Observational Study

Medicine®

OPEN

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

Wen-Hsun Chang, BS, MPH[a,b,g], Huann-Cheng Horng, MD[a,f], Chang-Ching Yeh, MD[a,f], Chao-Yu Guo, PhD[h], Yiing-Jeng Chou, MD, PhD[h], Nicole Huang, PhD[h], Hsin-Yi Huang, BS, MPH[c], Yi-Jen Chen, MD, PhD[a,f], Wen-Ling Lee, MD, PhD[d,e,g], Peng-Hui Wang, MD, PhD[a,f,g,i,*]

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, ICD9-CM = international classification of diseases, ninth revision, and clinical modifications, IR = incidence rate, LHID = longitudinal health insurance database, NHI = national health insurance, NHIRD = 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

Editor: Meixia Lu.

W-LL and P-HW contributed equally to this article.

This study is based in part on data from the NHI Research Database provided by the Bureau of NHI, Department of Health and managed by the National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the respective institutions or agencies.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

The corresponding authors have the right to grant and do grant on behalf of all authors a worldwide license to the Publishers and its licensees in perpetuity. The authors have no funding and conflicts of interest to disclose.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

[a] Department of Obstetrics and Gynecology, [b] Department of Nursing, [c] Biostatics Task Force, Taipei Veterans General Hospital, [d] Department of Nursing, Oriental Institute of Technology, New Taipei City, [e] Department of Medicine, Cheng-Hsin General Hospital, Taipei, [f] Department of Obstetrics and Gynecology, [g] Department of Nursing, [h] Institute of Hospital and Health Care Administration and Institute of Public Health, Taipei, National Yang-Ming University, [i] Department of Medical Research, China Medical University Hospital, Taichung, Taiwan.

[*] Correspondence: Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital and National Yang-Ming University, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan (e-mails: phwang@vghtpe.gov.tw, phwang@ym.edu.tw, pongpongwang@gmail.com).

Medicine (2018) 97:12(e0157)

Received: 24 November 2017 / Received in final form: 10 February 2018 / Accepted: 23 February 2018

http://dx.doi.org/10.1097/MD.0000000000010157

1. Introduction

Cancers are a major cause of death among the general population.[1] In Taiwan, cancer has become the most common cause of death since 1982.[2–5] 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 m^2] 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 heath 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,[6,11,20–31] 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 (23 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 this health insurance system.[32–37] The accuracy of diagnosis in the NIRD has been validated for several diseases, including stroke and CKD.[37–39]

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 obstetric/gynecological 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 χ^2 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).

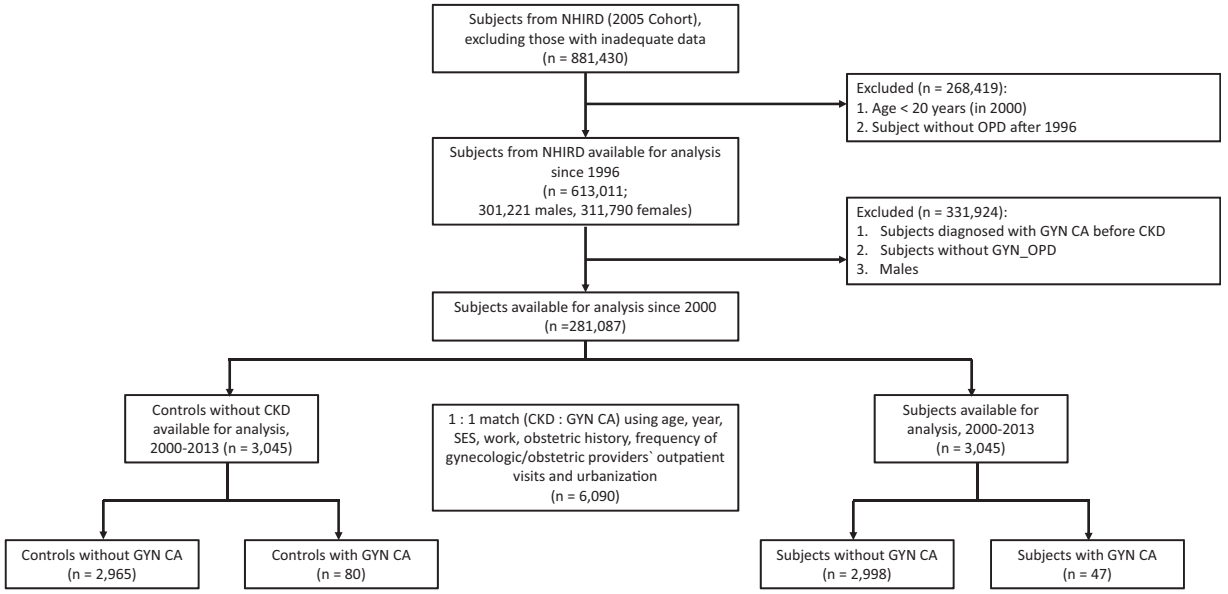

Figure 1. Cohort flow chart illustrating the inclusion and exclusion criteria of participants in the study.

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 HR3 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 ≥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 ≥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 ≥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 (HR3s) of the CKD women aged 40 to 49, 50 to 59, 60 to 69, and ≥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 ≥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 elder 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 ≥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 (menopuase 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 ≥ 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 ≥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).

Table 1

Baseline characteristics of the study subjects.

	Total (n = 6090)		CKD (n = 3045)		Controls (n = 3045)		
Person-years	**84556**		**42655**		**41901**		
Variable	**N**	**%**	**n**	**%**	**n**	**%**	***P***
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	98.95	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	3033	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 ($P = .9158$).

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 (n = 3045)	Controls (n = 3045)
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 (0.303–0.650)‡	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, 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), CKD = chronic kidney disease, GC = genital organ-related gynecological cancer, HR = hazard ratio.

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

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 0.14–18.00) years, compared with 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 ($P = .0773$).

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 (14.01 ± 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.

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% v. 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.[7–12,21–31] The further surprising finding was that our study showed a negative association between CKD and GC.

In 1999, Maisonneuve et al[28] 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.[28] In addition, significantly

Table 3

An increased risk of genital organ-related gynecological cancer (GC) in women with chronic kidney disease (CKD) with age.

Age	<40 y n = 4	40–49 y n = 6	50–59 y n = 14	60–69 y n = 17	≥70 y n = 6	P*
IR	9.151	8.095	12.523	12.287	10.246	
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	.4901	.4931	.7663	
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)	.5000
P†		.8470	.2115	.1678	.3754	
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 (0.47–6.79)	.5463
P†		.7381	.5704	.3418	.3949	
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	.9739	.9328	.7554	
Ad HR4	1.00 (Ref)	0.53 (0.15–1.90)	0.80 (0.25–2.54)	0.86 (0.27–2.74)	0.89 (0.23–3.42)	.8610
P†		.3264	.7041	.8002	.8672	

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), C HR = crude HR, HR = hazard ratio, IR = incidence rate (incidence per 10,000 person-years), Ref = reference.

* *P*: comparison among all groups.

† *P*: comparison between study group and reference group (age <40 years).

Table 4

Incidence and crude and adjusted risk of genital organ-related gynecological cancer (GC), according to age.

	Age <40 y (n=607)		Age 40–49 y (n=1052)		Age 50–59 y (n=1587)		Age 60–69 y (n=1873)		Age ≥70 y (n=971)	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
GC										
Yes	4	4	6	8	14	19	17	31	6	18
No	299	300	519	519	777	777	924	901	479	468
IR	9.151	9.184	8.095	10.835	12.523	17.169	12.287	23.113	10.246	31.672
Crude HR (95% CI)	0.862 (0.210–3.537)	1.00	0.751 (0.261–2.166)	1.00	0.735 (0.369–1.466)	1.00	0.510 (0.280–0.929)*	1.00	0.328 (0.130–0.826)*	1.00
Adjusted HR1 (95% CI)	0.543 (0.110–2.673)	1.00	1.021 (0.317–3.284)	1.00	0.806 (0.375–1.733)	1.00	0.575 (0.303–1.089)	1.00	0.336 (0.129–0.878)*	1.00
Adjusted HR2 (95% CI)	0.481 (0.092–2.513)	1.00	1.195 (0.369–3.867)	1.00	0.894 (0.415–1.927)	1.00	0.700 (0.367–1.335)	1.00	0.364 (0.138–0.956)*	1.00
Adjusted HR3 (95% CI)	0.217 (0.048–0.987)*	1.00	0.305 (0.095–0.980)*	1.00	0.449 (0.216–0.935)*	1.00	0.424 (0.226–0.795)†	1.00	0.308 (0.120–0.787)*	1.00
Adjusted HR4 (95% CI)	0.237 (0.054–1.053)	1.00	0.385 (0.120–1.239)	1.00	0.523 (0.245–1.117)	1.00	0.533 (0.280–1.017)	1.00	0.323 (0.125–0.835)*	1.00

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), C HR = crude HR, HR = hazard ratio, IR = incidence rate (incidence per 10,000 person-years), Ref = reference.

* *P*: comparison among all groups.

† *P*: comparison between study group and reference group (age <40 y).

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.[28] Maisonneuve et al[28] 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 previous treatment with immunosuppressive or cytotoxic drugs; nutritional deficiencies; altered DNA repair; and the underlying disease, such as DM or acquired renal cystic disease, which might predispose to cancer. Patients with CKD are often stated in the immunosuppressive status.[6–11,27] The CKD women might impair the ability to eradicate human papilloma virus (HPV) infection when they got infection. 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.[40–42] Furthermore, some studies showed that the CKD women were substantially less likely to undergo cervical cancer screening compared with women without CKD.[21,22] Both provided a good reason to explain the finding of an increased risk of cervical cancer in the CKD women with CKD.[28]

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.[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 to hospital for dialysis, which may make women to have a higher recommendation to receive cervical cancer screening, resulting in increasing opportunities to offer cervical cancer screening during 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.[44–49] 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.[50–52] To overcome

Table 5

Age and surveillance time between enrollment in the cohort and the diagnosis of gynecological cancers (GC).

GC	Total (n=127)	CKD (n=47)	Controls (n=80)	*P*
Age, y				
Mean±SD	59.9±10.9	57.6±11.0	61.2±10.7	.0773
Median (Min-Max)	61 (33–83)	58 (33–83)	63 (35–82)	
Interval, y				
Mean±SD	4.63±4.97	7.39±4.97	3.01±4.22	<.0001
Median (Min-Max)	3.24 (0–18.00)	6.17 (0.14–18.00)	0.17 (0–15.12)	

Age = age at the diagnosis of female genital tract-related cancer (gynecological cancers: GC), Interval = interval between enrollment in the cohort and the diagnosis of female genital tract-related cancer, Max = maximum, Min = minimum, SD = standard deviation.

Table 6

Age and surveillance time between enrollment in the cohort and the end of last follow-up.

All women	Total (n=6090)	CKD (n=3045)	Controls (n=3045)	*P*
Age, y				
Mean±SD	57.0±12.8	57.1±12.8	57.1±12.8	.9165
Median (Min-Max)	58 (16–93)	58 (16–93)	58 (16–93)	
Interval, y				
Mean±SD	13.88±5.19	14.01±5.12	13.76±5.27	<.0001
Median (Min-Max)	16.55 (0–18.11)	16.59 (0.03–18.11)	16.53 (0–18.00)	

Age = age at the time of enrolment, Interval = interval between enrollment in the cohort and the end of the last follow-up, Max = maximum, Min = minimum, SD = standard deviation.

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[53–57]; however, results are relatively disappointing.[53–55] 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).[55] 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).[55] The 2012 U.S. Preventive Services Task Force recommended against screening for ovarian cancer in women.[54] 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.[53–58] 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/TC 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.[58] In our previous nationwide population-based studies for the study of risk of EOC in the certain population, such as endometriosis or others,[13,59–61] 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.[53–57] 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/TC IR was 1.8 per 10,000 person-years of women aged ≥70 years in the general population,[58] 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.[56] 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 CKD in the certain population. Except PID, 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 risk 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

Conceptualization: P.-H. Wang.
Data curation: P.-H. Wang, H.-C. Horng, C.-C. Yeh.

Formal analysis: H.-C. Horng, W.-H. Chang, W.-L. Lee.
Funding acquisition: P.-H. Wang, C.-Y. Guo, Y.-J. Chou, N. Huang.
Investigation: P.-H. Wang, H.-C. Horng, W.-H. Chang.
Methodology: P.-H. Wang, W.-H. Chang, C.-Y. Guo, N. Huang, H.-Y. Huang, Y.-J. Chen.
Project administration: P.-H. Wang, W.-H. Chang.
Resources: Y.-J. Chou.
Software: W.-H. Chang.
Supervision: P.-H. Wang.
Validation: P.-H. Wang.
Writing – original draft: P.-H. Wang, H.-C. Horng, C.-C. Yeh, W.-L. Lee.
Writing – review & editing: P.-H. Wang, W.-L. Lee.

Acknowledgments

We thank the Medical Science & Technology Building of Taipei Veterans General Hospital for providing experimental space and facilities. We appreciate the help from the Task Force on Endometriosis-related Health Problems in the cooperation program of the National Yang-Ming University and Taipei Veterans General Hospital. This study is partly supported by grants from the Ministry of Science and Technology, Executive Yuan (MOST 106-2314-B-075-061-MY3), and Taipei Veterans General Hospital (V106C-129; V106D23-001-MY2-1; V106A-012; V107C-136; and V107A-022).

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[2] Lee YS, Hsu CC, Weng SF, et al. Cancer incidence in physicians: a Taiwan national population-based cohort study. Medicine (Baltimore) 2015;94:e2079.
[3] Wang PH, Yen MS, Chao KC, et al. Outstanding female cancer research paper awards of the 2015 Taiwan Association of Obstetrics and Gynecology and Hsu Chien-Tien Cancer Foundation. Taiwan J Obstet Gynecol 2016;55:757–9.
[4] Wang PH, Chen CP, Kuo TC. Outstanding female cancer research paper awards of the 2016 Taiwanese Association of Obstetrics and Gynecology and Hsu Chien Cancer Foundation. Taiwan J Obstet Gynecol 2017; 56:581–2.
[5] Wang PH, Chen CP, Kuo TC. Outstanding female cancer research paper awards of the Taiwanese Association of Obstetrics and Gynecology. Taiwan J Obstet Gynecol 2018;57:179–80.
[6] Tanaka A, Inaguma D, Watanabe Y, et al. Relationship between mortality and cancer-bearing status in patients with chronic kidney disease who attended an educational program. Ther Apher Dial 2018; 22:49–57.
[7] Pisano A, Cernaro V, Gembillo G, et al. Xanthine oxidase inhibitors for improving renal function in chronic kidney disease patients: an updated systematic review and meta-analysis. Int J Mol Sci 2017;18: E2283.
[8] Vart P, van Zon SKR, Gansevoort RT, et al. SES, chronic kidney disease, and race in the U.S.: a systematic review and meta-analysis. Am J Prev Med 2017;53:730–9.
[9] Bae E, Cha RH, Kim YC, et al. Circulating TNF receptors predict cardiovascular disease in patients with chronic kidney disease. Medicine (Baltimore) 2017;96:e6666.
[10] Cheng Z, Limbu MH, Wang Z, et al. MMP-2 and 9 in chronic kidney disease. Int J Mol Sci 2017;18:pii: E776.
[11] Tanaka A, Inaguma D, Shinjo H, et al. Relationship between mortality and cancer-bearing status at time of dialysis initiation. Ther Apher Dial 2017;21:345–53.
[12] Parrish AR. Advances in chronic kidney disease. Int J Mol Sci 2016;17: pii: E1314.
[13] Huang BS, Chang WH, Wang KC, et al. Endometriosis might be inversely associated with developing chronic kidney disease: a population-based cohort study in Taiwan. Int J Mol Sci 2016;17:pii: E1079.
[14] Tain YL, Hsu CN. Developmental origins of chronic kidney disease: should we focus on early life. Int J Mol Sci 2017;18:pii: E381.
[15] Mills KT, Xu Y, Zhang W, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 2015;88:950–7.
[16] GBD 2013 Mortality and Cause of Death CollaboratorsGlobal; regional; and national age-sex specific all-cause and cause-specific mortality for 240 causes of death; 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–71.
[17] Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group MembersEvaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825–30.
[18] Grams ME, Yang W, Rebholz CM, et al. CRIC Study InvestigatorsRisks of adverse events in advanced CKD: the chronic renal insufficiency cohort (CRIC) study. Am J Kidney Dis 2017;70:337–46.
[19] Sahutoglu T, Sakaci T, Hasbal NB, et al. Serum VEGF-C levels as a candidate biomarker of hypervolemia in chronic kidney disease. Medicine (Baltimore) 2017;96:e6543.
[20] Chien CC, Han MM, Chiu YH, et al. Epidemiology of cancer in end-stage renal disease dialysis patients: a national cohort study in Taiwan. J Cancer 2017;8:9–18.
[21] Wong G, Hayward JS, McArthur E, et al. Patterns and predictors of screening for breast and cervical cancer in women with CKD. Clin J Am Soc Nephrol 2017;12:95–104.
[22] Crews DC, Khaliq W. Screening women with CKD for the emperor of all maladies. Clin J Am Soc Nephrol 2017;12:5–6.
[23] Wang SM, Lai MN, Chen PC, et al. Increased upper and lower tract urothelial carcinoma in patients with end-stage renal disease: a nationwide cohort study in Taiwan during 1997–2008. Biomed Res Int 2014;2014:149750.
[24] Wang SM, Lai MN, Chen PC, et al. Increased risk of urothelial cancer in young and middle aged patients with end-stage renal disease. J Formos Med Assoc 2015;114:52–7.
[25] Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996–2009. Am J Kidney Dis 2015;65:763–72.
[26] Christensson A, Savage C, Sjoberg DD, et al. Association of cancer with moderately impaired renal function at baseline in a large, representative, population-based cohort followed for up to 30 years. Int J Cancer 2013;133:1452–8.
[27] Dugué PA, Rebolj M, Garred P, et al. Immunosuppression and risk of cervical cancer. Expert Rev Anticancer Ther 2013;13:29–42.
[28] Maisonneuve P, Agodoa L, Gellert R, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999;354:93–9.
[29] Stewart JH, Buccianti G, Agodoa L, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, and Australia and New Zealand. J Am Soc Nephrol 2003;14:197–207.
[30] Vajdic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. JAMA 2006;296:2823–31.
[31] Liang JA, Sun LM, Yeh JJ, et al. The association between malignancy and end-stage renal disease in Taiwan. Jpn J Clin Oncol 2011;41:752–7.
[32] Yu HC, Su NY, Huang JY, et al. Trends in the prevalence of periodontitis in Taiwan from 1997 to 2013: a nationwide population-based retrospective study. Medicine (Baltimore) 2017;96:e8585.
[33] Lai SW, Lin CL, Liao KF. Population-based cohort study investigating the correlation of diabetes mellitus with pleural empyema in adults in Taiwan. Medicine (Baltimore) 2017;96:e7763.
[34] Chiang JK, Lee YC, Kao YH. Trend analysis of end-of-life care between hospice and nonhospice groups of cancer patients in Taiwan for 2002–11. Medicine (Baltimore) 2017;96:e7825.
[35] Lin SC, Lin HW, Chiang BL. Association of croup with asthma in children: a cohort study. Medicine (Baltimore) 2017;96:e7667.
[36] Kao LT, Huang CY, Lin HC, et al. No increased risk of fracture in patients receiving antimuscarinics for overactive bladder syndrome: a retrospective cohort study. J Clin Pharmacol 2018;[Epub ahead of print].
[37] Wang YF, Chen YT, Luo JC, et al. Proton-pump inhibitor use and the risk of first-time ischemic stroke in the general population: a nationwide population-based study. Am J Gastroenterol 2017;112: 1084–93.
[38] Hsiao KC, Huang JY, Lee CT, et al. Different impact of aspirin on renal progression in patients with predialysis advanced chronic kidney disease with or without previous stroke. Eur J Intern Med 2017;39:63–8.

[39] Chou CY, Wang SM, Liang CC, et al. Peritoneal dialysis is associated with a better survival in cirrhotic patients with chronic kidney disease. Medicine (Baltimore) 2016;95:e2465.
[40] Li K, Yin R, Li Q, et al. Analysis of HPV distribution in patients with cervical precancerous lesions in Western China. Medicine (Baltimore) 2017;96:e7304.
[41] Yang-Chun F, Zhen-Zhen C, Yan-Chun H, et al. Association between PD-L1 and HPV status and the prognostic value for HPV treatment in premalignant cervical lesion patients. Medicine (Baltimore) 2017;96: e7270.
[42] Yang-Chun F, Yuan Z, Cheng-Ming L, et al. Increased HPV L1 gene methylation and multiple infection status lead to the difference of cervical epithelial cell lesion in different ethnic women of Xinjiang, China. Medicine (Baltimore) 2017;96:e6409.
[43] Chertow GM, Paltiel AD, Owen WFJr, et al. Cost-effectiveness of cancer screening in end-stage renal disease. Arch Intern Med 1996;156:1345–50.
[44] Tsai HW, Huang MT, Wang PH, et al. DcR3 promotes cell adhesion and enhances endometriosis development. J Pathol 2018;244: 189–202.
[45] Liu CH, Chang Y, Wang PH. Poly(ADP-ribose) polymerase (PARP) inhibitors and ovarian cancer. Taiwan J Obstet Gynecol 2017;56:713–4.
[46] Sung PL, Wen KC, Chen YJ, et al. The frequency of cancer predisposition gene mutations in hereditary breast and ovarian cancer patients in Taiwan: from BRCA1/2 to multi-gene panels. PLoS One 2017;12: e0185615.
[47] Wen KC, Sung PL, Hsieh SL, et al. α2,3-sialyltransferase type I regulates migration and peritoneal dissemination of ovarian cancer cells. Oncotarget 2017;8:29013–27.
[48] Chang CM, Chiou SH, Yang MJ, et al. Gene set-based integrative analysis of ovarian clear cell carcinoma. Taiwan J Obstet Gynecol 2016;55:552–7.
[49] Teng SW, Horng HC, Ho CH, et al. Taiwan Association of Gynecology Systematic Review GroupWomen with endometriosis have higher comorbidities: analysis of domestic data in Taiwan. J Chin Med Assoc 2016;79:577–82.
[50] Huang CY, Yang YC, Wang KL, et al. Possible surrogate marker for an effective dose-dense chemotherapy in treating ovarian cancer. Taiwan J Obstet Gynecol 2016;55:405–9.
[51] Chavan DM, Huang Z, Song K, et al. Incidence of venous thromboembolism following the neoadjuvant chemotherapy regimen for epithelial type of ovarian cancer. Medicine (Baltimore) 2017;96:e7935.
[52] Sung PL, Jan YH, Lin SC, et al. Periostin in tumor microenvironment is associated with poor prognosis and platinum resistance in epithelial ovarian carcinoma. Oncotarget 2016;7:4036–47.
[53] Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. N Engl J Med 2009;361:170–7.
[54] Moyer VA. U.S. Preventive Services Task ForceScreening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2012;157:900–4.
[55] Reade CJ, Riva JJ, Busse JW, et al. Risks and benefits of screening asymptomatic women for ovarian cancer: a systematic review and meta-analysis. Gynecol Oncol 2013;130:674–81.
[56] Murdoch J, Oram D, Rabideau DJ, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2016;387:945–56.
[57] Suh-Burgmann E, Kinney W. Potential harms outweigh benefits of indefinite monitoring of stable adnexal masses. Am J Obstet Gynecol 2015;213:816.e1–4.
[58] Chiang YC, Chen CA, Chiang CJ, et al. Trends in incidence and survival outcome of epithelial ovarian cancer: 30-year national population-based registry in Taiwan. J Gynecol Oncol 2013;24:342–51.
[59] Chang WH, Wang KC, Lee WL, et al. Endometriosis and the subsequent risk of epithelial ovarian cancer. Taiwan J Obstet Gynecol 2014;53:530–5.
[60] Lee WL, Chang WH, Wang KC, et al. The risk of epithelial ovarian cancer of women with endometriosis may be varied greatly if diagnostic criteria are different: a nationwide population-based cohort study. Medicine (Baltimore) 2015;94:e1633.
[61] Wang KC, Chang WH, Lee WL, et al. An increased risk of epithelial ovarian cancer in Taiwanese women with a new surgico-pathological diagnosis of endometriosis. BMC Cancer 2014;14:831.
[62] Minlikeeva AN, Freudenheim JL, Eng KH, et al. Ovarian Cancer Association Consortium; Australian Ovarian Cancer Study Group-History of comorbidities and survival of ovarian cancer patients, results from the Ovarian Cancer Association Consortium. Cancer Epidemiol Biomarkers Prev 2017;26:1470–3.
[63] Doherty JA, Jensen A, Kelemen LE, et al. Epidemiology Working Group Steering Committee, Ovarian Cancer Association Consortium Members of the EWG SC, in alphabetical orderCurrent gaps in ovarian cancer epidemiology: the need for new population-based research. J Natl Cancer Inst 2017;109: doi: 10.1093/jnci/djx144.
[64] Lai JC, Chen HH, Chu KH, et al. Nationwide trends and in-hospital complications of trachelectomy for surgically resectable cervical cancer in Taiwanese women: a population-based study, 1998–2013. Taiwan J Obstet Gynecol 2017;56:449–55.
[65] Huang CC, Huang YT, Chueh PJ, et al. The laparoscopic approach is more preferred among nurses for benign gynecologic conditions than among nonmedical working women: a nationwide study in Taiwan. Taiwan J Obstet Gynecol 2016;55:229–34.
[66] Chou CH, Lee JT, Lin CC, et al. Septicemia is associated with increased risk for dementia: a population-based longitudinal study. Oncotarget 2017;8:84300–8.
[67] Chang SS, Sung FC, Lin CL, et al. Association between hemorrhoid and risk of coronary heart disease: a nationwide population-based cohort study. Medicine (Baltimore) 2017;96:e7662.
[68] Hsieh MS, Chiu CS, How CK, et al. Contrast medium exposure during computed tomography and risk of development of end-stage renal disease in patients with chronic kidney disease: a nationwide population-based, propensity score-matched, longitudinal follow-up study. Medicine (Baltimore) 2016;95:e3388.
[69] Chen JS, Lu CL, Huang LC, et al. Chronic kidney disease is associated with upper tract urothelial carcinoma: a nationwide population-based cohort study in Taiwan. Medicine (Baltimore) 2016;95:e3255.
[70] Chen CY, Dai CS, Lee CC, et al. Association between macular degeneration and mild to moderate chronic kidney disease: a nationwide population-based study. Medicine (Baltimore) 2017;96:e6405.