# Association between Adjuvant Chemotherapy and Risk of Chronic Kidney Disease in Elderly Women Diagnosed with Early Stage Breast Cancer

Shuling Li, PhD,[1] Jiannong Liu, PhD,[1] Beth A. Virnig, PhD,[2] Allan J. Collins, MD, FACP,[1,2]
[1]Chronic Disease Research Group, Minneapolis, MN; [2]University of Minnesota, Minneapolis, MN

## Introduction

- Chronic kidney disease (CKD) and cancer are major public health problems in the elderly population. CKD is found more common in cancer patients than the general population.
- With the development of cancer screening and efficacious treatments including chemotherapy (chemo), the number of cancer survivors has been increasing.
- Studies of CKD as a late effect of chemo have mainly focused on childhood cancer survivors. In elderly cancer patients, however, little is known about CKD as a late effect of chemo.
- This study examined the association between adjuvant chemo and risk of CKD in elderly women diagnosed with early stage breast cancer.

## Methods

- Data source: SEER-Medicare linked data
- Inclusion criteria:
  - Diagnosed with stages I-III breast cancer as their first primary cancer at ages 66-89 years during 1992-2007
  - Surgically treated within 4 months of diagnosis
  - Continuously enrolled in Medicare Parts A and B for at least 1 year before diagnosis.
- Exclusion criteria:
  - Participated in an HMO
  - Received neoadjuvant chemotherapy
  - Had liver disease, AKI, chronic kidney disease (CKD) or end-stage renal disease before diagnosis of breast cancer.
- We performed 1-1 sequential matching on time-dependent propensity score on the day of adjuvant chemo initiation within 6 months after the first surgery. Balance in baseline characteristics between the matched cohorts was assessed using the standardized difference.
- Follow-up (F/U) began on the matching date and ended at CKD, death, change in enrollment status, second non-breast primary cancer, or December 31, 2009. For patients in the matched untreated cohort, F/U time was also censored at chemo initiation.
- Definitions
  - Chemo was identified in claims through billing codes indicating drugs or administration. Regimens of interest included anthracyclines (A), CMF, taxanes (w/o A), and others.
  - CKD was identified using ICD-9-CM diagnosis codes requiring ≥1 MedPAR/HHA claim or ≥2 OP/NCH claims on different dates within a 12-month interval.
  - Demographics and tumor characteristics were identified in SEER data.
  - Cancer treatments and comorbid conditions were identified in Medicare claims.
- Analyses:
  - The cumulative incidence of CKD was assessed using the Kaplan-Meier method.
  - The association between adjuvant chemo and risk of CKD was evaluated using a Cox proportional hazards model.
  - The analyses were repeated by regimen type. Association between regimen type and risk of CKD was adjusted for patient baseline characteristics.

## Results

- The matched study cohorts included 28,048 patients. After matching, differences in distribution of baseline characteristics were greatly reduced (Table 1).
- The mean (SD) F/U time was 5.1 (3.4) years for the chemo cohort and 3.3 (3.6) years for the matched no-chemo cohort.
- CKD rate (SE) was 29.0 (0.6) and 29.3 (0.8) per 1000 patient-years in chemo and matched no-chemo cohort, respectively.
- Overall, there was no significant difference in the cumulative incidence of CKD between the two cohorts (Figure 1).
- Though the association between adjuvant chemo and risk of CKD varied across regimen types, these associations were not statistically significant (Table 2).
- Increasing age, black race, diabetes, CHF, and hypertension were the major risk factors for recognized CKD (Figure 2). These findings were consistent with prior studies of risk factors for CKD.

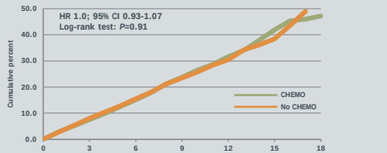
**Table 1. Assessment of Balance after Matching**

| | Before matching (n=84,018) | | | After matching (n=28,048) | | |
|---|---|---|---|---|---|---|
| | No CHEMO | CHEMO | Standardized difference | No CHEMO | CHEMO | Standardized difference |
| Sample size, n | 69293 | 14725 | | 14,024 | 14,025 | |
| Age, yrs | | | | | | |
| 66-69 | 17.8 | 38.8 | 0.480 | 35.4 | 37.8 | 0.050 |
| 70-74 | 26.1 | 34.3 | 0.179 | 35.1 | 34.6 | 0.010 |
| 75-79 | 26.6 | 19.6 | 0.168 | 21.2 | 20.1 | 0.027 |
| 80-84 | 19.6 | 6.2 | 0.409 | 6.1 | 6.4 | 0.012 |
| 85-89 | 9.8 | 1.1 | 0.392 | 2.2 | 1.1 | 0.086 |
| Race | | | | | | |
| White | 90.8 | 87.6 | 0.101 | 88.1 | 87.8 | 0.008 |
| Black | 5.3 | 7.8 | 0.101 | 7.6 | 7.7 | 0.003 |
| Other | 3.9 | 4.5 | 0.031 | 4.3 | 4.5 | 0.008 |
| Comorbidities | | | | | | |
| ASHD | 15.3 | 11.8 | 0.103 | 12.2 | 11.7 | 0.015 |
| CHF | 7.0 | 4.1 | 0.127 | 4.5 | 4.1 | 0.020 |
| Dysrhythmia | 13.5 | 9.0 | 0.142 | 9.8 | 9.0 | 0.025 |
| PVD | 8.0 | 5.1 | 0.115 | 5.6 | 5.2 | 0.018 |
| Diabetes | 16.1 | 17.5 | 0.039 | 17.9 | 17.3 | 0.015 |
| Hypertension | 54.8 | 53.6 | 0.025 | 54.0 | 53.3 | 0.013 |
| AJCC Stage | | | | | | |
| I | 65.6 | 19.0 | 1.069 | 18.9 | 19.8 | 0.022 |
| II | 30.2 | 62.6 | 0.689 | 66.0 | 62.7 | 0.070 |
| III | 4.3 | 18.3 | 0.456 | 15.0 | 17.5 | 0.067 |
| Size, cm | | | | | | |
| <2 | 65.3 | 36.1 | 0.611 | 36.6 | 36.6 | 0.002 |
| ≥2 | 32.3 | 61.6 | 0.616 | 61.3 | 61.1 | 0.004 |
| Unknown | 2.5 | 2.3 | 0.012 | 2.0 | 2.3 | 0.018 |
| Lymph node status | | | | | | |
| Negative | 68.5 | 34.7 | 0.721 | 36.9 | 36.0 | 0.019 |
| Positive | 16.6 | 60.7 | 1.016 | 57.8 | 59.2 | 0.028 |
| Unknown | 14.8 | 4.6 | 0.351 | 5.2 | 4.8 | 0.022 |
| ER/PR status | | | | | | |
| ER+ and/or PR+ | 77.0 | 59.3 | 0.387 | 64.0 | 60.5 | 0.071 |
| ER- and PR- | 8.9 | 30.1 | 0.556 | 24.6 | 28.6 | 0.091 |
| Unknown | 14.1 | 10.6 | 0.108 | 11.4 | 10.8 | 0.019 |

**Table 2. Association between type of adjuvant chemotherapy and risk of CKD during the 18-year follow-up**

| | Total, n | Mean (SD) F/U time, yrs | CKD, n (%) | Rate of CKD (1000 pt-yrs) | Adjusted HR (95% CI) | P |
|---|---|---|---|---|---|---|
| No chemo | 14024 | 3.3 (3.6) | 1335 (9.5) | 29.3 | Reference | |
| Anthracyclines | 7465 | 4.8 (3.0) | 1001 (13.4) | 27.7 | 0.96 (0.88, 1.04) | 0.31 |
| CMF | 4389 | 6.0 (3.9) | 762 (17.4) | 29.1 | 1.04 (0.95, 1.14) | 0.44 |
| Taxanes | 1030 | 2.8 (1.8) | 114 (11.1) | 39.4 | 0.91 (0.74, 1.12) | 0.38 |
| Others | 1140 | 5.1 (4.0) | 181 (15.9) | 31.2 | 1.04 (0.89, 1.22) | 0.60 |

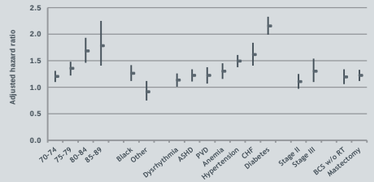
**Figure 1. Cumulative percent of patients developing CKD during the 18-year follow-up period, by adjuvant chemotherapy status**




Number of patients at risk

| Years of F/U | 0 | 1 | 2 | 3 | 4 | 5 | 10 | 15 |
|---|---|---|---|---|---|---|---|---|
| CHEMO | 14024 | 12881 | 11441 | 9416 | 7633 | 6109 | 1164 | 176 |
| No CHEMO | 14024 | 8461 | 7294 | 5923 | 4734 | 3744 | 791 | 123 |

**Figure 2. Major Risk Factors for developing CKD during the 18-year follow-up period**




## Conclusions

- Adjuvant chemotherapy was not found to be associated with long-term risk of recognized CKD in elderly women diagnosed with early stage breast cancer.
- The risk factors for developing CKD identified in the elderly women with breast cancer are similar to those reported in the general elderly population.
- Limitations
  - Residual confounding
  - Limited information on the dosage and intensity of chemotherapy
  - Potential misclassification on CKD defined using diagnosis codes
  - Findings may not be generalized to patients at younger age or with other cancers.

cdrg
CHRONIC DISEASE RESEARCH GROUP

www.cdrg.org