Risks of female genital tract related cancers (gynecological cancers) or breast cancer in women with and without chronic kidney disease

A population-based cohort study in Taiwan

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Abstract

This article aims to test the hypothesis that the risk of female genital tract related cancer (gynecological cancer: GC) or breast cancer (BC) of women with chronic kidney disease (CKD) might be different from that of those women without CKD.

A nationwide 17-year historic cohort study using the National Health Insurance Research Database (NHIRD) of Taiwan and the Registry for Catastrophic Illness Patients was conducted. A total of 3045 women with a diagnosis of CKD from 1996 to 2013 and 3045 multivariable-matched controls (1:1) were selected. We used Cox regression, and computed hazard ratios (HRs) with 95% confidence intervals (95% CIs) to determine the risk of GC or BC in women.

The GC incidence rates (IRs, per 10,000 person-years) of the CKD and non-CKD women were 11.02 and 19.09, respectively, contributing to a significantly decreased risk of GCs (crude HR 0.57, 95% CI 0.39–0.81; adjusted HR 0.44, 95% CI 0.30–0.65) in the CKD women. The GC IR was relatively constant in the CKD women among the different age categories (IR ranged from 8.10 to 12.29). On contrast, the non-CKD women had a progressive and continuous increase of GC IR in the advanced age, which was more apparent at age ≥50 years (IR 17.16 for 50–59; IR 23.05 for 60–69; and IR 31.62 for ≥70, respectively), contributing to the lower risk of GC in the CKD women than that in the non-CKD women. There was no difference of BC incidence between women with and without CKD.

The findings of the lower risk of GCs in the CKD women in Taiwan are worthy of further evaluation.

Abbreviations:

BC = breast cancer, CCI = Charlson comorbidity index, CI = confidence interval, CKD = chronic kidney disease, CVD = cardiovascular disease, DM = diabetes mellitus, EOC = epithelial ovarian cancer, ESRD = end-stage renal disease, GC = gynecological cancers (female genital-tract cancers), GFR = glomerular filtration rate, HPV = human papilloma virus, HR = hazard ratio, ICD-9-CM = international classification of diseases, ninth revision, and clinical modifications, IR = incidence rate, LHID = longitudinal health insurance database, NHI = national health insurance, NHI-RD = national health insurance research database, OPD = outpatient clinics, PID = pelvic inflammatory disease, PPSC = primary peritoneal serous carcinoma, RCIP = Registry for Catastrophic Illness Patients, RR = relative risk, SES = social-economic status, TC = Fallopian tube cancer.

Keywords: breast cancer, chronic kidney disease, cohort study, gynecological cancers, risk
1. Introduction

Cancers are a major cause of death among the general population.[11] In Taiwan, cancer has become the most common cause of death since 1982.[12–15] In patients with chronic kidney disease (CKD), impairment of immune system, impairment of DNA repair, reduced clearance of toxic or carcinogenic compounds, and increased infection and chronic inflammation, are in theory related to development of cancer.[6–11] CKD is defined as kidney damage or decreased kidney function [glomerular filtration rate (GFR) lower than 60 mL/min per 1.73 m²] for 3 months or longer.[12–14] The prevalence and incidence of CKD is significantly increasing in decades.[15–17]

Compared with other countries, Taiwan has a remarkably high incidence and prevalence of patients with CKD, and end-stage of renal disease (ESRD).[18]

CKD is a major global health burden because of its high prevalence and associated risk of ESRD, cardiovascular disease (CVD) events, such as congestive heart failure, stroke, myocardial infarction, peripheral artery disease, and premature death.[19,20] These adverse events have almost certainly underestimated the disease burden of CKD because it probably only captures deaths due to ESRD.[15] Although it is well documented that CVD causes most deaths in patients with CKD,[15,19] and cancer might be a relatively rare cause of death among patients on dialysis, who primarily died of CVD or infectious causes,[21,22] therefore, the risk of cancer is often overlooked. For the majority of women with CKD, most of whom might have much comorbidity, it is rationale to suppose that these CKD women have limited life expectancy, contributing to neglecting cancer screening. However, studies from different countries have found that the incidence rate (IR) of cancers varied greatly in the CKD patients,[6,13,20–31] and some reports showed that cancer IR in the CKD patients was higher than that in the general population.[6,11] Among these studies, most found that these CKD patients had a higher risk of urinary tract system cancers.[31] Except the increased risk of urinary tract cancers, cancer risk from the other organs in women is not consistent. This uncertainty of female genital tract related cancer [gynecological cancer (GC), including cervical cancer, uterine cancer, and ovarian/tubal/primary peritoneal serous cancer-EOC/TC/PPSC] or breast cancer (BC) is much apparent in the CKD women.

The aim of this study was to investigate whether the CKD women had a higher risk of GC or not. In addition, BC risk was also evaluated. In order to achieve our aim, we conducted the following large-scale, nationwide, controlled cohort study.

2. Methods

This was a retrospective cohort study, approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No.: 2017-06-027BC). The source population consisted of nearly the entire population of Taiwan (2.3 million inhabitants), which was covered by the National Health Insurance (NHI).[32–34] The study used the Longitudinal Health Insurance Database (LHID) obtained from the NHI Research Database (NHIRD), consisting of 1 million beneficiaries randomly sampled from the original NHI beneficiaries.[35,36] The National Health Research Institute in Taiwan permitted the access to the data in the NHIRD and the database includes the entire registry and claims data from this health insurance system.[32–37] The accuracy of diagnosis in the NIRD has been validated for several diseases, including stroke and CKD.[137–39]

To minimize the bias of uncertain diagnosis for GC in the current study, the following strategy was used. Women without a visit to an obstetrician or gynecologist during the study period were excluded. The diagnosis, which was not validated by the Registry for Catastrophic Illness Patients (RCIP), was excluded. The diagnostic criterion of women with CKD was based on ICD-9-CM 58 and 40 [International Classification of Diseases, Ninth Revision, and Clinical Modifications (ICD9-CM) code 585.586, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, and 404.93] from the RCIP during the period between January 1, 1996, and December 31, 2013, were included among the incident women with CKD (n = 3045). To decrease the influence of hysterectomy, bilateral salpingo-oophorectomy, and bilateral oophorectomy on the development of future GC, women with hysterectomy, except those women with a diagnosis of GC during the follow-up period, were excluded. Each CKD case was matched with 1 female control by age, index year, obstetric history, frequency of gynecological/obstetric providers’ outpatient visits, contraception methods, socioeconomic status (SES), work, and urbanization, which resulted in an overall sample size of 3045 matched controls without CKD (Fig. 1).

2.1. Statistical analysis

For the women with CKD, the index date was the date of a diagnosis of CKD. For the controls, the index date was the first visit to an obstetrician/gynecologist provider or admission during the study period. GCs or BC was initially detected using inpatients with ICD-9-CM 180.X (cervical cancer), 182.X (uterine cancer), 183.X (EOC or TC), 158.X (PPSC), and 174.X (BC) from the RCIP. Starting from the cohort index date, the study subjects were followed until hospitalization with GC or to the end of the study (December 31, 2013), whichever came first, if no GC had occurred. Patients without GC events were treated as censored subjects. Dropouts or those who were lost to follow-up were also treated as censored. Basic characteristics are presented as percentages. The incidence of GC was compared between the CKD women and the non-CKD women using the IR.

The χ² test was used to compare the IR estimates of occurrence of GC among subsamples. The robust Cox proportional hazards model was used to calculate the HR and 95% CI to determine whether newly diagnosed CKD is a risk factor for GC. Variables adjusted in the Cox model were pelvic inflammatory disease (PID), infertility status, menopause, CVD, diabetes mellitus (DM), chronic liver disease (CLD), and rheumatoid disease (RD). Statistical analyses were implemented with SAS version 9.3 (SAS Institute Inc., Cary, NC), STATA version 10.0 (STATA Corp, College Station, TX), and SPSS version 20 (SPSS, Chicago, IL).

3. Results

Among the entire cohort of the total 6090 women, the total person-years of follow-up were 84,556, including 42,655 for women with CKD and 41,901 for the non-CKD women. During the follow-up period (1996–2015), 127 had a diagnosis of GC and 116 women had a diagnosis of BC (Table 1). Women with CKD had higher rates of comorbid CVD, DM, CLD, and high Charison Comorbidity Index score (CCI >2) than the non-CKD women did (all P <.05). By contrast, women with CKD had lower rates of PID and menopausal status. There was no statistically significant difference of infertility and RD in both groups (Table 1).
The GC IR in the CKD women and non-CKD women was 11.02 and 19.09 per 10,000 person-years, respectively, contributing to a crude hazard ratio (HR) of 0.57 [95% confidence interval (CI) 0.39–0.81, \( P < .01 \)]. This finding suggested that the CKD women had a lower risk of GC than the non-CKD women did. After adjusting for confounders (menopause was excluded), the CKD women had a lower risk of GC than the non-CKD women did (adjusted HR1 0.55, 95% CI 0.37–0.81, \( P < .01 \) and adjusted HR2 0.38, 95% CI 0.26–0.55, \( P < .001 \)). We further adjusted the confounder-menopause; results showed that the CKD women still had a significantly lower risk of GC than the non-CKD women did (adjusted HR2 0.64, 95% CI 0.44–0.95, \( P < .05 \) and adjusted HR4 0.44, 95% CI 0.30–0.65, \( P < .001 \)) (Table 2).

In an effort to clarify the role of age in the relationship between CKD and GC, we performed subgroup analysis based on age, using 5 age groups (those <40, 40–49, 50–59, 60–69, and \( \geq 70 \) years, respectively). It is surprising for us to find that the GC IR in the CKD women was relatively stable without a significant difference between each age group. The GC IR in the CKD women was around 8 to 12 per 10,000 person-years in all age groups with a mean IR of 10.46 per 10,000 person-years [standard deviation (SD) 1.93], which was ranged from 9.15 per 10,000 person-years at age <40 years to 10.25 at age \( \geq 70 \) years (Table 3). Using the youngest group (women <40 years) as the reference, the HRs (95% CI) of the CKD women aged 40 to 49, 50 to 59, 60 to 69, and \( \geq 70 \) years were 0.94 (95% CI 0.27–3.35), 1.48 (95% CI 0.48–4.54), 1.47 (95% CI 0.49–4.40), and 1.21 (95% CI 0.34–4.34), respectively, in the crude model (\( P = .8429 \)).

After adjusting for confounders (menopause was excluded), the adjusted HR1s (HR1s) of the CKD women aged 40 to 49, 50 to 59, 60 to 69, and \( \geq 70 \) years were 1.13 (0.68), 2.09 (0.98), 2.26 (0.95), and 1.83 (0.81), respectively (no statistically significant difference for all). After adjusting for confounders and menopausal status, the GC IR in the CKD women at older age was not significantly changed compared with that in those aged <40 years (adjusted HR2 and HR4 0.80 and 0.53 at age between 40 and 49 years; adjusted HR2 and HR4 1.40 and 0.80 at age between 50 ad 59 years; adjusted HR2 and HR4 1.75 and 0.86 at age between 60 and 69 years; and adjusted HR2 and HR4 1.79 and 0.89 at age \( \geq 70 \) years, respectively). All analyses revealed that the GC IR in the CKD women was relatively similar, regardless of what age group was analyzed, suggesting that the GC IR in the CKD women was independent of age (Table 3).

Contrast to noncorrelation between the risk of GC and age in the CKD women, the risk of GC in the non-CKD women showed a positive correlation with age. For non-CKD women, the GC IR was apparently increased when the age was increasing (at least a 3-fold increase in older population compared with the youngest population). The lowest GC IR was 9.18 per 10,000 person-years in the non-CKD women aged <40 years, and the highest GC IR was 31.62 per 10,000 person-years at age \( \geq 70 \) years (Table 4), suggesting that age was the most important and independent risk factor for the development of GC in the non-CKD women.

Because of the constant risk of GC in the CKD women, regardless of younger or older age, and a progressive and continuous increase of GC IR in the non-CKD women with advanced age, contributing to the lower risk of GC in the CKD women compared to the non-CKD women. The crude HRs were ranged from 0.86 to 0.33 at the different age groups (Table 4). The trend of a lowering risk of GC in the CKD women was relatively positive correlation with advanced age, even after adjusting for confounders (menopause was excluded or included). The adjusted HR1s were ranged from 0.54 to 0.34, and the adjusted HR3 were ranged from 0.22 to 0.31 at the different age groups, respectively. The lower risk of GC could be found initially in the CKD women with age \( \geq 50 \) years (the adjusted HR3 0.45, 95% CI 0.22–0.94, \( P < .05 \), at the age between 50 and 59 years), and the most apparently lowest risk of GC in the CKD women was found at age \( \geq 70 \) years, with the crude HR of 0.33 (95% CI 0.13–0.83, \( P < .05 \)), the adjusted HR1 of 0.34 (95% CI 0.13–0.88, \( P < .05 \)), the adjusted HR2 0.37 (95% CI 0.14–0.96, \( P < .05 \)), the adjusted HR3 0.31 (95% CI 0.12–0.79, \( P < .05 \)), and the adjusted HR4 0.32 (95% CI 0.13–0.84), suggesting that age is the most important factor contributing to the risk estimation in the current study (Table 4).
| Variable | Total (n = 6090) | CKD (n = 3045) | Controls (n = 3045) | P |
|----------|-----------------|----------------|---------------------|---|
|          |     N    |    %   |     n     |    %    |     n     |    %    |   |
| Person-years |     84556 |       |     42655 |       |     41901 |       |   |
| **Target (All)** |        |    .0031 |          |     |          |     |   |
| Gyn Ca | 127 | 2.09 | 47 | 1.54 | 80 | 2.63 |   |
| No Gyn Ca | 5963 | 97.91 | 2998 | 98.46 | 2965 | 97.37 |   |
| **Target** |        |    .0894 |          |     |          |     |   |
| Cx Ca | 79 | 1.30 | 32 | 1.05 | 47 | 1.54 |   |
| No Cx Ca | 6011 | 98.70 | 3013 | 98.96 | 2998 | 98.46 |   |
| **Target** |        |    .0051 |          |     |          |     |   |
| Ut Ca | 37 | 0.61 | 10 | 0.33 | 27 | 0.89 |   |
| No Ut Ca | 6053 | 99.39 | 3035 | 99.67 | 3018 | 99.11 |   |
| **Target** |        |    .0452 |          |     |          |     |   |
| EOC/TC | 16 | 0.26 | 4 | 0.13 | 12 | 0.39 |   |
| No EOC/TC | 6074 | 99.74 | 3041 | 99.87 | 3032 | 99.61 |   |
| **Target** |        |    .5636 |          |     |          |     |   |
| PPSC | 3 | 0.05 | 2 | 0.07 | 1 | 0.03 |   |
| No PPSC | 6087 | 99.95 | 3043 | 99.93 | 3044 | 99.97 |   |
| **Target** |        |    .1077 |          |     |          |     |   |
| EOC/TC/PPSC | 19 | 0.31 | 6 | 0.20 | 13 | 0.43 |   |
| No EOC/TC/PPSC | 6071 | 99.69 | 3039 | 99.80 | 3032 | 99.57 |   |
| **Target** |        |    .1894 |          |     |          |     |   |
| BC | 116 | 1.90 | 51 | 1.67 | 65 | 2.13 |   |
| No BC | 5974 | 98.10 | 2994 | 98.33 | 2980 | 97.87 |   |
| **Age** |        |    .8375 |          |     |          |     |   |
| <58 | 3102 | 50.94 | 1547 | 50.80 | 1555 | 51.07 |   |
| >58 | 2988 | 49.06 | 1498 | 49.20 | 1490 | 48.93 |   |
| **SES** |        |    .9884 |          |     |          |     |   |
| ≥ 40,000 | 172 | 2.82 | 88 | 2.89 | 84 | 2.76 |   |
| 20,000–39,999 | 736 | 12.09 | 369 | 12.12 | 367 | 12.05 |   |
| < 20,000 | 2812 | 46.17 | 1407 | 46.21 | 1405 | 46.14 |   |
| Others | 2370 | 38.92 | 1181 | 38.78 | 1189 | 39.05 |   |
| **Work** |        | 1     |          |     |          |     |   |
| Yes | 4842 | 79.51 | 2421 | 79.51 | 2421 | 79.51 |   |
| No | 1248 | 20.49 | 624 | 20.49 | 624 | 20.49 |   |
| **Urbanization** |        | .9995 |          |     |          |     |   |
| Urban | 1553 | 25.50 | 776 | 25.48 | 777 | 25.52 |   |
| Suburban | 2471 | 40.57 | 1236 | 40.59 | 1235 | 40.56 |   |
| Rural | 2066 | 33.92 | 1033 | 33.92 | 1033 | 33.92 |   |
| **PID** |        | <.0001 |          |     |          |     |   |
| Yes | 2490 | 40.89 | 1064 | 34.94 | 1426 | 46.83 |   |
| No | 3600 | 59.11 | 1981 | 65.06 | 1619 | 53.17 |   |
| **Infertility** |        | .8270 |          |     |          |     |   |
| Yes | 21 | 0.34 | 11 | 0.36 | 10 | 0.33 |   |
| No | 6069 | 99.66 | 3034 | 99.64 | 3035 | 99.67 |   |
| **Menopause** |        | <.0001 |          |     |          |     |   |
| Yes | 1982 | 32.55 | 764 | 25.09 | 1218 | 40.00 |   |
| No | 4108 | 67.45 | 2281 | 74.91 | 1827 | 60.00 |   |
| **CVD** |        | <.0001 |          |     |          |     |   |
| Yes | 3124 | 51.30 | 1985 | 65.19 | 1139 | 37.41 |   |
| No | 2966 | 48.70 | 1060 | 34.81 | 1906 | 62.59 |   |
| **DM** |        | <.0001 |          |     |          |     |   |
| Yes | 2679 | 43.99 | 1765 | 57.96 | 914 | 30.02 |   |
| No | 3411 | 56.01 | 1280 | 42.04 | 2131 | 69.98 |   |
| **CLD** |        | .0178 |          |     |          |     |   |
| Yes | 423 | 6.95 | 235 | 7.72 | 188 | 6.17 |   |
| No | 5667 | 93.05 | 2810 | 92.28 | 2857 | 93.83 |   |
| **RD** |        | .9649 |          |     |          |     |   |
| Yes | 569 | 9.34 | 285 | 9.36 | 284 | 9.33 |   |
| No | 5521 | 90.66 | 2760 | 90.64 | 2761 | 90.67 |   |
| **CCI** |        | <.0001 |          |     |          |     |   |
| 0 | 919 | 15.09 | 192 | 6.31 | 727 | 23.88 |   |
| 1 | 888 | 14.58 | 306 | 10.05 | 582 | 19.11 |   |
| 2 | 978 | 16.06 | 434 | 14.25 | 544 | 17.87 |   |
| 3 | 3305 | 54.27 | 2113 | 69.39 | 1192 | 39.15 |   |

BC = breast cancer, CCI = Charlson Comorbidity Index score, CKD = chronic kidney disease, CLD = chronic liver disease, CVD = cardiovascular disease, Cx Ca = cervical cancer, DM = diabetes mellitus, EOC = epithelial ovarian cancer, Gyn Ca = female genital tract-related (gynecological) cancers, PID = pelvic inflammatory disease, PPSC = primary peritoneal serous carcinoma, RD = rheumatic disease, SES = socioeconomic status, TC = Fallopian tube cancer, Ut Ca = uterine cancer.

*Age variable was matched by the exact year of age, but the table shows age quartile groups. The median age of women with and without CKD was 58 and 58 years, respectively (P = .9158).*
Finally, to evaluate the duration before the patients in this cohort would develop GC, the time interval between enrollment in each cohort and the diagnosis of newly developing GC (exposure time or surveillance time) was calculated. The median time for all women with GC was 3.24 (range 0–18.00) years (Table 5). The median time of the women with CKD was 6.17 (range 0–15.12) years in the non-CKD women, which reached a statistically significant difference (P < .0001). In addition, the median age of CKD and non-CKD women was diagnosed with GCs was 58 (range 33–83) and 63 years (range 35–82 years), respectively, although it did not reach a statistically significant difference (P = .0773).

4. Discussion

Our study indicated that the women with CKD had a lower risk of female genital tract related cancer (GC) than the non-CKDs women did (crude HR 0.57, 95% CI 0.39–0.81, P < .01). To further clarify which one contributed to this finding, we compared the rate of each cancer between women with and without CKD. We found that all the following cancers, including cervical cancer (1.05% vs 1.54%), uterine cancer (0.33 vs 0.89%), EOC/TC (0.13% vs 0.39%), EOC/TC/PPSC (0.20% vs 0.43%), and BC (1.67% vs 2.13%) occurred at the lower rate in the CKD women than those in the non-CKD women (Table 1). Only the rate of PPSC was higher in the non-CKD women than that in the women with CKD (0.07% vs 0.03%). This is an unexpected finding, as many studies suggested that cancer risk would be increased in the CKD patients. The further surprising finding was that our study showed a negative association between CKD and GC.

In 1999, Maisonneuve et al. assembled a cohort of 831,804 patients, including men and women who received dialysis in the USA, Europe, Australia, and New Zealand, and found a higher risk of cancer in patients with CKD [relative risk (RR) 1.18, 95% CI 1.17–1.20]. The authors found that the excess of cancer varied in the different areas, ranging from the highest RR of 1.8 (95% CI 1.7–2.0) in Australia and New Zealand to the lowest RR of 1.1 (95% CI 1.0–1.1) in Europe. In addition, significantly

| Table 2 |
| --- |
| Incidence and crude and adjusted risk of genital organ-related gynecological cancers (GC), according to chronic kidney disease (CKD) status. |
| Patients with CKD | Controls |
| --- | --- |
| Number of patients with GC | 47 | 80 |
| Incidence per 10,000 person-years | 11.02 | 19.09 |
| Crude HR (95% CI) | 0.565 (0.393–0.812) | 1.00 |
| Ad HR1 (95% CI) | 0.550 (0.374–0.810) | 1.00 |
| Ad HR2 (95% CI) | 0.642 (0.435–0.946) | 1.00 |
| Ad HR3 (95% CI) | 0.377 (0.259–0.547) | 1.00 |
| Ad HR4 (95% CI) | 0.444 (0.303–0.665) | 1.00 |

95% CI = 95% confidence interval, Ad HR1 = After adjustment of pelvic inflammatory diseases, infertility, cardiovascular disease, diabetes mellitus, chronic liver disease, and rheumatoid arthritis, we obtained the adjusted HR1 (Ad HR1), Ad HR2 = After adjustment of pelvic inflammatory diseases, infertility, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatoid arthritis, and menopausal status, we obtained the adjusted HR2 (Ad HR2), Ad HR3 = After adjustment of pelvic inflammatory diseases, infertility, Cardiovascular Comorbidity Index score, we obtained the adjusted HR3 (Ad HR3), Ad HR4 = After adjustment of pelvic inflammatory diseases, infertility, menopause, and Charlson Comorbidity Index score, we obtained the adjusted HR4 (Ad HR4), CI = confidence interval.

To further evaluate the reason of lower risk of GC in the women with CKD, we evaluated the age and surveillance time between enrollment in the cohort, and at the end of last follow-up, we found that age was similar between 2 groups (Table 6). However, there was statistically significant difference of surveillance time between 2 groups (4.01 ± 5.12 vs 13.76 ± 5.27 years, P < .0001), although there may be no clinical significance (the difference of surveillance time in 2 groups was less than 4 months).

Taken together, these data suggested that the women with CKD in Taiwan seemed to have a lower risk of the development of female genital-tract related cancers.

| Table 3 |
| --- |
| An increased risk of genital organ-related gynecological cancer (GC) in women with chronic kidney disease (CKD) with age. |
| Age | <40 y | 40–49 y | 50–59 y | 60–69 y | ≥70 y | P* |
| --- | --- | --- | --- | --- | --- | --- |
| R | 9.151 | 8.095 | 12.523 | 12.287 | 10.246 | 1.00 |
| C HR | 1.00 (Ref) | 0.94 (0.27–3.35) | 1.48 (0.484–4.54) | 1.47 (0.49–4.40) | 1.21 (0.34–4.34) | .8429 |
| P* | .9255 | 0.4901 | 0.4931 | 0.7663 | 0.5000 |
| Ad HR1 | 1.00 (Ref) | 1.13 (0.32–4.08) | 2.09 (0.66–6.61) | 2.26 (0.71–7.23) | 1.83 (0.48–6.99) | .5463 |
| P* | .8470 | 2.115 | .1678 | 3.754 | 5.0000 |
| Ad HR2 | 1.00 (Ref) | 0.80 (0.22–2.90) | 1.40 (0.44–4.43) | 1.75 (0.55–5.55) | 1.79 (0.47–6.78) | .3949 |
| P* | .7381 | 5.704 | .3418 | 3.949 | 5.0000 |
| Ad HR3 | 1.00 (Ref) | 0.68 (0.19–2.44) | 0.98 (0.31–3.12) | 0.95 (0.30–3.03) | 0.81 (0.21–3.08) | .9529 |
| P* | .5490 | 9.739 | 9.528 | 7.554 | 9.0000 |
| Ad HR4 | 1.00 (Ref) | 0.55 (0.15–1.90) | 0.80 (0.26–2.54) | 0.86 (0.27–2.74) | 0.89 (0.23–3.42) | .8610 |
| P* | .3264 | 0.7041 | 8.002 | 8.672 | 8.672 |

Data are presented as HR and (95% confidence interval). 95% CI = 95% confidence interval, Ad HR1 = After adjustment of pelvic inflammatory diseases, infertility, cardiovascular disease, diabetes mellitus, chronic liver disease, and rheumatoid arthritis, we obtained the adjusted HR1 (Ad HR1), Ad HR2 = After adjustment of pelvic inflammatory diseases, infertility, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatoid arthritis, and menopausal status, we obtained the adjusted HR2 (Ad HR2), Ad HR3 = After adjustment of pelvic inflammatory diseases, infertility, and Charlson Comorbidity Index score, we obtained the adjusted HR3 (Ad HR3), Ad HR4 = After adjustment of pelvic inflammatory diseases, infertility, menopause, and Charlson Comorbidity Index score, we obtained the adjusted HR4 (Ad HR4), CI = confidence interval, IR = incidence rate (per 10,000 person-years), Ref = reference.

* P comparison among all groups.
* P comparison between study group and reference group (age <40 years).
increased cancer risks were seen in younger patients (RR 3.68, 95% CI 3.39–3.99), and for several sites of cancer, including the well-known kidney and urinary bladder and lower genital tract in women.\cite{1,11} Maisonneuve et al.\cite{23} supposed that those excess cancers appeared in the CKD patients could be explained by several reasons, such as the presence of chronic infection, especially in the urinary tract; a weaken immune system; a few deficiencies; altered DNA repair; and the underlying cancer, which might predispose to cancer. Patients with CKD are often stated in the immunosuppressive status.\cite{2,12,13}

The CKD women might impair the ability to eradicate human papilloma virus (HPV) infection when they got infected. In addition, these CKD women subsequently may have a prolonged latency of HPV infection or persistent HPV infection, which is a key factor for the development of cervical pre-cancer lesions and cancers in women.\cite{30,34,35,36,37,38} Furthermore, some studies showed that the CKD women were substantially less likely to undergo cervical cancer screening compared with women without CKD.\cite{21,22} Both provided a good reason to explain the increased risk of cervical cancer in the CKD women with CKD.\cite{23}

However, the value of cervical cancer screening for women with CKD is still debated. One study suggested that routine cancer screening in the population with CKD is a relatively inefficient allocation of financial resources, because the net gain in life expectancy from a typical cancer screening program was calculated to be 5 days or less and the gain of survival could be obtained via a reduction of 0.02% or less in the baseline CKD-related mortality rate.\cite{42,43} In the current study, we did not find the increased risk of GC in the younger group (Table 4). By contrast, we found that the GC risk was similar in these younger women (<40 years), regardless of women with or without CKD. In addition, we did not find that women with CKD had an increased risk of the development of cervical cancer compared with those without CKD did (Table 1). The possible reason was that the CKD women are often hospitalized and frequently visited their hospitalization or hospital stay. It may be much more apparent in Taiwan due to convenience of medical care under the government’s support (NHI).

In term of risk of EOC/TC, there are a lot factors relating to the risk of EOC/TC, including genetic background, parity, the use of oral pills, hysterectomy, endometriosis, and PID.\cite{30,39,40,41} The diagnosis of EOC/TC is often difficult and always delayed, contributing to more than two-thirds of cases of EOC/TC diagnosed when the disease has progressed to stage III or IV and involves the peritoneal cavity or other organs.\cite{50,51,52} To overcome...
the above-mentioned limitation, many researchers attempted to make an early diagnosis of EOC/TC and decrease the EOC/TC-related morbidity or mortality using the different kinds of strategies[13–57]; however, results are relatively disappointing.[13–55] Ovarian cancer screening did not reduce all-cause mortality (RR 1.0, 95% CI 0.96–1.06), EOC-specific mortality (RR 1.08, 95% CI 0.84–1.38), or risk of diagnosis at FIGO stages III and IV (RR 0.86, 95% CI 0.68–1.11).[155] Furthermore, the screening resulted in a significantly increased cancer-specific distress in women with false-positive results and surgery was associated with severe complications in 6% of women (95% CI 1–11).[155] The 2012 U.S. Preventive Services Task Force recommended against screening for ovarian cancer in women.[154] In the current study, we found that the women with CKD had a lower risk of EOC/TC than the non-CKD women (IR 0.94 per 10,000 person-years in the CKD women vs IR 2.86 per 10,000 person-years in the non-CKD women), contributing to the crude HR of 0.33 (95% CI 0.11–1.00) and adjusted HR3 and adjusted HR4 of 0.20 (95% CI 0.06–0.63, P < .01), and 0.20 (95% CI 0.06–0.66, P < .01), respectively (Supplement Table 1, http://links.lww.com/MD/C164).

There are a number of plausible explanations. First, the lifetime risk of EOC is approximately 1.4%, but two-thirds of cases of EOC are diagnosed in women at age ≥55 years.[13–55] As summarized in the Tables 3 and 4 of the current study, GC IR of women with CKD was relatively constant, regardless of age status, but that of women without CKD was continuously increased when the age was increasing. For EOC/TC IR, this finding was also present. The IRs of EOC in the women with CKD aged <40, 40 to 49, 50 to 59, 60 to 69, and ≥70 years were 0, 0, 1.79, 0.72, and 1.7, respectively, and the mean of these IRs (0.84 per 10,000 persons) was consistent to age-standardized IR (SIR) of EOC in the general population in Taiwan.[158] In our previous nationwide population-based studies for the study of risk of EOC in the certain population, such as endometriosis or others,[15,59–61] IRs of EOC in the controls ranged from 0.77 to 0.89, which were very much similar to age-SIR in Taiwan and also consistent with the reports from the world.[15–57] By contrast, IRs of EOC in the non-CKD women were 2.30, 2.71, 3.61, 1.49, and 5.28 with a mean of at the age <40, 40 to 49, 50 to 59, 60 to 69, and ≥70 years, respectively (Supplement Table 2, http://links.lww.com/MD/C164), which were significantly higher than the age-SIR of EOC/TC in the general population (0.7–0.9 per 10,000 person-years), contributing to the underestimated risk of EOC/TC in the women with CKD.

Furthermore, the highest risk of EOC/TC in the general population occurred at the age between 50 and 59 years with IR of 2.9 per 10,000 person-years; however, the EOC/TCIR was 1.8 per 10,000 person-years of women aged ≥70 years in the general population,[158] which is also less than that of the non-CKD women aged ≥70 years in the current study. This may further underestimate risk of EOC/TC in the CKD women in the current study.

Moreover, as summarized in Table 5, we found that surveillance time between enrollment in the cohort and the diagnosis of GC was significantly shorter in the non-CKD women (controls), which supported that the above-mentioned explanation that women with CKD highly possibly had increasing opportunities to offer other medical service, including gynecologist’s consultation or examination during their hospitalization or hospital stay.

In addition, we did not evaluate reproductive and hormonal-related factors, such as parity, and the use of combined oral contraceptives or many medical therapies, which might be important to the development of EOC/TC in women. Furthermore, the study population, including our study, might be not totally reflective of the general population. For example, recent studies used control data from 4 population-based studies to investigate the lifetime risk of EOC/TC after analyzing the joint distribution of risk/protective factor profiles and the results showed the lifetime risk estimates ranging from 0.35 to 8.78,[62,63] which is different from 1.4% of the general population as shown above.[156] In the current study, we found that the CKD women belonged to the low SES. In order to match this, we found that our studied subjects for controls were stayed in the low SES, and these controls were significantly different from those in the other nationwide, population-based studies in Taiwan.[13,64–67] As expected, much comorbidity is associated with the women with CKD. In fact, some is the cause of CKD, such as DM as the first leading cause, and chronic glomerulonephritis and CVD as followings in Taiwan.[68–70] Therefore, these factors should be adjusted for the estimation of the risk of GC in the certain population. Except Pd, menopause, and RD, we found that the CKD women had a higher rate of these unfavorable comorbidities, including DM, CVD, and CLD than the non-CKD women did. We further adjusted these confounders to estimate the risk of GCs in the CKD women. Consistent with the results in the crude model, the CKD women still had a lower risk of GCs than the non-CKD women did.

Besides comorbidity, age is a very important factor, relating to many acute and chronic diseases, including GCs. Our study further confirmed the important role of age for GC in the controls. The GC IR was lowest in the youngest non-CKD women (age <40 years), but the dramatic increase in the non-CKD women aged ≥50 years. However, this trend for increasing GC IR was not found in the CKD women. This may be most plausible reason to explain our finding that the most apparently lowest risk of GC in the CKD women was noted at age ≥70 years than that in the non-CKD women at the same age group, and this significantly decreased risk of GC in the CKD women became obvious when these women were ≥50 years of age, suggesting that 50 years age of the women might be an important checking point (the need of cancer screening) associated with the development of GC.

The most important strength of the current study was unlikely to the well-known higher rate of upper tract urothelial carcinoma in the CKD women in the world, including Taiwan,[6,16,20–26,69] and it might be the first nationwide, population-based study to investigate the risk of GC in the CKD women in Asia. In addition, using this national population-based study, we further confirmed that GC is an age-dependent disease. Third, the prevalence of GC is relatively stable in the CKD women. Fourth, the CKD women belonged the low social-economic status compared with those in the general population, needing our attention. This study had some limitations. First, we did not classify the CKD by GFR. Second, we did not evaluate the effect of medication or reproductive factors, which may influence the risk estimation.

In conclusion, it is surprising to find that the CKD women had a lower risk of GC during the following-up period than the non-CKD women did, especially for those women were older than 50 years, although the risk might be underestimated. A further study is worthy of testing our findings.

**Author contributions**

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