these conditions (or nonuser for G-CSF).

Table 3

Total and Ovarian Cancer–Specific Mortality Associated With Chemotherapy Dose Reduction

		Overall Ovarian Cancer Mortality				Ovarian Cancer–Specific Mortality		
Dose Reduction	**No.**	**Events**	**Median Survival, mo**	**HR (95% CI)[a]**	***P* Value[c]**	**Events**	**HR (95% CI)[a]**	***P* Value**
Paclitaxel RDI, %								
Dichotomized variable								
≥85	584	227	44	1 [Reference]	.02	195	1 [Reference]	.007
<85	222	107	39[b]	1.35 (1.05–1.73)		96	1.44 (1.11–1.88)	
Four-level variable								
>100	141	52	41	0.95 (0.68–1.32)	.005	41	0.82 (0.57–1.17)	.003
100–85	443	175	47	1 [Reference]		154	1 [Reference]	
<85–70	163	74	43	1.21 (0.90–1.62)		69	1.32 (0.98–1.78)	
<70	59	33	28[b]	1.78 (1.18–2.69)		27	1.62 (1.03–2.56)	
Carboplatin RDI, %								
Dichotomized variable								
≥85	339	135	47	1 [Reference]	.05	114	1 [Reference]	.03
<85	467	199	40	1.28 (1.00–1.64)		177	1.35 (1.03–1.76)	
Four-level variable								
>100	89	41	54	1.05 (0.71–1.56)	.29	34	0.98 (0.64–1.51)	.17
100–85	250	94	46	1 [Reference]		80	1 [Reference]	
<85–70	262	116	40	1.38 (1.03–1.85)		103	1.42 (1.04–1.94)	
<70	205	83	41	1.16 (0.82–1.64)		74	1.19 (0.82–1.73)	
Average RDI, %								
Dichotomized variable								
≥85	465	177	46	1 [Reference]	.04	151	1 [Reference]	.02
<85	341	157	39[b]	1.29 (1.01–1.64)		140	1.36 (1.05–1.77)	
Four-level variable								
>100	79	35	54	0.84 (0.57–1.25)	.006	29	0.78 (0.51–1.20)	.003

		Overall Ovarian Cancer Mortality				Ovarian Cancer–Specific Mortality		
Dose Reduction	**No.**	**Events**	**Median Survival, mo**	**HR (95% CI)[a]**	***P* Value[c]**	**Events**	**HR (95% CI)[a]**	***P* Value**
100–85	386	142	44	1 [Reference]		122	1 [Reference]	
<85–70	253	113	42	1.16 (0.88–1.52)		101	1.21 (0.90–1.62)	
<70	88	44	28[b]	1.62 (1.10–2.37)		39	1.69 (1.12–2.55)	

Abbreviations: HR, hazard ratio; RDI, relative dose intensity.

[a] Adjusted for age at diagnosis, race, body mass index at diagnosis, stage, grade, histologic type, toxic effects during chemotherapy, granulocyte colony-stimulating factor use, diabetes mellitus, hypertension, cardiovascular disease, renal disease, and cancer antigen 125 levels after treatment.

[b] *P* value <.05 (log-rank test).

[c] For each agent's RDI and average RDI, *P* value for dichotomized variables corresponds to type 3 *P* value. For the 4-level variables, *P* value for trend is presented. Type 3 *P* value tests are an overall test of whether there are significance differences in mortality across levels of exposure. *P* for trend tests whether there is a significant dose-response relationship.