



ARTICLE

Erythropoiesis-stimulating agents and incident malignancy in chronic kidney and end-stage renal disease: A population-based study

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Abstract

Research investigating incident malignancy risk in erythropoiesis-stimulating agent (ESA) users with chronic kidney disease (CKD) is lacking. We aimed to compare the incident cancer risk between ESA and non-ESA users with CKD or end-stage renal disease (ESRD). In this retrospective cohort study, all adults newly diagnosed with CKD or ESRD between 2000 and 2012 were enrolled. The study population included 98,748 patients. After case-control matching, 7115 patients were included. The defined daily dose (DDD) of ESA was used as the unit for measuring the amount of ESA prescribed. The primary outcome was the risk of incident malignancy. The secondary outcomes were incident malignancy risk in different tertiles of cumulative ESA doses and the risk of different types of cancers. The risk of incident malignancy was 1.84 times higher with ESA treatment than without ESA treatment (hazard ratio, 1.84; 95% confidence interval, 1.43–2.36; $p < 0.001$). The malignancy risk was positively correlated with the cumulative dose of ESA (p -for-trend = 0.001) and a significant difference in the high annual cumulative DDD cohort (hazard ratio [HR], 2.39; 95% confidence interval [CI], 1.76–3.25; $p < 0.001$). The risk of genitourinary malignancy was 12.55 times higher with ESA treatment than without ESA treatment (HR, 12.55; 95% CI, 5.78–27.24; $p < 0.001$). ESA usage is associated with an increased risk of malignancy, particularly genitourinary cancers, in patients with CKD or ESRD. Clinicians should be aware of the occurrence of malignancy, and keep ESA dosage as low as possible.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Erythropoiesis-stimulating agents (ESAs) are known to impact the outcomes of pre-existing cancer.

Funding information

No funding was received for this work

WHAT QUESTION DID THIS STUDY ADDRESS?

The de novo cancer risk for users of ESAs has not been fully examined. We aimed to compare the incident cancer risk between ESA and non-ESA users with chronic kidney disease (CKD) or end-stage renal disease (ESRD).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Users of erythropoiesis-stimulating agents had 1.84 times increasing risk of overall de novo cancer, and a 12-fold risk of genitourinary tract cancer. The risk of overall de novo cancer increased proportionally with the dosage of ESAs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Clinicians should more aggressively taper the dosage of ESAs while achieving the target hemoglobin level. Patients with CKD or ESRD treated with ESAs should be more alert to occurrence of malignancies, particularly genitourinary tract cancers.

INTRODUCTION

Erythropoiesis-stimulating agent (ESA) administration, the cornerstone treatment for anemia in patients with chronic kidney disease (CKD), significantly reduces blood transfusion requirements.¹ The production of erythropoietin is stimulated by the hypoxia-inducible factor system, which is greatly impaired in patients with CKD.² According to the Kidney Disease: Improving Global Outcomes 2012 guideline,³ ESA treatment can be initiated in non-dialysis patients with CKD when their hemoglobin level is <10.0 g/dl, and in patients undergoing dialysis when the hemoglobin level is 9–10 g/dl. However, using ESA raises concerns regarding cancer progression.

ESA may be associated with increased cancer progression risk in certain patient subsets, particularly those with target hemoglobin of ≥ 12 g/dl.^{4–6} When maintaining hemoglobin levels higher than 14 and 15 g/dl in female and male patients, respectively, ESA reportedly increases the risk of locoregional progression and mortality in patients with head and neck cancer receiving curative radiotherapy.⁴ Patients with squamous cell carcinomas of the head and neck under ESA treatment (maintaining hemoglobin levels >15.5 g/dl) had a 1.53 times higher 5-year locoregional failure risk than did those without ESA treatment.⁶ In a meta-analysis of >10,000 patients, ESAs were related to a 17% increased risk of mortality, regardless of chemotherapy use.⁵

The association between de novo cancer risk and ESA use in patients with CKD or end-stage renal disease (ESRD) remains unclear. In 2009, the TREAT trial found no cancer-related adverse events in patients with diabetes with CKD and anemia treated with ESA (maintaining hemoglobin levels >12.5 g/dl).⁷ In 2010, the SEASCAN study found no differences in the de novo or ongoing cancer risk among patients with CKD who did not receive ESA, those who received ESA for <6 months, and those who received ESA for >6 months.⁸ A 2017 nested case-control study of

4574 patients undergoing chronic dialysis concluded that ESAs, particularly high-dose ESAs (>70 μ g/week), were associated with increased de novo cancer risk.⁹

Thus, our study aimed to compare the de novo cancer risk in patients with CKD and ESRD with and without ESA exposure. We also examined ESA dose effects on de novo cancer risk and analyzed the cancer epidemiology.

METHODS

Data source

Taiwan National Health Insurance (NHI) has covered >97% of Taiwan residents since 1996. All historical diagnoses in the database are coded per the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM; Table S1). De-identified study data were extracted from the longitudinal health insurance research dataset (LHIRD) 2000 submitted to the Taiwan Bureau of NHI from 2000 to 2013. The LHIRD 2000 includes 1,000,000 beneficiaries randomly selected from the entire population of Taiwan in the year 2000. The LHIRD 2000 contains claim records, including inpatient and outpatient visits and examinations, prescriptions, and treatment services. The 2000–2013 dataset of the LHIRD 2000 was collated for this study. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved this study (CMUH-104-REC2-115-[AR4]). The need for informed consent was waived because of the retrospective nature of the study.

Study design and cohort

A specific comorbidity was identified if a patient had a discharge diagnosis or at least two outpatient visits within

1 year for that comorbidity. The medical coding interval between the first and last dates was >90 days. Figure S1 describes patient selection from January 1, 1996, to December 31, 2013. Adults (≥ 20 years of age) with CKD were identified as individuals with a CKD diagnosis and at least two outpatient visits or one inpatient visit. Data for patients with incident CKD from 2000 to 2013 were retrieved after excluding patients with CKD diagnosed before 2000. A 4-year look-back period (1996–1999) was used to ensure that all patients with CKD in our cohort were newly diagnosed and to avoid false incident cases. Patients were divided into ESA or non-ESA treatment cohorts when an ESA prescription (Anatomical Therapeutic Chemical [ATC] code B03XA01–B03XA03) or no ESA prescription, respectively, was noted on claims data prescription records from inpatient visits, outpatient visits, and refills in the pharmacy for chronic illness from 2000 to 2012. The index date of the ESA treatment cohort was the ESA treatment start date. For the index date of the non-ESA treatment cohort, we randomly selected the index date between the date of first CKD diagnosis and the last day of follow-up to avoid immortal time bias.

Exclusion criteria

We excluded patients who had cancer before the index date, were diagnosed with a malignancy within 1 year of the index date, received renal transplantation, had missing basic information, or were <20 or >100 years old.

Variables and comorbidities

Baseline demographic characteristics included age, sex, monthly income, and urbanization level of the patients' places of residence. The health status of patients was systematically assessed using the Charlson Comorbidity Index (CCI). Each increase in the CCI score represents a stepwise increase in cumulative mortality. Scores of zero and five correspond to 99% and 34% 10-year survival rates, respectively. Instances of comorbidity were designated by at least two outpatient medical claims or one inpatient medical claim of obesity, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, valvular heart disease, coronary artery disease, stroke, cirrhosis, or autoimmune disease in the previous year.

Annual ESA cumulative exposure

We used the defined daily dose (DDD) as the unit for measuring a prescribed ESA amount. The DDD is the

assumed average maintenance dose of a drug consumed for its main indication in adults per day. DDD of (ATC code B03XA01) was 1 TU, equal to 1000 U, and 1000 U was equal to 8.4 μg ; DDD of darbepoetin alfa (ATC dose B03XA02) was 4.5 μg ; DDD of methoxy polyethylene glycol-epoetin beta (ATC code B03XA03) was 4.5 μg .¹⁰ To explore the dose effect and incident malignancy risk and to avoid higher cumulative ESA doses with longer patient follow-up periods, the cumulative ESA use was calculated as the total prescribed annual cumulative DDD (cDDD). The cumulative ESA dosage was recorded as the total annual cDDDs from drug initiation to the day of malignancy diagnosis.

Outcome measures

The primary outcome was the incident malignancy risk in the ESA and non-ESA treatment cohorts after the index date. Patients who met both the following conditions were considered as having incident malignancy: (1) at least two outpatient medical claims or one inpatient medical claim of malignancy, and (2) a catastrophic illness certification card for the corresponding cancer. The validation of the cancer diagnosis by ICD-9-CM in the NHI database shows a high positive predictive value (94%) for all cancers and ranged from 82% for cervical cancer to 95% for lung cancer.¹¹

The incident malignancy risk was analyzed between cohorts in different stratifications (sex, age at baseline, monthly income, urbanization, and CCI score). The correlation between ESA supplementation and increased incident malignancy risk based on the tertile of annual DDDs was estimated. The incidence of different malignancies, categorized as gallbladder, pancreas, hepatic, lung, genitourinary, stomach, thyroid, colon, and head and neck malignancies, was examined. The risk difference of incident malignancy was compared between cohorts with different follow-up periods.

Statistical analyses and case-control matching

The age, sex, and comorbidity distributions in the two treatment cohorts are indicated by numbers and percentages. Differences between the two cohorts were evaluated using the chi-square test and *t*-test for categorical and continuous variables, respectively. Among patients without event occurrence, follow-up duration (in person-years) was calculated from the index date to either the date of death or diagnosis, or the last follow-up before December 31, 2013. Associations between

treatment selection and malignancy were investigated using case–control matching to reduce bias in patient selection and generate matched pairs of patients, thereby enabling comparisons of the ESA and non-ESA treatment cohorts. Possible variables associated with treatment selection, including age, gender, index year, and year of first diagnosis of CKD, were included in case–control matching generation.¹²

We used Cox proportional hazard model to evaluate the hazard ratio (HR) and 95% confidence interval (CI) of the incidence of incident malignancy among both cohorts after adjusting for sex, age, monthly income, urbanization, CCI score, and all comorbidities. Schoenfeld residuals were used to evaluate Cox proportion assumptions. The link between ESA treatment and incident malignancy was evaluated using stratification analysis based on age, sex, CCI, monthly income, and urbanization. Interaction tests were used to determine interactions between subgroups and the incident malignancy risk.

We divided the ESA treatment cohort into three subgroups according to ESA type and ESA annual cDDDs (low, median, and high) and compared the incident malignancy risk with a matched cohort separately. Whereas the incidence of malignancy between different ranges of defined daily ESA doses (low, median, and high) was analyzed, survey-weighted logistic regression was used to calculate a *p*-for-trend. The statistical significance of the trends was evaluated using a two-sided test at the $\alpha = 0.05$ level. An “increase” of association represents a ratio of >1 and a *p*-for-trend value of <0.05 .

Survival curves were plotted using the Kaplan–Meier method and tested using the log-rank test. A Kaplan–Meier plot was plotted using R software. Statistical significance was determined using two-tailed tests ($p < 0.05$). Other statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC).

Sensitivity analysis

Because cystic kidney disease, ESRD, and glomerulonephritis may bias cancer risk, the first sensitivity analysis, A, was performed by case–control matching of both cohorts with sex, age, CCI score, proportion of glomerulonephritis, cystic kidney disease, and ESRD. A Cox proportional hazard model was used to estimate the HR of incident malignancy between cohorts after adjusting for age, sex, CCI score, glomerulonephritis, cystic kidney disease, and ESRD.

A second sensitivity analysis, B, was conducted with treatment ESA use as a time-varying exposure. The status

of drug use was reassessed 30 days after the index date during follow-up. Owing to the potential for treatment indication bias, comparisons were made only for the exposure periods with ESA. A sub-distribution model was used to estimate the risk difference of incident malignancy between both cohorts after adjusting for age, sex, CCI score, urbanization, and comorbidities.

RESULTS

Patient characteristics

Our study population included 98,748 patients with CKD, with 3558 and 95,190 patients in the ESA and non-ESA treatment cohorts, respectively. After case–control matching, 7115 patients were included (3558 in ESA cohort and 3557 in non-ESA cohort). There was no statistical difference in covariates of sex, age, urbanization, obesity, atrial fibrillation, and autoimmune disease at baseline. The baseline characteristics revealed statistical difference in covariates of monthly income, CCI score, diabetes, hypertension, hyperlipidemia, valvular heart disease, coronary artery disease, stroke, and cirrhosis (Table S2). The mean ages in the ESA treatment and matched cohort groups were 62.7 (SD, 14.1) and 62.8 (SD, 14.1) years, respectively.

Overall incident malignancy risk

The incident malignancy risk was 1.84 times higher in the ESA treatment cohort than in the matched cohort (adjusted HR, 1.84; 95% CI, 1.43–2.36; $p < 0.001$; Table 1). Male patients had 1.32 times higher incident malignancy risk than female patients. Compared with that among patients aged <40 years, incident malignancy risk was 2.26 times higher among patients aged 40–65 years and 4.54 times higher among those aged ≥ 65 years. Compared with that among patients with a CCI score of 0, incident malignancy risk was 0.68 times lower among patients with CCI scores of ≥ 3 , respectively, in the entire cohort. The incident malignancy risk was 0.73 times lower in patients with diabetes than in those without diabetes. Patients with cirrhosis had a 1.40 times higher risk of incident malignancy than patients without cirrhosis. Schoenfeld residuals showed that the proportional hazards might not be against the assumption ($p = 0.1485$).

Figure 1 presents the Kaplan–Meier analysis of the cumulative malignancy incidence, wherein the incidence had no difference in the ESA treatment cohort than in the matched cohort (log-rank, $p = 0.1511$).

TABLE 1 HR of cancer among patients with CKD

Characteristics	Event no. (n = 351)	Crude		Adjusted	
		HR (95% CI)	p Value	HR (95% CI)	p Value
ESA treatment					
No	168	Ref.		Ref.	
Yes	183	1.33 (1.08–1.64)	0.008	1.84 (1.43–2.36)	<0.001
Sex					
Female	168	Ref.		Ref.	
Male	183	1.24 (1.01–1.54)	0.042	1.32 (1.06–1.64)	0.014
Age at baseline					
<40	29	Ref.		Ref.	
40–65	162	1.97 (1.33–2.93)	0.001	2.26 (1.51–3.39)	<0.001
≥65	160	3.33 (2.23–4.97)	<0.001	4.54 (2.95–6.99)	<0.001
Monthly income					
0–15,840	106	Ref.		Ref.	
15,841–28,800	181	1.02 (0.80–1.30)	0.879	1.04 (0.81–1.33)	0.760
28,801–45,800	48	1.13 (0.80–1.59)	0.483	1.20 (0.84–1.71)	0.314
>45,800	16	0.92 (0.53–1.58)	0.755	1.04 (0.60–1.81)	0.901
Urbanization					
1 (highest)	97	Ref.		Ref.	
2	107	1.03 (0.78–1.36)	0.826	1.02 (0.77–1.35)	0.884
3	54	0.92 (0.66–1.29)	0.629	0.92 (0.66–1.28)	0.619
4	92	1.08 (0.81–1.43)	0.615	1.00 (0.75–1.35)	0.989
CCI score					
0	191	Ref.		Ref.	
1–2	98	1.16 (0.91–1.48)	0.227	0.91 (0.70–1.18)	0.464
≥3	62	0.91 (0.68–1.21)	0.496	0.68 (0.48–0.95)	0.025
Baseline comorbidity					
Obesity	5	1.29 (0.53–3.13)	0.570	1.63 (0.67–3.96)	0.285
Diabetes	141	0.85 (0.69–1.06)	0.143	0.73 (0.57–0.93)	0.011
Hypertension	263	1.20 (0.94–1.53)	0.139	0.83 (0.62–1.11)	0.205
Hyperlipidemia	169	0.96 (0.78–1.18)	0.689	0.93 (0.73–1.18)	0.532
Atrial fibrillation	11	1.41 (0.77–2.57)	0.267	1.21 (0.65–2.23)	0.554
Valvular heart disease	27	0.88 (0.60–1.31)	0.530	0.74 (0.49–1.11)	0.141
Coronary artery disease	154	1.23 (1.00–1.53)	0.053	1.06 (0.83–1.35)	0.657
Stroke	68	0.97 (0.75–1.27)	0.842	0.79 (0.59–1.06)	0.116
Cirrhosis	157	1.31 (1.06–1.62)	0.012	1.40 (1.12–1.74)	0.003
Autoimmune disease	3	1.27 (0.41–3.97)	0.677	1.50 (0.48–4.72)	0.489

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; HR, hazard ratio.

Incident malignancy risk: Stratification and interaction tests

In sex subgroup, individuals of both sexes with ESA treatment had a higher risk of developing malignancy (women: adjusted HR, 2.33; 95% CI, 1.62–3.33; $p < 0.001$;

men: adjusted HR, 1.43; 95% CI, 1.01–2.03; $p < 0.043$) than those without ESA treatment, whereas there was also a significant interaction by sex group (p for interaction 0.041; [Table 2](#)). In the age subgroup, individuals of age <40 years old and 40–65 years old with ESA treatment had a higher risk of developing malignancy. There was also

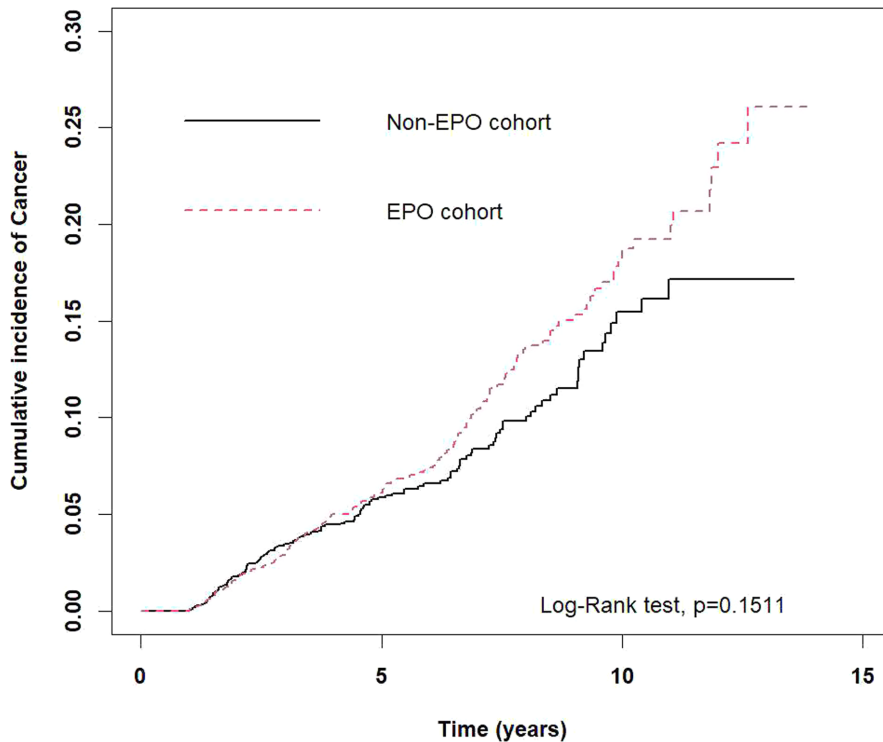


FIGURE 1 Comparison of cumulative incidence of malignancy between ESA and non-ESA treatment cohorts. Kaplan–Meier analysis demonstrates that the risk of incident malignancy in the ESA treatment cohort and in the matched cohort had no significant difference (log-rank, $p = 0.1511$). ESA, erythropoiesis-stimulating agent.

a significant interaction by age subgroup (p for interaction = 0.005). In the CCI score subgroup, individuals with CCI score 0 in the ESA treatment group had 2.21 times higher risk of developing malignancy than in the matched cohort. There was also a significant interaction by CCI score group (p for interaction = 0.005).

Annual cumulative ESA exposure and incident malignancy risk

Malignancy incidence risk was 2.39 times higher in the high annual cDDD ESA treatment cohort (>144 annual cDDD) than in the matched cohort (Table 3). There was a trend for a more significant difference in higher ESA dosage groups (p -for-trend = 0.001). In the erythropoietin (ATC code B03XA01) group, malignancy incidence risk was 2.28 times higher in the high annual cDDD ESA treatment cohort (>102 annual cDDD) than in the matched cohort. There was also significant difference in higher ESA dosage groups (p -for-trend = 0.003). In the darbepoetin alfa (ATC code B03XA02) group, malignancy incidence risk was 2.07 times higher in the high annual cDDD ESA treatment cohort (>58 annual cDDD) than in the matched cohort, whereas there was no trend for dosage effect (p -for-trend = 0.346). In the methoxy polyethylene glycol-epoetin beta group (ATC code B0XA03), there was no risk difference of malignancy in the different annual cDDD group.

Incident malignancy risk for different cancer types

Genitourinary malignancy risk was 12.55 times higher in the ESA treatment cohort than in the matched cohort ($p < 0.001$; Table 4). There were no significant differences in the incidence of gallbladder, pancreatic, liver, lung, stomach, thyroid, colon, and head and neck malignancies between the ESA treatment and matched cohorts.

Incident malignancy risk by different follow-up periods

Incident malignancy risk was 2.3 times higher in the ESA treatment cohort with >4 years follow-up period than in the matched cohort, and was 1.65 times higher in the ESA treatment cohort with 2–4 years follow-up period. There were no risk differences between cohorts with a follow-up period of <2 years (Table S3).

Sensitivity analysis

Sensitivity analysis A, which considered patients with glomerulonephritis, cystic kidney disease, and ESRD, was consistent with our primary analyses (Table S4). The patient baseline characteristics in the sensitivity analysis are shown in Table S5.

TABLE 2 Risk of incident malignancy in patients with CKD or ESRD according to different stratifications

Variables	Matched cohort		ESA cohort		Compared to matched cohort			p Value for interaction		
	n = 3557		n = 3558		Crude HR (95% CI)	p Value	Adjusted HR (95% CI)			
	Event	Person years	IR	Person years					IR	
ESA treatment	168	15,112	11.12	183	13,096	13.97	1.33 (1.08–1.64)	0.008	1.84 (1.43–2.36)	<0.001
Sex										
Female	73	8015	9.11	95	6676	14.23	1.67 (1.23–2.27)	0.001	2.33 (1.62–3.33)	<0.001
Male	95	7096	13.39	88	6420	13.71	1.06 (0.80–1.42)	0.676	1.43 (1.01–2.03)	0.043
Age at baseline										
<40	10	2264	4.42	19	2232	8.51	2.01 (0.94–4.33)	0.074	3.45 (1.30–9.13)	0.013
40–65	64	7523	8.51	98	6488	15.11	1.91 (1.39–2.62)	<0.001	2.61 (1.78–3.82)	<0.001
≥65	94	5325	17.65	66	4376	15.08	0.92 (0.67–1.26)	0.608	1.08 (0.75–1.54)	0.695
Monthly income										
0–15,840	50	4681	10.68	56	4157	13.47	1.33 (0.91–1.95)	0.145	1.59 (1.01–2.51)	0.046
15,841–28,800	85	7747	10.97	96	6893	13.93	1.35 (1.01–1.81)	0.044	1.89 (1.33–2.67)	<0.001
28,801–45,800	26	1953	13.31	22	1494	14.72	1.14 (0.64–2.00)	0.662	1.78 (0.89–3.53)	0.101
>45,800	7	730	9.59	9	551	16.34	1.63 (0.61–4.40)	0.332	4.92 (1.13–21.48)	0.034
Urbanization										
1 (highest)	50	4403	11.36	47	3460	13.58	1.31 (0.88–1.95)	0.189	1.93 (1.20–3.12)	0.007
2	48	4469	10.74	59	3973	14.85	1.47 (1.00–2.15)	0.049	1.89 (1.20–2.96)	0.006
3	26	2508	10.37	28	2280	12.28	1.27 (0.74–2.18)	0.383	1.84 (0.95–3.57)	0.071
4	43	3707	11.60	49	3382	14.49	1.28 (0.85–1.93)	0.238	1.85 (1.12–3.04)	0.016
CCI score										
0	120	11,404	10.52	71	3646	19.47	1.97 (1.46–2.64)	<0.001	2.21 (1.61–3.03)	<0.001
1–2	38	2855	13.31	60	4186	14.34	1.04 (0.69–1.56)	0.852	1.54 (0.98–2.41)	0.060
≥3	10	853	11.73	52	5264	9.88	0.76 (0.38–1.50)	0.424	0.85 (0.41–1.77)	0.671

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; HR, hazard ratio; IR, incidence rate.

TABLE 3 Incident malignancy risk in patients with CKD or ESRD according to annual cumulative ESA doses and different ESA

Treatment	N	Event	Person years	IR	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
ESA (annual cDDD)								
No	3557	168	15,112	11.12	Ref.		Ref.	
Yes	3558	183	13,096	13.97	1.33 (1.08–1.64)	0.008	1.84 (1.43–2.36)	<0.001
Low (<60)	1167	53	4266	12.42	1.20 (0.88–1.63)	0.251	1.59 (1.13–2.23)	0.008
Median (60–144)	1216	62	4977	12.46	1.15 (0.86–1.53)	0.359	1.59 (1.15–2.20)	0.005
High (>144)	1175	68	3853	17.65	1.74 (1.31–2.31)	<0.001	2.39 (1.76–3.25)	<0.001
p-for-trend						0.001		
Erythropoietin								
No	3557	168	15,112	11.12	Ref.		Ref.	
Yes	3182	176	12,501	14.08	1.32 (1.07–1.63)	0.010	1.76 (1.37–2.27)	<0.001
Low (<34)	1053	49	3754	13.05	1.30 (0.94–1.78)	0.113	1.70 (1.20–2.41)	0.003
Median (34–102)	1080	55	4734	11.62	1.05 (0.77–1.42)	0.754	1.39 (0.99–1.94)	0.055
High (>102)	1049	72	4013	17.94	1.68 (1.27–2.21)	<0.001	2.28 (1.67–3.10)	<0.001
p-for-trend						0.003		
Darbepoetin alfa								
No	3557	168	15,112	11.12	Ref.		Ref.	
Yes	1582	68	6360	10.69	1.00 (0.75–1.33)	0.994	1.40 (1.01–1.94)	0.043
Low (<15)	518	21	2535	8.28	0.74 (0.47–1.17)	0.197	1.05 (0.65–1.71)	0.840
Median (15–58)	539	24	2179	11.02	1.03 (0.67–1.58)	0.891	1.36 (0.86–2.16)	0.184
High (>58)	525	23	1646	13.98	1.40 (0.91–2.17)	0.131	2.07 (1.30–3.31)	0.002
p-for-trend						0.346		
Methoxy polyethylene glycol-epoetin beta								
No	3557	168	15,112	11.12	Ref.		Ref.	
Yes	484	15	1443	10.40	1.07 (0.63–1.81)	0.817	1.43 (0.82–2.52)	0.210
Low (<37)	161	8	630	12.70	1.21 (0.59–2.46)	0.605	1.60 (0.76–3.37)	0.219
Median (37–121)	164	3	509	5.89	0.61 (0.19–1.90)	0.390	0.80 (0.25–2.55)	0.710
High (>121)	159	4	304	13.16	1.61 (0.59–4.35)	0.352	2.45 (0.88–6.76)	0.085
p-for-trend						0.792		

Note: Erythropoietin (DDD = 1 TU = 1000 U = 8.4 µg); Darbepoetin alfa (DDD = 4.5 µg); Methoxy polyethylene glycol-epoetin beta (DDD = 4.5 µg); Each 1000 IU of ESA are equal to 8.4 µg.

Adjusted HR: adjusted for sex, age, monthly income, urbanization, CCI score and all comorbidities in Cox proportional hazards model.

Abbreviations: cDDD, cumulative defined daily dose; CI, confidence interval; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; HR, hazard ratio; IR, incidence rates, per 1000 person-years.

A sensitivity analysis B, of differences in risk of incident malignancy between cohorts, was obtained using ESA as a time-varying exposure to treatment (Table S6). The use of ESA was associated with a 2.37 times higher risk of developing incident malignancy. This result was also consistent with the primary analyses.

DISCUSSION

Results regarding ESA use in patients with pre-existing malignancies in different randomized controlled trials

(RCTs) are conflicting. The 2003 ENHANCE RCT investigated whether correction of anemia using ESA could improve outcomes in patients with head and neck malignancies. The results revealed a higher locoregional progression risk in ESA users.⁴ In 2005, the BEST RCT examined the survival of patients with metastatic breast cancer who underwent chemotherapy while using ESA to maintain hemoglobin levels between 12 and 14 g/dl.¹² The ESA treatment group had a 36% higher 12-month mortality risk than did the placebo group. Most of the survival difference observed at 12 months was already present at 4 months, and about 70% of mortality within

TABLE 4 Risk of different cancers in patients with CKD or ESRD

Cancer	ESA treatment											
	No					Yes						
	Event	PY	IR	IR	Event	PY	IR	IR	Crude HR HR (95% CI)	p Value	Adjusted HR HR (95%CI)	p Value
Gallbladder (156)	0	19,290	0.00	0.00	1	19,355	0.05	0.05	-	-	-	-
Pancreas (157)	7	19,290	0.36	0.36	2	19,355	0.10	0.10	0.35 (0.07-1.68)	0.188	0.81 (0.14-4.58)	0.808
Liver (155)	35	19,290	1.81	1.81	20	19,355	1.03	1.03	0.70 (0.41-1.23)	0.215	0.89 (0.44-1.80)	0.748
Lung (162)	22	19,290	1.14	1.14	12	19,355	0.62	0.62	0.65 (0.32-1.32)	0.231	0.71 (0.31-1.64)	0.422
Genitourinary (188, 189.1, 189.2)	9	19,290	0.47	0.47	53	19,355	2.74	2.74	7.38 (3.64-14.97)	<0.001	12.55 (5.78-27.24)	<0.001
Stomach (151)	9	19,290	0.47	0.47	10	19,355	0.52	0.52	1.31 (0.53-3.22)	0.562	2.34 (0.81-6.78)	0.118
Thyroid (193)	1	19,290	0.05	0.05	4	19,355	0.21	0.21	4.76 (0.53-42.79)	0.163	-	-
Colon (153, 154)	25	19,290	1.30	1.30	23	19,355	1.19	1.19	1.11 (0.63-1.96)	0.713	1.65 (0.86-3.16)	0.134
Head and neck (140-149, 161)	9	19,290	0.47	0.47	7	19,355	0.36	0.36	0.98 (0.36-2.63)	0.966	0.40 (0.11-1.48)	0.170

Note: Adjusted HR: adjusted for sex, age, monthly income, urbanization, CCI score, and all comorbidities in Cox proportional hazards model.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; HR, hazard ratio; IR, incidence rate, per 1000-person years; PY, person-years.

4 months was due to breast cancer progression.¹² In 2009, the TREAT RCT examined cardiovascular and renal outcomes in patients with diabetes and CKD who received ESA to maintain hemoglobin at ~13g/dl.⁷ For patients with pre-existing malignancies, the ESA group experienced significantly more cancer deaths than did the placebo group.⁷ However, other studies found no significant differences between the ESA and non-ESA treatment groups. In 2010, Blohmerand et al. conducted an RCT to investigate the effect of ESA in patients with stage IB to II cervical cancer who underwent adjuvant chemotherapy and radiotherapy.¹³ There was no difference in recurrence-free and overall survival between ESA and non-ESA users. Subsequently, a comprehensive meta-analysis of 60 RCTs (15,323 patients in total) concluded that mortality was similar between ESA and non-ESA users with malignancy undergoing radiotherapy or chemotherapy.¹⁴ Furthermore, there was also no difference in disease progression between ESA and non-ESA users with malignancy.¹⁴ Although this meta-analysis demonstrated the neutral effect of ESA on survival and cancer progression in patients with pre-existing cancer, ESA use should be considered carefully in these patients in terms of the balance of anemia and cancer progression.

In our cohort, male patients are associated with higher risk of malignancy than female patients (Table 2), and the finding is consistent with the current situation in Taiwan. According to the annual statistics of Department of Gender Equality of Taiwan, the case number of newly diagnosed cancer over the general population was 121,254, male patients accounted for 52.8% and female patients for 47.1%.¹⁵ According to the Kidney Disease in Taiwan Annual Report 2020, male patients with CKD had higher risk of incident malignancy (male: female patients = 7.6%: 6.6%).¹⁶

Studies on the association of ESA with de novo malignancy are scarce and report divergent results. As mentioned earlier, the SEASCAN trial demonstrated no increased de novo cancer or ongoing cancer risk among patients with CKD according to whether or not ESA was administered or for how long.⁸ On the other hand, a 2017 case-control study concluded that ESA use (particularly high-dose ESA use) was associated with greater de novo cancer risk than was non-ESA use.⁹ Our results are consistent with those of the case-control study as we found a 1.84 times higher de novo cancer risk in patients with CKD. We observed a dose effect of ESA in developing malignancy, especially in the matched cohort which was the most common prescribed ESA in Taiwan. However, in the methoxy polyethylene glycol-epoetin beta cohort, the risk difference of malignancy was similar with the matched cohort, and this may due to small sample size of methoxy polyethylene glycol-epoetin beta cohort. According to an

analysis of the Taiwan NHI Research Database (NHIRD), genitourinary cancers are the most prevalent, accounting for 30%–40% of all cancers in patients with ESRD.¹⁷ Our subgroup analysis further demonstrated that patients with CKD or ESRD with ESA exposure had a 12.55 times higher risk of developing genitourinary cancers than did those without ESA exposure. There are a few studies that have evaluated the link between ESA and genitourinary cancer risk. However, further research is warranted to elucidate the mechanisms underlying the effects of ESA on genitourinary cancer.

There were six limitations to our study. First, we did not evaluate the impact of ESA exposure duration on incident malignancy. Second, this study did not assess cancer risk for different hemoglobin and iron levels. Although high prevalence of ESA utilization of 85% was reported by the Taiwan Department of Health in 2012, they also established restrictions for ESA prescription. According to the Taiwan NHI reimbursement criteria for prescribing ESA for patients with CKD, ESA should be considered in patients with CKD with Hgb ≤ 9 mg/dl, and ESA could not be prescribed to patients with hemoglobin levels >11.5 g/dl, otherwise the NHI may not cover the expenses. Consequently, patients in the ESA treatment cohort were under the same ESA prescription guidance. Third, this study did not assess cancer risk for smoking, estimated glomerular filtration rate, and CKD progression because of the ICD coding limitation of the Taiwan NHI database. Fourth, renal and urothelial cell carcinomas were not differentiated; therefore, we presented them as genitourinary cancers because of ICD-9 coding limitations. Thus, we could not evaluate the impact of ESA on renal or urothelial cell carcinomas separately. Fifth, this was an observational study and, therefore, cannot prove causality. Although we adjusted for common health conditions, other risk factors that cannot be identified from the NHIRD may have contributed to the occurrence of malignancy. Sixth, incident malignancy risk was lower in patients with high CCI, as unmeasured confounding factors may have biased our study.

In conclusion, this study demonstrated that ESA use is associated with increased incident malignancy risk in patients with CKD or ESRD. The risk increases with increasing cumulative ESA dosage, and the highest risk was reached with a cumulative dose of >144 annual cDDDs. Genitourinary cancers were the most common neoplasm in patients with CKD or ESRD exposed to ESA. These results may provide clinicians another reason to keep ESA dosage as low as possible.

AUTHOR CONTRIBUTIONS

Y.-S.H. wrote the manuscript. H.-Y.C. designed the research. M.-C.L., J.-H.W., M.-F.L., J.-S.C., and

H.-Y.C. performed the research. M.-C.L., J.-H.W., S.-H.O., C.-W.H., P.-T.L., K.-J.C., H.-C.F., and C.-Y.H. analyzed the data.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

Raw data compliant with the institutional confidentiality policies are available upon request. Data requests should be sent to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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