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ORIGINAL PAPER

# Comparative effectiveness of platinum-based chemotherapy versus taxane and other regimens for ovarian cancer

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**Abstract** The aim was to compare the two most commonly recommended chemotherapy regimens (platinum-based chemotherapy and platinum–taxane combination) with non-platinum-based chemotherapy and those with no chemotherapy in a large nationwide and population-based cohort of patients with ovarian cancer with up to 17 years of follow-up. We studied 12,181 patients diagnosed with stages I–IV ovarian cancer at age ≥65 in 1991–2005 from the 16 areas of the United States. We also performed matched cohort analyses based on conditional probability of receiving platinum chemotherapy in 3,428 patients. In patients with early stage ovarian cancer, those who received platinum–taxane combination had the highest 5-year all-cause (62.5 %) and cancer-specific (65.1 %) survival rates, as compared to 51.5 and 63.7 % in those without chemotherapy. After adjusting for potential confounders, hazard ratios of all-cause mortality (0.66, 95 % CI 0.55–0.79) and cancer-specific mortality (0.74, 0.61–0.90) were significantly lower in patients receiving platinum–taxane combination as compared to those without chemotherapy. Among patients with late-stage ovarian cancer, risks of mortality were significantly reduced in patients who received both platinum and taxane (0.38, 0.36–0.41 for all-cause mortality; 0.40, 0.37–0.42 for cancer-specific mortality). Dose–response relationship appeared strong within each of the three chemotherapy regimens. These results and trends were almost identical in the matched cohort. Platinum–taxane combination chemotherapy and platinum-based chemotherapy without taxane were effective in prolonging survival with a significant dose–response relationship among patients with late-stage ovarian cancer. Among those with early stage tumors, platinum–taxane combination appeared more effective than other chemotherapy regimens.

**Keywords** Ovarian cancer · Chemotherapy · Survival · Mortality · Comparative effectiveness

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## Introduction

Unlike other malignancies in the female reproductive organs or perhaps in all human cancers except for lung cancer [1–3], ovarian cancer is often diagnosed at late stage due to lack of effective screening tools and lack of clear symptoms that can trigger women to seek medical attention. However, survival rates have improved over the past decade because of effective surgical resection or tumor debulking followed by various efficacious chemotherapy regimens [3–14]. Kyrgiou et al. [9] reviewed 198 clinical trials which examined the benefits of chemotherapy for ovarian cancer over the past 40 years (1971–2006).

They concluded that platinum- and taxane-based combination chemotherapy with intraperitoneal administration can reduce the risk of ovarian cancer–related death by 55 %, of which >30 % of the benefit may also be achieved with a standard platinum-based combination. Reviews that summarized more recent clinical trials showed similar findings [10, 12, 13]. Based on strong evidence of chemotherapy efficacy from clinical trials, the National Institutes of Health's consensus conference recommended all women with stage IC–IV ovarian cancer receive adjuvant chemotherapy following surgery [1, 15].

Over the past 10 years, a number of studies have documented that many chemotherapy agents for ovarian cancer are cost effective in the trial settings [16–21]. Some population-based studies described the patterns of chemotherapy utilization in women with ovarian cancer [22–41]. One study particularly reported the effectiveness of platinum-based chemotherapy among patients with stage III–IV ovarian cancer diagnosed in 1992–1996 [32]. Our current nationwide population-based cohort study of early and late-stage ovarian cancer aimed to compare the effectiveness of two most commonly recommended chemotherapy regimens (platinum-based chemotherapy and platinum–taxane combination) with non-platinum-based chemotherapy and those with no chemotherapy from 1991 through 2005 with up to 17 years of follow-up.

## Patients and methods

### Data sources

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) cancer registries, and Medicare linked databases were used for this analysis. SEER program, supported by the National Cancer Institute, includes population-based tumor registries in selected geographic areas: San Francisco/Oakland, Detroit, Seattle, Atlanta, Rural Georgia, Los Angeles county, the San Jose-Monterey area, and the rest of California; and the states of Connecticut, Iowa, New Mexico, Utah, Hawaii, Kentucky, Louisianan, and New Jersey [42]. Medicare program is administered by the Center for Medicare and Medicaid Services and covers hospital, physician, and other medical services for >97 % of persons aged ≥65 years. The Committee for the Protection of Human Subjects at the University of Texas Health Science Center approved this study.

### Study population

The study consisted of 20,060 women diagnosed with AJCC (American Joint Committee on Cancer) stages I–IV ovarian cancer or unstaged at age ≥65 in 1991–2005 from the 16 SEER areas. We excluded 550 patients that were identified from the reporting sources of autopsy or death certificates only, 5,240 patients who did not have full coverage of both Medicare Parts A and B, or who were members of Health Maintenance Organizations to ensure the completeness of Medicare claims, and 2,084 subjects who died within 30 days of diagnosis, leaving 12,181 patients in the final analysis.

### Matched cohort

In order to minimize selection bias due to factors that may have influenced physicians or patients to choose chemotherapy, we first calculated the propensity (or conditional probability) of receiving platinum-based chemotherapy for all patients and then matched patients who actually received platinum-based chemotherapy with those who had the same or similar propensity but did not receive platinum-based chemotherapy (including those with no chemotherapy). The propensity of receiving chemotherapy was estimated with logistic regression model based on the following characteristics: age, ethnicity, marital status, tumor stage, grade, size, number of positive lymph nodes, comorbidity, surgery, radiation therapy, socioeconomic status, and year of diagnosis. The matching through the 5–1 digit propensity of receiving chemotherapy was performed using the validated matching algorithm [43]. A total of 3,428 patients receiving platinum-based chemotherapy were matched with 3,428 patients who did not receive platinum-based chemotherapy or receive no chemotherapy.

### Study variables

#### *Treatment variables*

Cancer-directed surgery was defined as receiving subtotal or partial, unilateral or bilateral (salpingo)-oophorectomy with or without hysterectomy, or omentectomy, or pelvic exenteration (partial or total), as defined in SEER data (surgery codes 10–70) [42, 44] or in Medicare claims if there were procedure codes for cancer-directed surgeries within 6 months of diagnosis [45–47]. The methods of identifying chemotherapy use through the Medicare claims were discussed elsewhere [44–47], and the validity of Medicare claims for chemotherapy has been reasonably well confirmed [48–50]. In brief, patients were defined as having received chemotherapy if there was a claim for chemotherapy from any of the following Medicare codes that were made within 6 months of diagnosis: the ICD-9-CM procedure code of 9925 and V codes of V58.1, V66.2, or V67.2, the Common Procedure Terminology codes of 96400-96549, J8510, J8520, J8521, J8530-J8999, J9000-J9999, and

Q0083-Q0085, and revenue center codes of 0331, 0332, and 0335. Specific chemotherapy agents were defined using J codes: carboplatin (J9045), cisplatin (J9060 or J9062), oxaliplatin (J9263), and Taxanes (J9170 for docetaxel and J9265 for paclitaxel). Patients were then divided into 4 categories in hierarchical order: no chemotherapy ($n = 3,892$); other chemotherapy agents without platinum ($n = 1,767$); platinum-based chemotherapy alone without taxane, including carboplatin or cisplatin ($n = 1,523$); and both platinum and taxane ($n = 4,999$). Patients were considered to be on "platinum and taxane" only if both claims for platinum and taxane were found within a period of 141 days (6 cycles, each of 3 weeks plus allowing 15 days grace period). Of all patients, 54 received bevacizumab (J9035, C9214, or S0116) which was not included in the analysis.

*Survival variables*

Survival time in months was calculated from the date of diagnosis to the date of death or the date of last follow-up (December 31, 2006). All-cause mortality was defined as death from any cause that was the underlying cause of death indicated in the SEER registry data. Patients still alive at the last date of follow-up were censored. Cancer-specific mortality was defined as any cancer as the underlying cause of death, including those with unknown or missing causes of death. The effect of this assumption was examined in a sensitivity analysis by excluding patients with unknown cause of death. In this specific analysis, patients who died of causes other than ovarian cancer or unknown or who were still alive at the date of last follow-up were censored.

*Socioeconomic status*

Socioeconomic status (SES) was based on the percent of persons living below poverty at the census tract level from the 1990 census for cases in 1991–1999 and from the 2000 census for cases in 2000–2005. For 47 cases in 1991–1999 with missing data for the 1990 census, the values from the 2000 census were assigned. SES was then recorded into quartiles.

*Comorbidity score*

Comorbidity was ascertained from Medicare claims data through diagnoses or procedures that were made between 1 year prior to and 1 month after the diagnosis of ovarian cancer, using comorbidity index created by Charlson et al. [51] and later modified and validated using the ICD-9-CM diagnosis and procedure codes [52–54].

*Other characteristics*

Other characteristics include age at diagnosis, ethnicity, marital status, tumor stage, grade, size, histological type, year of diagnosis, and geographic area. The side-effects were identified within 3, 3–6, and 6–12 months of diagnosis from claims data using the diagnosis codes that were reported previously [55]. These toxicities were divided into the grades 1–2 if they were identified from the outpatient claims or grade 3–4 if they were identified from the inpatient hospitalization claims, based on the methods from a previous study [16].

Analysis

The differences in the distribution of baseline characteristics among the four groups according to chemotherapy status were tested using the Chi square statistic. These Chi square statistics were also used to compare differences in the distribution of baseline characteristics between platinum-based and non-platinum groups for both the entire and matched cohorts. Cox proportional hazard regression model was used for analysis of survival. The proportionality assumption was considered to be satisfied when the log–log Kaplan–Meier curves for survival functions by the chemotherapy groups were parallel. Median survival rates were also derived from the Kaplan–Meier survival analyses. The 5-year observed all-cause survival rate was calculated as the proportion of those patients with 5-year follow-up who survived past the 5th year, whereas the 5-year cancer-specific survival rate was the proportion of those patients with 5-year follow-up who did not die of ovarian cancer within 5 years.

## Results

Table 1 presents the distribution of patient, tumor and treatment characteristics among four different groups of patients with ovarian cancer according to chemotherapy status. The proportion of patients receiving chemotherapy decreased with age and was similar by ethnicity. Patients with advanced tumor stage, poorer tumor grades, serous histologic tumors, lower comorbidity scores, married, and higher SES were more likely to receive chemotherapy. About 50 % of those without chemotherapy did not receive cancer-directed surgery, while >70 % of those receiving chemotherapy received surgery. The proportion of patients receiving platinum–taxane combination chemotherapy increased from 1991 to 2005, while those receiving other chemotherapy agents slightly decreased during these time periods, but the proportion of not receiving chemotherapy

**Table 1** Distribution of characteristics by chemotherapy status in patients with ovarian cancer

| Column *N* (%) | | | | |
|---|---|---|---|---|
| Characteristics<br>Total $N = 12,181$ | No chemotherapy<br>$N = 3,892$ | Other non-platinum chemotherapy<br>$N = 1,767$ | Platinum-based chemotherapy<br>$N = 1,523$ | Platinum and taxane<br>$N = 4,999$ |
| Median age (range) | 80 (65–102) | 74 (65–99) | 73 (65–94) | 73 (65–94) |
| Age (years) | | | | |
| 65–69 | 475 (12.2) | 471 (26.7) | 437 (28.7) | 1,385 (27.7) |
| 70–74 | 595 (15.3) | 504 (28.5) | 403 (26.5) | 1,451 (29.0) |
| 75–79 | 784 (20.1) | 429 (24.3) | 359 (23.6) | 1,256 (25.1) |
| 80–84 | 914 (23.5) | 226 (12.8) | 213 (14.0) | 703 (14.1) |
| 85+ | 1,124 (28.9) | 137 (7.7) | 111 (7.3) | 204 (4.1) |
| Race/ethnicity | | | | |
| Caucasians | 3,269 (84.0) | 1,497 (84.7) | 1,382 (90.7) | 4,507 (90.2) |
| African Americans | 309 (7.9) | 141 (8.0) | 57 (3.7) | 220 (4.4) |
| Others | 314 (8.1) | 129 (7.3) | 84 (5.5) | 272 (5.4) |
| Marital status | | | | |
| Married | 1,036 (26.6) | 751 (42.5) | 666 (43.7) | 2,434 (48.7) |
| Unmarried | 2,716 (69.8) | 971 (54.9) | 816 (53.6) | 2,402 (48.0) |
| Unknown | 140 (3.6) | 45 (2.5) | 41 (2.7) | 163 (3.3) |
| Tumor AJCC stage | | | | |
| I-AB | 584 (15.0) | 49 (2.8) | 53 (3.5) | 189 (3.8) |
| I-C | 207 (5.3) | 73 (4.1) | 68 (4.5) | 246 (4.9) |
| II | 250 (6.4) | 94 (5.3) | 122 (8.0) | 387 (7.7) |
| III | 830 (21.3) | 667 (37.7) | 562 (36.9) | 2,407 (48.1) |
| IV | 1,240 (31.9) | 747 (42.3) | 603 (39.6) | 1,509 (30.2) |
| Unstaged | 781 (20.1) | 137 (7.7) | 115 (7.5) | 261 (5.2) |
| Tumor grade | | | | |
| Well differentiated | 228 (5.9) | 55 (3.1) | 38 (2.5) | 155 (3.1) |
| Moderately differentiated | 413 (10.6) | 225 (12.7) | 241 (15.8) | 669 (13.4) |
| Poorly differentiated | 865 (22.2) | 659 (37.3) | 632 (41.5) | 2,131 (42.6) |
| Undifferentiated | 177 (4.5) | 159 (9.0) | 144 (9.5) | 526 (10.5) |
| Unknown/missing | 2,209 (56.8) | 669 (37.9) | 468 (30.7) | 1,518 (30.4) |
| Histology subtype | | | | |
| Serous | 864 (22.2) | 648 (36.7) | 655 (43.0) | 2,549 (51.0) |
| Mucinous | 301 (7.7) | 108 (6.1) | 74 (4.9) | 192 (3.8) |
| Endometrioid | 366 (9.4) | 226 (12.8) | 161 (10.6) | 504 (10.1) |
| Clear cell | 72 (1.8) | 41 (2.3) | 39 (2.6) | 121 (2.4) |
| Other epithelial | 1,776 (45.6) | 694 (39.3) | 550 (36.1) | 1,555 (31.1) |
| Other | 513 (13.2) | 50 (2.8) | 44 (2.9) | 78 (1.6) |
| Comorbidity scores | | | | |
| 0 | 2,006 (51.5) | 1,144 (64.7) | 1,057 (69.4) | 3,310 (66.2) |
| 1 | 1,022 (26.3) | 378 (21.4) | 321 (21.1) | 1,104 (22.1) |
| 2 | 478 (12.3) | 138 (7.8) | 105 (6.9) | 358 (7.2) |
| ≥3 | 386 (9.9) | 107 (6.1) | 40 (2.6) | 227 (4.5) |
| Cancer-directed surgery | | | | |
| No | 1,945 (50.0) | 506 (28.6) | 312 (20.5) | 962 (19.2) |
| Yes | 1,947 (50.0) | 1,261 (71.4) | 1,211 (79.5) | 4,037 (80.8) |
| SES (poverty) | | | | |
| 1st (low SES) | 1,150 (29.5) | 468 (26.5) | 320 (21.0) | 1,106 (22.1) |
| 2nd | 1,006 (25.8) | 440 (24.9) | 375 (24.6) | 1,230 (24.6) |

**Table 1** continued

| Column *N* (%) | | | | |
|---|---|---|---|---|
| Characteristics<br>Total $N = 12,181$ | No chemotherapy<br>$N = 3,892$ | Other non-platinum chemotherapy<br>$N = 1,767$ | Platinum-based chemotherapy<br>$N = 1,523$ | Platinum and taxane<br>$N = 4,999$ |
| 3rd | 912 (23.4) | 411 (23.3) | 415 (27.2) | 1,295 (25.9) |
| 4th (high SES) | 824 (21.2) | 448 (25.3) | 413 (27.1) | 1,368 (27.4) |
| Year of diagnosis | | | | |
| 1991 | 226 (5.8) | 277 (15.7) | 182 (11.9) | 0 (0.0) |
| 1992 | 230 (5.9) | 148 (8.4) | 251 (16.5) | 0 (0.0) |
| 1993 | 237 (6.1) | 175 (9.9) | 265 (17.4) | 13 (0.3) |
| 1994 | 216 (5.5) | 135 (7.6) | 206 (13.5) | 62 (1.2) |
| 1995 | 198 (5.1) | 169 (9.6) | 101 (6.6) | 135 (2.7) |
| 1996 | 199 (5.1) | 150 (8.5) | 64 (4.2) | 187 (3.7) |
| 1997 | 168 (4.3) | 103 (5.8) | 51 (3.3) | 231 (4.6) |
| 1998 | 166 (4.3) | 115 (6.5) | 34 (2.2) | 241 (4.8) |
| 1999 | 199 (5.1) | 60 (3.4) | 30 (2.0) | 276 (5.5) |
| 2000 | 343 (8.8) | 82 (4.6) | 58 (3.8) | 613 (12.3) |
| 2001 | 356 (9.1) | 79 (4.5) | 52 (3.4) | 606 (12.1) |
| 2002 | 331 (8.5) | 77 (4.4) | 47 (3.1) | 696 (13.9) |
| 2003 | 335 (8.6) | 81 (4.6) | 67 (4.4) | 650 (13.0) |
| 2004 | 357 (9.2) | 55 (3.1) | 65 (4.3) | 640 (12.8) |
| 2005 | 331 (8.5) | 61 (3.4) | 50 (3.3) | 649 (13.0) |
| SEER areas | | | | |
| California | 1,197 (30.8) | 476 (26.9) | 468 (30.7) | 1,498 (30.0) |
| Connecticut | 301 (7.7) | 173 (9.8) | 252 (16.5) | 411 (8.2) |
| Georgia | 183 (4.7) | 72 (4.1) | 86 (5.6) | 269 (5.4) |
| Hawaii | 47 (1.2) | 20 (1.1) | 24 (1.6) | 55 (1.1) |
| Iowa | 423 (10.9) | 217 (12.3) | 192 (12.6) | 413 (8.3) |
| Kentucky | 172 (4.4) | 28 (1.6) | 18 (1.2) | 311 (6.2) |
| Louisiana | 139 (3.6) | 29 (1.6) | 25 (1.6) | 265 (5.3) |
| Michigan | 487 (12.5) | 349 (19.7) | 153 (10.0) | 393 (7.9) |
| New Jersey | 324 (8.3) | 87 (4.9) | 33 (2.2) | 685 (13.7) |
| New Mexico | 135 (3.5) | 63 (3.6) | 36 (2.4) | 136 (2.7) |
| Utah | 168 (4.3) | 54 (3.1) | 78 (5.1) | 169 (3.4) |
| Washington (Seattle-Puget sound) | 316 (8.1) | 199 (11.3) | 158 (10.4) | 394 (7.9) |

was relatively stable. There were also some geographic variations in receiving various chemotherapy regimens.

Table 2 presents the distribution of baseline characteristics between platinum-based chemotherapy and non-platinum groups for the entire cohort and matched cohort. Over 50 % of the entire cohort populations were in the matched cohort for both platinum and non-platinum groups. While the baseline characteristics were significantly different between the platinum-based chemotherapy and non-platinum groups of the entire cohort, these characteristics were no longer significantly different between the two groups in the matched cohort.

Table 3 presents the 5-year survival rates and hazard ratio of mortality by four chemotherapy groups in patients with early stage tumor (stages I–II). Patients receiving platinum–taxane combination had the highest 5-year all-cause (62.5 %) and cancer-specific (65.1 %) survival rates in the entire cohort, while the matched cohort had remarkably similar results. After adjusting for potential confounders, the hazard ratios of all-cause mortality and cancer-specific mortality were significantly lower in those patients of the entire cohort receiving platinum–taxane combination (0.66, 95 % CI 0.55–0.79 for all-cause mortality; 0.74, 0.61–0.90 for cancer-specific mortality) as

**Table 2** Comparisons of characteristics among women with ovarian cancer according to the receipt of platinum-based chemotherapy in both entire cohort and propensity-matched cohort

| Characteristics | Column *N* (%) of the entire cohort | | | Column *N* (%) of the matched cohort | | |
|---|---|---|---|---|---|---|
| | Non-platinum and no chemo $N = 5{,}659$ | Platinum $N = 6{,}522$ | *P* value | Non-platinum and no chemo $N = 3{,}428$ | Platinum $N = 3{,}428$ | *P* value |
| Median age (range) | 78 (65–102) | 73 (65–94) | | 75 (65–99) | 75 (65–94) | |
| Age (years) | | | <0.0001 | | | 0.8407 |
| 65–69 | 946 (16.7) | 1,822 (27.9) | | 749 (21.8) | 756 (22.0) | |
| 70–74 | 1,099 (19.4) | 1,854 (28.4) | | 839 (24.5) | 834 (24.3) | |
| 75–79 | 1,213 (21.4) | 1,615 (24.8) | | 856 (25.0) | 865 (25.2) | |
| 80–84 | 1,140 (20.1) | 916 (14.0) | | 648 (18.9) | 664 (19.4) | |
| 85+ | 1,261 (22.3) | 315 (4.8) | | 336 (9.8) | 309 (9.0) | |
| Race/ethnicity | | | <0.0001 | | | 0.8049 |
| Caucasians | 4,766 (84.2) | 5,889 (90.3) | | 2,996 (87.4) | 2,990 (87.2) | |
| African Americans | 450 (7.9) | 277 (4.2) | | 200 (5.8) | 212 (6.2) | |
| Others | 443 (7.8) | 356 (5.5) | | 232 (6.8) | 226 (6.6) | |
| Marital status | | | <0.0001 | | | 0.9807 |
| Married | 1,787 (31.6) | 3,100 (47.5) | | 1,351 (39.4) | 1,344 (39.2) | |
| Unmarried | 3,687 (65.1) | 3,218 (49.3) | | 1,969 (57.4) | 1,977 (57.7) | |
| Unknown | 185 (3.3) | 204 (3.1) | | 108 (3.1) | 107 (3.1) | |
| Tumor AJCC stage | | | <0.0001 | | | 0.9915 |
| I-AB | 633 (11.2) | 242 (3.7) | | 227 (6.6) | 227 (6.6) | |
| I-C | 280 (4.9) | 314 (4.8) | | 181 (5.3) | 172 (5.0) | |
| II | 344 (6.1) | 509 (7.8) | | 251 (7.3) | 247 (7.2) | |
| III | 1,497 (26.4) | 2,969 (45.5) | | 1,186 (34.6) | 1,209 (35.3) | |
| IV | 1,987 (35.1) | 2,112 (32.4) | | 1,291 (37.7) | 1,284 (37.4) | |
| Unstaged | 918 (16.2) | 376 (5.7) | | 292 (8.5) | 289 (8.4) | |
| Tumor grade | | | <0.0001 | | | 0.9555 |
| Well differentiated | 283 (5.0) | 193 (3.0) | | 136 (4.0) | 140 (4.1) | |
| Moderately differentiated | 638 (11.3) | 910 (13.9) | | 439 (12.8) | 427 (12.5) | |
| Poorly differentiated | 1,524 (26.9) | 2,763 (42.4) | | 1,178 (34.4) | 1,202 (35.1) | |
| Undifferentiated | 336 (5.9) | 670 (10.3) | | 273 (8.0) | 263 (7.7) | |
| Unknown/missing | 2,878 (50.9) | 1,986 (30.4) | | 1,402 (40.9) | 1,396 (40.7) | |
| Histology subtype | | | <0.0001 | | | 0.9494 |
| Serous | 1,512 (26.7) | 3,204 (49.1) | | 1,239 (36.1) | 1,267 (37.0) | |
| Mucinous | 409 (7.2) | 266 (4.1) | | 211 (6.2) | 203 (5.9) | |
| Endometrioid | 592 (10.5) | 665 (10.2) | | 391 (11.4) | 383 (11.2) | |
| Clear cell | 113 (2.0) | 160 (2.4) | | 86 (2.5) | 81 (2.4) | |
| Other epithelial | 2,470 (43.6) | 2,105 (32.3) | | 1,393 (40.6) | 1,377 (40.2) | |
| Other | 563 (9.9) | 122 (1.9) | | 108 (3.1) | 117 (3.4) | |
| Comorbidity scores | | | <0.0001 | | | 0.9022 |
| 0 | 3,150 (55.7) | 4,367 (67.0) | | 2,092 (61.0) | 2,102 (61.3) | |
| 1 | 1,400 (24.7) | 1,425 (21.8) | | 816 (23.8) | 792 (23.1) | |
| 2 | 616 (10.9) | 463 (7.1) | | 309 (9.0) | 316 (9.2) | |
| ≥3 | 493 (8.7) | 267 (4.1) | | 211 (6.2) | 218 (6.4) | |
| Cancer-directed surgery | | | <0.0001 | | | 0.677 |
| No | 2,451 (43.3) | 1,274 (19.5) | | 1,066 (31.1) | 1,082 (31.6) | |
| Yes | 3,208 (56.7) | 5,248 (80.5) | | 2,362 (68.9) | 2,346 (68.4) | |
| SES (poverty) | | | <0.0001 | | | 0.952 |
| 1st (low SES) | 1,618 (28.6) | 1,426 (21.9) | | 869 (25.3) | 855 (24.9) | |

**Table 2** continued

| Characteristics | Column *N* (%) of the entire cohort | | | Column *N* (%) of the matched cohort | | |
|---|---|---|---|---|---|---|
| | Non-platinum and no chemo $N = 5{,}659$ | Platinum $N = 6{,}522$ | *P* value | Non-platinum and no chemo $N = 3{,}428$ | Platinum $N = 3{,}428$ | *P* value |
| 2nd | 1,446 (25.5) | 1,605 (24.6) | | 858 (25.0) | 869 (25.3) | |
| 3rd | 1,323 (23.4) | 1,710 (26.2) | | 850 (24.8) | 863 (25.2) | |
| 4th (high SES) | 1,272 (22.5) | 1,781 (27.3) | | 851 (24.8) | 841 (24.5) | |
| Year of diagnosis | | | <0.0001 | | | 0.9991 |
| 1991 | 503 (8.9) | 182 (2.8) | | 189 (5.5) | 182 (5.3) | |
| 1992 | 378 (6.7) | 251 (3.8) | | 202 (5.9) | 211 (6.2) | |
| 1993 | 412 (7.3) | 278 (4.3) | | 231 (6.7) | 237 (6.9) | |
| 1994 | 351 (6.2) | 268 (4.1) | | 192 (5.6) | 203 (5.9) | |
| 1995 | 367 (6.5) | 236 (3.6) | | 189 (5.5) | 193 (5.6) | |
| 1996 | 349 (6.2) | 251 (3.8) | | 210 (6.1) | 193 (5.6) | |
| 1997 | 271 (4.8) | 282 (4.3) | | 173 (5.0) | 170 (5.0) | |
| 1998 | 281 (5.0) | 275 (4.2) | | 175 (5.1) | 177 (5.2) | |
| 1999 | 259 (4.6) | 306 (4.7) | | 169 (4.9) | 167 (4.9) | |
| 2000 | 425 (7.5) | 671 (10.3) | | 287 (8.4) | 297 (8.7) | |
| 2001 | 435 (7.7) | 658 (10.1) | | 294 (8.6) | 300 (8.7) | |
| 2002 | 408 (7.2) | 743 (11.4) | | 290 (8.5) | 294 (8.6) | |
| 2003 | 416 (7.3) | 717 (11.0) | | 292 (8.5) | 277 (8.1) | |
| 2004 | 412 (7.3) | 705 (10.8) | | 279 (8.1) | 289 (8.4) | |
| 2005 | 392 (6.9) | 699 (10.7) | | 256 (7.5) | 238 (6.9) | |

compared to those without chemotherapy, while the risks of mortality were not significantly different in patients with platinum alone or other chemotherapy. In the matched cohort, patients receiving platinum-based chemotherapy were significantly less likely to die of all-causes or cancer-specific cause as well. Table 3 also presents the number of chemotherapy claims (as a proxy measure of chemotherapy cycles) in association with the risk of mortality and survival rates. There appeared to be an inverse dose–response relationship between the number of chemotherapy cycles and the risk of mortality, but confidence intervals were wide due to small numbers in each category.

Table 4 presents information similar to that described in Table 3 for patients with advanced tumor stages (stages III–IV). Although the observed 5-year survival rates were lower in patient with late-stage tumors than those with early stage tumors, the effectiveness of various chemotherapy regimens in prolonging survival was even more dramatic. Survival rates were higher in patients receiving both platinum and taxane, followed by those receiving platinum-based chemotherapy without taxane and those receiving other chemotherapy agents as compared to patients without chemotherapy. The adjusted hazard ratios of mortality were significantly reduced in patients receiving chemotherapy with the highest mortality reduction in patients who received both platinum and taxane (0.38, 0.36–0.41 for all-cause mortality and 0.40, 0.37–0.42 for cancer-specific mortality). In addition, the dose–response relationship appeared strong within each of three chemotherapy regimens. These results and trends were almost identical in the matched cohort. The dose–response relationship was observed in patients aged <70 as well as in those aged ≥70 (data not shown).

Table 5 presents the median survival time in months by various chemotherapy regimens, stratified by tumor stage. There was a clear pattern for chemotherapy in association with median survival times among patients with late-stage tumors, that is, patients receiving platinum–taxane combination had the longest median survival, which was followed by those receiving platinum-based chemotherapy without taxane, those with other chemotherapy, and patients without chemotherapy. Among patients with early stage tumors, median survival times were also higher in those receiving the platinum–taxane combination, and those receiving platinum-based chemotherapy without taxane and those with other chemotherapy, respectively. However, in those with early stage tumors, median overall survival times in patients without chemotherapy were higher than those receiving other chemotherapy but lower than those with platinum-based chemotherapy. For median cancer-specific survival times, patients without chemotherapy had even longer median overall survival times than

**Table 3** Effects of various chemotherapy regimens on 5-year all-cause and cancer-specific mortality in early stage (stage IAB, IC, II)

| | Number of patients (%) | Observed survival rate (%) | | Hazard ratio (95 % CI)[b] of mortality | |
|---|---|---|---|---|---|
| | | 5 year all-cause | 5 year cancer-specific[a] | 5 year all-cause | 5 year cancer-specific |
| *Chemotherapy categories* | | | | | |
| For entire cohort | 2,322 (100) | 55.3 | 63.0 | | |
| No chemotherapy | 1,041 (44.8) | 51.5 | 63.7 | 1.000 | 1.000 |
| Other non-platinum chemotherapy | 216 (9.3) | 48.5 | 54.0 | 1.120 (0.893–1.404) | 1.274 (0.991–1.638) |
| Platinum-based chemotherapy | 243 (10.5) | 54.5 | 61.2 | 0.863 (0.685–1.088) | 0.968 (0.747–1.254) |
| Platinum and taxanes | 822 (35.4) | 62.5 | 65.1 | 0.659 (0.551–0.789) | 0.738 (0.605–0.900) |
| For matched cohort | 1,305 (100) | 54.9 | 61.2 | | |
| No chemotherapy | 512 (39.2) | 51.6 | 59.8 | 1.000 | 1.000 |
| Other non-platinum chemotherapy | 147 (11.3) | 48.5 | 53.4 | 0.932 (0.689–1.261) | 1.012 (0.728–1.408) |
| Platinum-based chemotherapy | 195 (14.9) | 53.3 | 61.6 | 0.692 (0.519–0.923) | 0.677 (0.490–0.936) |
| Platinum and taxanes | 451 (34.6) | 62.0 | 65.6 | 0.492 (0.391–0.619) | 0.522 (0.407–0.669) |
| Dose response | | | | | |
| *Chemotherapy categories with number of claims* | | | | | |
| For entire cohort | 2,322 (100) | 55.3 | 63.0 | | |
| No chemotherapy | 1,041 (44.8) | 51.5 | 63.7 | 1.000 | 1.000 |
| Other non-platinum chemotherapy 1–5 | 91 (3.9) | 48.5 | 54.0 | 1.646 (1.222–2.217) | 1.747 (1.248–2.445) |
| Other non-platinum chemotherapy 6–8 | 37 (1.6) | | | 0.790 (0.448–1.395) | 0.905 (0.485–1.690) |
| Other non-platinum chemotherapy 8+ | 88 (3.8) | | | 0.852 (0.609–1.191) | 1.049 (0.735–1.497) |
| Platinum-based chemotherapy 1–5 | 126 (5.4) | 54.5 | 61.2 | 0.956 (0.716–1.276) | 1.061 (0.767–1.467) |
| Platinum-based chemotherapy 6–8 | 83 (3.6) | | | 0.796 (0.550–1.154) | 0.894 (0.594–1.345) |
| Platinum-based chemotherapy 8+ | 34 (1.5) | | | 0.678 (0.396–1.159) | 0.798 (0.446–1.426) |
| Platinum and taxanes 1–5 | 394 (17.0) | 62.5 | 65.1 | 0.600 (0.475–0.758) | 0.655 (0.507–0.847) |
| Platinum and taxanes 6–8 | 268 (11.5) | | | 0.664 (0.511–0.864) | 0.725 (0.546–0.964) |
| Platinum and taxanes 8+ | 160 (6.9) | | | 0.748 (0.568–0.986) | 0.892 (0.667–1.193) |
| For matched cohort | 1,305 (100) | 54.9 | 61.2 | | |
| No chemotherapy | 512 (39.2) | 51.6 | 59.8 | 1.000 | 1.000 |
| Other non-platinum chemotherapy 1–5 | 57 (4.4) | 48.5 | 53.4 | 1.278 (0.853–1.916) | 1.262 (0.804–1.982) |
| Other non-platinum chemotherapy 6–8 | 27 (2.1) | | | 0.552 (0.272–1.117) | 0.599 (0.279–1.284) |
| Other non-platinum chemotherapy 8+ | 63 (4.8) | | | 0.843 (0.561–1.268) | 0.993 (0.646–1.527) |
| Platinum-based chemotherapy 1–5 | 105 (8.0) | 53.3 | 61.6 | 0.767 (0.546–1.078) | 0.746 (0.508–1.095) |
| Platinum-based chemotherapy 6–8 | 65 (5.0) | | | 0.593 (0.380–0.924) | 0.582 (0.353–0.959) |
| Platinum-based chemotherapy 8+ | 25 (1.9) | | | 0.558 (0.289–1.076) | 0.563 (0.273–1.165) |
| Platinum and taxanes 1–5 | 254 (19.5) | 62.0 | 65.6 | 0.512 (0.385–0.682) | 0.554 (0.406–0.755) |
| Platinum and taxanes 6–8 | 124 (9.5) | | | 0.507 (0.355–0.725) | 0.513 (0.348–0.756) |
| Platinum and taxanes 8+ | 73 (5.6) | | | 0.435 (0.292–0.647) | 0.471 (0.309–0.717) |

[a] Includes patients for whom cause of death was reported as unknown or missing; [b] Hazard ratio was adjusted for age, race, marital status, tumor stage, tumor grade, histology cell type, comorbidity scores, surgery, socioeconomic status, year of diagnosis, and SEER states

**Table 4** Effects of various chemotherapy regimens on 5-year all-cause and cancer-specific mortality in late stage (stage III, IV, unknown)

| | Number of patients (%) | Observed survival rate (%) | | Hazard ratio (95 % CI)[b] of mortality | |
|---|---|---|---|---|---|
| | | 5 year all-cause | 5 year cancer-specific[a] | 5 year all-cause | 5 year cancer-specific[a] |
| *Chemotherapy categories* | | | | | |
| For entire cohort | 9,859 (100) | 14.1 | 15.9 | | |
| No chemotherapy | 2,851 (28.9) | 5.3 | 7.8 | 1.000 | 1.000 |
| Other non-platinum chemotherapy | 1,551 (15.7) | 13.3 | 15.4 | 0.628 (0.583–0.676) | 0.642 (0.594–0.693) |
| Platinum-based chemotherapy | 1,280 (13.0) | 14.7 | 16.7 | 0.485 (0.448–0.525) | 0.495 (0.456–0.538) |
| Platinum and taxanes | 4,177 (42.4) | 20.4 | 21.3 | 0.382 (0.358–0.408) | 0.395 (0.369–0.422) |
| For matched cohort | 5,551 (100) | 12.6 | 14.4 | | |
| No chemotherapy | 1,581 (28.5) | 6.6 | 8.6 | 1.000 | 1.000 |
| Other non-platinum chemotherapy | 1,188 (21.4) | 15.0 | 17.0 | 0.585 (0.535–0.640) | 0.593 (0.540–0.650) |
| Platinum-based chemotherapy | 978 (17.6) | 14.1 | 16.3 | 0.440 (0.398–0.485) | 0.445 (0.402–0.493) |
| Platinum and taxanes | 1,804 (32.5) | 15.6 | 16.6 | 0.382 (0.354–0.412) | 0.392 (0.363–0.424) |
| Dose response | | | | | |
| *Chemotherapy categories with number of claims* | | | | | |
| For entire cohort | 9,859 (100) | 14.1 | 15.9 | | |
| No chemotherapy | 2,851 (28.9) | 5.3 | 7.8 | 1.000 | 1.000 |
| Other non-platinum chemotherapy 1–5 | 610 (6.2) | 13.3 | 15.4 | 1.415 (1.209–1.554) | 1.459 (1.324–1.608) |
| Other non-platinum chemotherapy 6–8 | 194 (2.0) | | | 0.558 (0.474–0.658) | 0.567 (0.478–0.673) |
| Other non-platinum chemotherapy 8+ | 747 (7.6) | | | 0.377 (0.342–0.415) | 0.386 (0.350–0.427) |
| Platinum-based chemotherapy 1–5 | 629 (6.4) | 14.7 | 16.7 | 0.641 (0.581–0.707) | 0.652 (0.589–0.722) |
| Platinum-based chemotherapy 6–8 | 302 (3.1) | | | 0.430 (0.376–0.493) | 0.440 (0.382–0.506) |
| Platinum-based chemotherapy 8+ | 349 (3.5) | | | 0.287 (0.251–0.328) | 0.297 (0.259–0.341) |
| Platinum and taxanes 1–5 | 1,363 (13.8) | 20.4 | 21.3 | 0.583 (0.539–0.630) | 0.592 (0.546–0.642) |
| Platinum and taxanes 6–8 | 1,231 (12.5) | | | 0.350 (0.321–0.382) | 0.363 (0.332–0.397) |
| Platinum and taxanes 8+ | 1,583 (16.1) | | | 0.251 (0.231–0.273) | 0.264 (0.243–0.287) |
| For matched cohort | 5,551 (100) | 12.6 | 14.4 | | |
| No chemotherapy | 1,581 (28.5) | 6.6 | 8.6 | 1.000 | 1.000 |
| Other non-platinum chemotherapy 1–5 | 427 (7.7) | 15.0 | 17.0 | 1.465 (1.306–1.642) | 1.490 (1.323–1.678) |
| Other non-platinum chemotherapy 6–8 | 147 (2.6) | | | 0.517 (0.426–0.627) | 0.523 (0.428–0.639) |
| Other non-platinum chemotherapy 8+ | 614 (11.1) | | | 0.360 (0.321–0.402) | 0.366 (0.326–0.411) |
| Platinum-based chemotherapy 1–5 | 502 (9.0) | 14.1 | 16.3 | 0.559 (0.498–0.629) | 0.564 (0.499–0.637) |
| Platinum-based chemotherapy 6–8 | 229 (4.1) | | | 0.416 (0.355–0.486) | 0.420 (0.357–0.494) |
| Platinum-based chemotherapy 8+ | 247 (4.4) | | | 0.254 (0.216–0.299) | 0.262 (0.222–0.310) |
| Platinum and taxanes 1–5 | 693 (12.5) | 15.6 | 16.6 | 0.615 (0.558–0.678) | 0.626 (0.566–0.693) |
| Platinum and taxanes 6–8 | 475 (8.6) | | | 0.365 (0.325–0.410) | 0.376 (0.333–0.424) |
| Platinum and taxanes 8+ | 636 (11.5) | | | 0.240 (0.215–0.268) | 0.250 (0.224–0.280) |

[a] Includes patients for whom cause of death was reported as unknown or missing; [b] Hazard ratio was adjusted for age, race, marital status, tumor stage, tumor grade, histology cell type, comorbidity scores, surgery, socioeconomic status, year of diagnosis, and SEER states

**Table 5** Median survival for all-cause mortality and cancer-specific mortality by stage at diagnosis

| Chemotherapy categories | Median survival months (95 % CI) | | | |
|---|---|---|---|---|
| | All-cause mortality | | Cancer-specific mortality[a] | |
| | Entire cohort | Matched cohort | Entire cohort | Matched cohort |
| | Early stage (stage IAB, IC, II) | | | |
| No chemotherapy | 63.7 (54.8–71.7) | 63.1 (50.5–75.8) | 143.4 (108.6–167.0) | 102.1 (76.6–NA) |
| Other non-platinum chemotherapy | 57.7 (38.4–82.3) | 58.4 (42.5–85.5) | 83.5 (53.9–121.6) | 76.0 (50–122.7) |
| Platinum-based chemotherapy | 72.4 (52.6–81.1) | 72.4 (50.1–86.8) | 88.9 (72.4–129.5) | 92.8 (73.5–132.2) |
| Platinum and taxanes | 101.7 (95.6–120.2) | 97.7 (91.8–NA) | 110.3 (97.7–140.3) | 118.7 (97.7–NA) |
| | Late stage (stage III, IV, unknown) | | | |
| No chemotherapy | 3.5 (3.3–3.6) | 3.7 (3.4–4) | 3.8 (3.6–4) | 4.0 (3.7–4.5) |
| Other non-platinum chemotherapy | 15.1 (14.1–16.6) | 17.5 (16.1–18.8) | 16.5 (15–17.8) | 18.5 (17.1–20) |
| Platinum-based chemotherapy | 22.4 (21.2–23.8) | 21.3 (19.9–22.7) | 23.2 (22.1–25.2) | 22.2 (20.7–23.8) |
| Platinum and taxanes | 27.7 (26.6–28.7) | 22.6 (20.8–24.2) | 28.6 (27.6–29.6) | 23.9 (22.4–24.9) |

*NA* not enough patients died to estimate the upper bound

[a] Includes patients for whom cause of death was reported as unknown or missing

**Table 6** All-cause and cancer-specific 5-year mortality in association with other factors in patients with epithelial ovarian cancer in entire cohort

| Patient characteristics | All-cause mortality | | Cancer-specific mortality[a] | |
|---|---|---|---|---|
| | Hazard ratio | 95 % confidence interval | Hazard ratio | 95 % confidence interval |
| Age | | | | |
| 65–69 | 1.000 | Reference | 1.000 | Reference |
| 70–74 | 1.129 | 1.059–1.205 | 1.125 | 1.053–1.203 |
| 75–79 | 1.168 | 1.095–1.247 | 1.150 | 1.075–1.230 |
| 80–84 | 1.378 | 1.283–1.480 | 1.365 | 1.267–1.469 |
| 85+ | 1.525 | 1.407–1.652 | 1.441 | 1.324–1.568 |
| Race/ethnicity | | | | |
| Caucasian | 1.000 | Reference | 1.000 | Reference |
| African–American | 0.906 | 0.825–0.995 | 0.907 | 0.822–1.001 |
| All others | 0.956 | 0.870–1.050 | 0.950 | 0.860–1.049 |
| Marital status | | | | |
| Married | 1.000 | Reference | 1.000 | Reference |
| Unmarried | 1.063 | 1.014–1.113 | 1.060 | 1.010–1.112 |
| Unknown | 0.923 | 0.814–1.046 | 0.903 | 0.792–1.030 |
| Tumor AJCC stage | | | | |
| I-AB | 1.000 | Reference | 1.000 | Reference |
| I-C | 3.120 | 2.588–3.761 | 4.966 | 3.919–6.293 |
| II | 4.823 | 4.066–5.722 | 8.038 | 6.447–10.021 |
| III | 8.704 | 7.471–10.140 | 15.323 | 12.487–18.801 |
| IV | 10.659 | 9.140–12.431 | 19.104 | 15.556–23.461 |
| Un-staged | 5.746 | 4.887–6.755 | 9.756 | 7.888–12.067 |
| Tumor grade | | | | |
| Well differentiated | 1.000 | Reference | 1.000 | Reference |
| Moderately differentiated | 1.672 | 1.422–1.966 | 1.738 | 1.456–2.075 |
| Poorly differentiated | 1.916 | 1.641–2.239 | 1.984 | 1.673–2.351 |
| Undifferentiated | 1.852 | 1.565–2.193 | 1.934 | 1.610–2.323 |
| Unknown | 1.952 | 1.670–2.283 | 2.028 | 1.708–2.408 |

**Table 6** continued

| Patient characteristics | All-cause mortality | | Cancer-specific mortality[a] | |
|---|---|---|---|---|
| | Hazard ratio | 95 % confidence interval | Hazard ratio | 95 % confidence interval |
| Histology type | | | | |
| Serous | 1.000 | Reference | 1.000 | Reference |
| Mucinous | 1.481 | 1.335–1.643 | 1.512 | 1.355–1.688 |
| Endometrioid | 1.087 | 1.001–1.179 | 1.075 | 0.986–1.172 |
| Clear cell | 0.927 | 0.776–1.109 | 0.947 | 0.785–1.144 |
| Other epithelial | 1.110 | 1.050–1.173 | 1.123 | 1.060–1.189 |
| Other | 0.987 | 0.890–1.094 | 0.981 | 0.879–1.095 |
| Comorbidity scores | | | | |
| 0 | 1.000 | Reference | 1.000 | Reference |
| 1 | 1.192 | 1.132–1.254 | 1.139 | 1.079–1.201 |
| 2 | 1.280 | 1.190–1.377 | 1.178 | 1.089–1.274 |
| ≥3 | 1.489 | 1.368–1.619 | 1.324 | 1.208–1.450 |
| Cancer-directed surgery | | | | |
| No | 1.000 | Reference | 1.000 | Reference |
| Yes | 0.484 | 0.456–0.515 | 0.486 | 0.456–0.517 |
| SES (poverty) | | | | |
| 1st (low SES) | 1.000 | Reference | 1.000 | Reference |
| 2nd | 1.023 | 0.963–1.087 | 1.033 | 0.970–1.101 |
| 3rd | 0.975 | 0.916–1.039 | 0.994 | 0.931–1.062 |
| 4th (high SES) | 0.995 | 0.931–1.063 | 1.018 | 0.950–1.090 |

[a] Includes patients for whom cause of death was reported as unknown or missing; Hazard ratio adjusted for variables listed in the tables plus chemotherapy (4 categories), the year of diagnosis and SEER areas

**Table 7** Percentages (column) of patients having chemotherapy-related toxicities, by chemotherapy status

| Toxicities, by grades | Time period when toxicity occurred (months) | No chemotherapy ($n$ = 3,892) | Other non-platinum chemotherapy ($n$ = 1,767) | Platinum-based chemotherapy ($n$ = 4,999) | Platinum and taxane ($n$ = 1,523) |
|---|---|---|---|---|---|
| Grades 1–2 | | | | | |
| Nausea/vomiting | <3 | 59 (1.5) | 210 (11.9) | 1,667 (33.3) | 309 (20.3) |
| | 3–6 | 32 (0.8) | 101 (5.7) | 1,283 (25.7) | 217 (14.2) |
| | 6–12 | 29 (0.7) | 136 (7.7) | 927 (18.5) | 183 (12.0) |
| Neutropenia | <3 | 33 (0.8) | 160 (9.0) | 1,289 (25.8) | 238 (15.6) |
| | 3–6 | 25 (0.6) | 129 (7.3) | 1,196 (23.9) | 201 (13.2) |
| | 6–12 | 13 (0.3) | 100 (5.7) | 726 (14.5) | 157 (10.3) |
| Fatigue | <3 | 39 (1.0) | 224 (12.7) | 713 (14.3) | 125 (8.2) |
| | 3–6 | 24 (0.6) | 84 (4.7) | 577 (11.5) | 78 (5.1) |
| | 6–12 | 24 (0.6) | 119 (6.7) | 743 (14.8) | 124(8.1) |
| Grades 3–4 | | | | | |
| Nausea/vomiting | <3 | <11[a] | 107 (6.1) | 164 (3.3) | 41 (2.7) |
| | 3–6 | <11[a] | 33 (1.9) | 62 (1.2) | 20 (1.3) |
| | 6–12 | <11[a] | 28 (1.6) | 95 (1.9) | 28 (1.8) |
| Neutropenia | <3 | 17 (0.4) | 184 (10.4) | 318 (6.4) | 73 (4.8) |
| | 3–6 | <11[a] | 52 (2.9) | 115 (2.3) | 42 (2.8) |
| | 6–12 | <11[a] | 44 (2.5) | 80 (1.6) | 42 (2.8) |
| Fatigue | <3 | <11[a] | 14 (0.8) | 58 (1.2) | 12 (0.8) |
| | 3–6 | <11[a] | <11[a] | 33 (0.7) | <11[a] |
| | 6–12 | <11[a] | <11[a] | 36 (0.7) | <11[a] |

[a] Numbers less than 11 were not reported as the SEER-medicare data user agreement required

those receiving other chemotherapy agents or platinum-based chemotherapy.

Table 6 presents the effects of other patient and tumor factors on the risk of mortality. The risks of all-cause and cancer-specific mortality significantly increased with age, unmarried, higher tumor stages, poorer tumor grades, and higher comorbidity scores. The risk of mortality varied by histological type, in which patients with mucinous and endometrioid tumors had higher risks of both all-cause and cancer-specific mortality relative to serous tumors. Patients receiving cancer-directed surgery were almost 50 % less likely to die than those who did not. There was no significant association between SES or ethnicity and mortality risk.

Table 7 compared some selected side-effects such as neutropenia and fatigue likely associated with chemotherapy. Patients receiving platinum and taxane had lower grades 1–2 toxicity rates and similar grades 3–4 toxicity rates as compared to patients receiving platinum-based chemotherapy without taxane, although they had higher toxicity rates than those with other non-platinum chemotherapy or without chemotherapy. The results were similar when the analyses were stratified by age ($<70$ vs. $\geq 70$) or comorbidity ($\leq 1$ vs. $>1$) (data not shown).

## Discussion

Overall, platinum–taxane combination chemotherapy and platinum-based chemotherapy without taxane as primary therapies appeared effective in prolonging survival among patients with late-stage ovarian cancer, with a significant dose–response relationship. Among those with early stage tumors, platinum–taxane combination was more effective than other chemotherapy regimens as adjuvant chemotherapy. The findings were reconfirmed after controlling for potential confounders and after performing cohort matching based on the probability of receiving platinum-based chemotherapy to minimize selection bias and confounding. The selected toxicity rates were lower in patients receiving platinum–taxane combination than those receiving platinum-based chemotherapy without taxane, but higher than those receiving other non-platinum agents.

Prognosis for ovarian cancer is generally poor, and the 5-year relative survival rate in 2002–2008 was 43.7 % for all stages, 91.5 % for women with early stage, and 26.9 % for women with advanced disease [42]. However, the 5-year relative survival rates improved from 36.1 % in 1975–1977 to 43.7 % in 2002–2008 [42], which is in large part attributable to improvement in cancer therapy, particularly chemotherapy. The National Institute of Health consensus expert panel recommended that patients with higher grades and/or higher stage ovarian tumors (i.e., stages IA or IB with grade 3, stages IC, II, III, and IV tumors) receive systemic chemotherapy [1–3]. For patients with stage IA or IB and grade I ovarian cancer, observation is recommended following surgery because of the high cure rate for these patients with surgery alone, whereas for patients with stage IA and grade II tumors, either observation or chemotherapy would be appropriate. In general, chemotherapy can be an appropriate option for almost all ovarian cancer patients. Our study confirmed that chemotherapy regimens, particularly platinum and taxane combination as well as platinum-based regimens without taxane were effective in prolonging survival in community-dwelling patients with ovarian cancer. In our study, platinum–taxane combination appeared to have similar cancer-specific 5-year and median survival benefit compared to platinum-based regimens without taxane in later stage cancer. The reason could be that, in late-stage cancer, there are multiple lines of chemotherapy combinations including addition of taxane after patients failed in their first line platinum-based regimens without taxane. Therefore, it could obscure the benefit using platinum–taxane as front line combination in the first 6 months of diagnosis which was identified in this study.

This study has a number of strengths and uniqueness. First, because findings from clinical trials have limited generalizability to patients in community, this study that assessed the effectiveness of chemotherapy should provide important information to a large number of community-based patients and care providers. Second, this study evaluated the effectiveness of all available chemotherapy regimens simultaneously in routine practice, which would be difficult to achieve in any single clinical trial. Third, our study populations were from the nationwide and population-based registries, accounting for 26 % of the US population [42]. These large populations in the community settings together with long-term follow-up on survival offered unique opportunities to address more appropriately the real world effectiveness of chemotherapy agents. Furthermore, in addition to adjustment for multiple confounders in regression models, the matched cohort analysis was conducted based on the conditional probability of receiving platinum-based chemotherapy. The findings from the matched cohort analyses were consistent, further reconfirming what were found from the entire cohort analyses.

There are several limitations in this study. First, the major concern about addressing the effectiveness of therapies in non-randomized studies was the potential selection bias. Unlike the randomized clinical trials, observational studies have no control over the receipt of therapies. Hence, there may be some factors from patients or care providers that could have influenced patients to receive or not receive chemotherapy. Although our study carefully

utilized the propensity-score matched analyses based on numerous factors, there could still be substantial bias because of unmeasured or unknown confounding factors that might be unbalanced between comparison groups. Other statistical approaches may help examine this potential confounding, such as propensity weighting and instrumental variable analysis, but due to the nature of observational study design, subtle unknown confounding is unlikely removed completely. Second, study population only included patients aged ≥65 years and those with both Medicare Parts A and B without enrolment in health maintenance organizations. The study findings may not be generalizable to younger patients or others. Third, information on chemotherapy was based on claims data in which missing chemotherapy data may occur and actual chemotherapy doses cannot be measured. Although the number of chemotherapy cycles based on the number of claims for chemotherapy as proxy was taken into account in the analyses, estimates for the dose–response relationship are not precise.

In conclusion, platinum–taxane combination chemotherapy and platinum-based chemotherapy without taxane as primary therapies were effective in prolonging survival with a significant dose–response relationship among patients with late-stage ovarian cancer. Among those with early stage tumors, platinum–taxane combination appeared more effective than other chemotherapy regimens. Although survival rates were improved due to chemotherapy for patients with late-stage ovarian cancer, overall prognosis and survival in these patients are much poorer than those with early stage disease. Thus, more emphases in research should be on how to identify the disease at earlier stages, while at the same time to improve the treatment-related outcomes and ensure the appropriate receipt of well-documented chemotherapy regimens.

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