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Association between L-α-glycerylphosphorylcholine use and risk of kidney cancer: A nationwide representative retrospective cohort study

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ABSTRACT

Background: L-α-glycerylphosphorylcholine (α-GPC) is widely prescribed for cognitive impairment and Alzheimer's dementia. Previous cohort studies have reported that dietary free choline intake was associated with decreased kidney cancer risk. The oncologic safety of supplemental α-GPC remains uncertain given its role in producing trimethylamine N-oxide (TMAO), a metabolite implicated in renal injury and certain malignancies. This study aimed to test the hypothesis whether α-GPC use was associated with the reduction of incident kidney cancer.

Methods: Using the Korean National Health Insurance Service database, we conducted a nationwide retrospective cohort study among adults aged ≥ 50 who underwent health screening in 2009–2010. After exclusion criteria and 1:5 exact propensity score matching, 81,970 α-GPC users and 409,801 non-users were analyzed using Cox proportional hazards models. Incident kidney cancer events were identified from 2011 to 2024.

Results: α-GPC use was not associated with kidney cancer risk (adjusted HR 0.95, 95% CI 0.84–1.08; 280 events in α-GPC users, 1570 in non-users). Results were consistent across lag-time sensitivity analyses and subgroup analyses by age, sex, income, Charlson comorbidity index, and estimated glomerular filtration rate.

Conclusions: α-GPC use was not associated with incident kidney cancer in this large Korean cohort. Further studies in diverse populations are warranted in order to confirm these findings.

1. Introduction

L-α-glycerylphosphorylcholine (α-GPC), also known as choline alfoscerate, commonly used along with acetylcholinesterase inhibitors, is an acetylcholine precursor widely used as a cholinergic supplement for cognitive impairment and dementia. [1] Since insurance coverage for α-GPC was extended in South Korea in 2007, its use among newly diagnosed neurologic disease patients, including those with Alzheimer's disease, increased steeply from 16% in 2012 to 48% in 2019, [2,3] warranting evaluation of its long-term oncologic safety.

As an essential nutrient, choline and its metabolites are fundamental to cell membrane integrity, lipid metabolism, neurotransmitter synthesis, and signal transduction. [4,5] Choline, along with folate and methionine, is an essential mediator for the one-carbon methyl metabolism. [6] Moreover, choline-methionine deficient diets in rodents have been linked to tumorigenesis, [7] and human choline intake has been linked to decreased risk of chronic kidney disease [8] and overall cancer in a meta-analysis of previous literature. [9] Importantly, a prospective cohort study comprising more than 120,000 participants from the US Nurses' Health Study and Health Professionals Follow-up Study revealed that dietary free choline intake has been associated with a lower risk of renal cell carcinoma (RCC). [10] Taken together,

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these observations suggest that supplemental α-GPC use may be associated with a decreased risk of kidney cancer considering the apparent protective effect seen with dietary free choline.

However, the metabolites of α-GPC should also be considered when predicting its effects. From a mechanistic point of view, part of α-GPC is converted to trimethylamine via gut microbiota and oxidized into trimethylamine-N-oxide (TMAO) via hepatic FMO3 enzymes. [11] TMAO, which has been implicated in various cancers, [12] can potentially trigger renal tubular oxidative stress and epigenetic dysregulation. TMAO has been inversely associated with eGFR and positively with albuminuria, [13] and a randomized controlled trial [14] showed that supplemental choline bitartrate raised fasting plasma TMAO levels higher than equivalent dietary choline from eggs. Thus, the protective dietary evidence predicted in choline nutrients may not be directly extrapolated to supplemental α-GPC.

No study has previously investigated whether α-GPC prescription is associated with kidney cancer risk. Given rapidly increasing α-GPC prescription rates in aging populations and the biologically plausible pathway via essential choline, we conducted a nationwide population-based cohort study using the Korean National Health Insurance Service (NHIS) database to test whether α-GPC use was associated with a decreased risk of kidney cancer.

2. Methods

2.1. Data sources

This study employed a nationwide retrospective cohort design using health insurance claims data from the NHIS of South Korea. The NHIS operates as a compulsory, single-payer health insurance system encompassing approximately 97% of the South Korean population. Eligible participants undergo standardized biennial health examinations collecting anthropometric measurements, blood pressure, laboratory tests, and lifestyle questionnaires (smoking, alcohol, physical activity). The NHIS database integrates sociodemographic variables, income-based insurance contribution levels as an indicator of household income, medical diagnoses based on the 10th revision of the International Classification of Diseases (ICD−10), prescription drug records, and mortality data.

Access to the NHIS database is restricted to authorized investigators following a formal review and approval process. This study used data under approved access number NHIS−2024–10–1–030. All data were anonymized per NHIS confidentiality guidelines, and informed consent was waived. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (E−2601–125–1710) and conducted in compliance with the Declaration of Helsinki.

2.2. Study population

Among 8235,374 participants aged ≥ 50 who underwent national health screening in 2009–2010, we applied the following exclusion criteria: participants who died before the index date between 2002 and 2010 (n = 49,286), those with a history of any cancer diagnosis during the same period (n = 343,912), those with a prior history of α-GPC prescription between 2002 and 2006 (n = 37,297), those prescribed anti-dementia medications during the same period (n = 10,321), and those with a history of end-stage renal disease (ESRD) between 2002 and 2010 (n = 68,218). In addition, participants with missing values for estimated glomerular filtration rate (eGFR) (n = 4733,135) and other covariates (n = 77,885) were excluded.

After applying these exclusion criteria, 2915,320 participants comprised the final analysis cohort, including 81,977 α-GPC users and 2833,343 non-users. Subsequently, 1:5 propensity score (PS) matching was performed based on age, sex, household income, Charlson Comorbidity Index (CCI), and eGFR resulting in a matched cohort of 81,970 α-GPC users and 409,801 non-users (Fig. 1). Participants were followed from the index date (January 1, 2011) until the diagnosis of kidney cancer, death, or the end of follow-up (December 31, 2024), whichever occurred first.

2.3. Exposure to L-α-glycerylphosphorylcholine

The primary exposure of interest was α-GPC use identified from prescription claims in the NHIS database. Cumulative α-GPC prescription days were calculated from January 1, 2007, to December 31, 2010. Participants were classified as α-GPC users or non-users and further

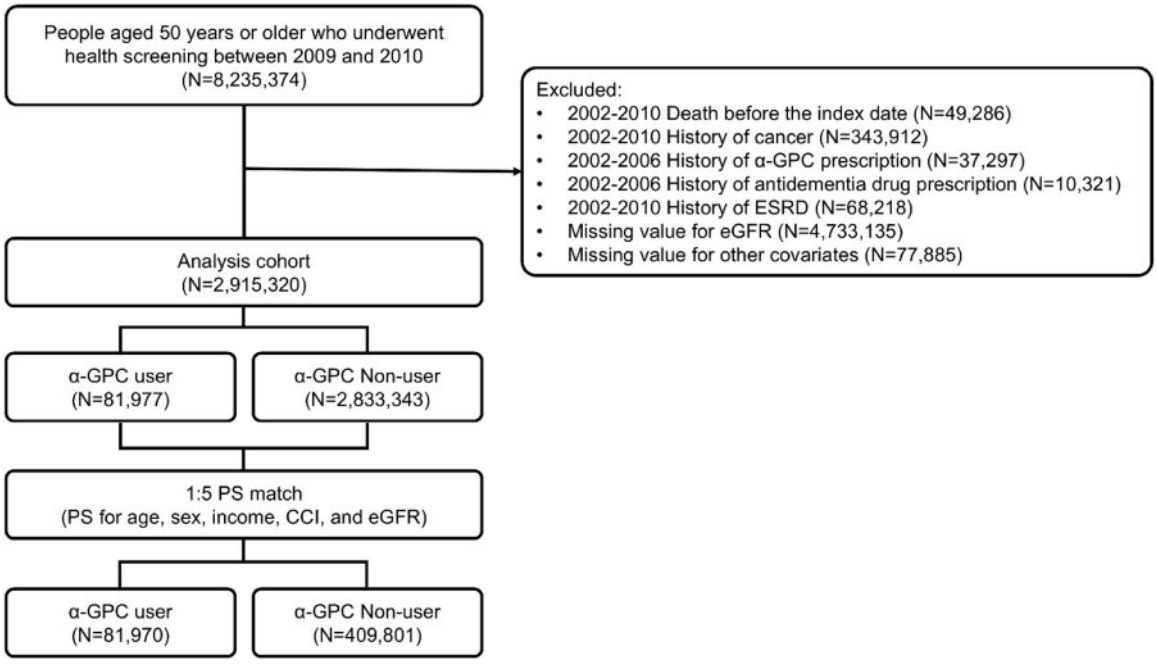

Fig. 1. Flow chart of study population. Abbreviations: α-GPC, L-α-glycerylphosphorylcholine; ESRD, end-stage renal disease; PS, propensity score; CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate.

categorized by cumulative duration: < 180 days or ≥ 180 days.

2.4. Primary outcome of kidney cancer

The primary outcome was newly diagnosed kidney cancer (ICD−10 code C64) combined with critical condition codes V193 or V194, which confirm cancer diagnoses eligible for insurance benefit coverage in the NHIS claims database. [15]

2.5. Statistical analysis

Baseline characteristics of α-GPC users and non-users were summarized before and after PS matching. PS were estimated using a logistic regression model including age group, sex, household income, CCI, and eGFR. These five variables were selected as the PS matching variables because they represent the primary sociodemographic and comorbidity determinants of α-GPC prescription; all other potential confounders (lifestyle factors and laboratory values) were directly adjusted in the Cox outcome model. This approach follows recommended doubly-robust practice, where the PS model balances key demographic confounders and the outcome model handles the remaining covariates.

To evaluate covariate balance after matching, standardized mean differences (SMDs) were calculated for all covariates (Table 1); an SMD < 0.1 was considered acceptable balance. The Love plot is provided in Supplementary Figure S1. α-GPC users were matched to non-users in a 1:5 ratio using greedy nearest-neighbor matching with a caliper of 0.25 on the logit of the PS, with exact matching on age group, sex, income, and CCI.

Cox proportional hazards regression models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). Model 1 was adjusted for age group and sex. Model 2 was additionally adjusted for household income, CCI, smoking status, physical activity, alcohol consumption, body mass index (BMI), systolic blood pressure, total cholesterol, fasting serum glucose, hypertension, diabetes, dyslipidemia, statin use, non-steroidal anti-inflammatory drugs (NSAIDs) use, aspirin use, and eGFR. Trend tests were performed by modeling cumulative α-GPC prescription days as a continuous variable.

Sensitivity analyses were conducted using lag periods of > 1, > 2, > 3, > 5, and > 7 years to assess the robustness of the findings against potential reverse causation and to account for the latency period of kidney carcinogenesis. Subgroup analyses were stratified by sex, age group, household income, CCI, and eGFR; interaction terms were tested for each stratifying variable. As an additional sensitivity analysis, we conducted a full-cohort analysis that included participants previously

Table 1
Descriptive characteristics of the participants.

	Before the matching			After the matching		
Characteristics	**α-GPC Non-user**	**α-GPC User[a]**	**SMD**	**α-GPC Non-user[a]**	**α-GPC User[a]**	**SMD**
Total participants, n	2833,343	81,977		409,801	81,970	
Kidney cancer, n (%)	10,355	280		1570	280	
Age, mean (SD)	61.37 (8.49)	67.11 (8.72)	0.667	66.3 (8.71)	67.11 (8.72)	0.093
Age, n (%)			0.595			0.000
< 65	1874,156 (66.15)	30,882 (37.67)		154,376 (37.67)	30,878 (37.67)	
≥ 65	959,187 (33.85)	51,095 (62.33)		255,425 (62.33)	51,092 (62.33)	
Sex, n (%)			0.099			0.000
Men	1193,832 (42.14)	30,566 (37.29)		152,776 (37.28)	30,561 (37.28)	
Women	1639,511 (57.86)	51,411 (62.71)		257,025 (62.72)	51,409 (62.72)	
Household income, n (%)			0.040			0.000
1st quartile (highest)	1045,620 (36.9)	33,089 (40.36)		165,402 (40.36)	33,087 (40.36)	
2nd quartile	733,536 (25.89)	20,361 (24.84)		101,803 (24.84)	20,361 (24.84)	
3rd quartile	521,321 (18.4)	13,616 (16.61)		68,060 (16.61)	13,614 (16.61)	
4th quartile (lowest)	532,866 (18.81)	14,911 (18.19)		74,536 (18.19)	14,908 (18.19)	
Charlson comorbidity index, n (%)			0.460			0.000
0	1138,782 (40.19)	9101 (11.1)		45,498 (11.1)	9100 (11.1)	
1–2	1209,352 (42.68)	34,704 (42.33)		173,492 (42.34)	34,702 (42.34)	
≥ 3	485,209 (17.12)	38,172 (46.56)		190,811 (46.56)	38,168 (46.56)	
Alcohol intake, times/week, n (%)			0.146			0.050
None	1914,000 (67.55)	63,928 (77.98)		306,101 (74.7)	63,926 (77.99)	
1–2	544,177 (19.21)	10,542 (12.86)		60,119 (14.67)	10,541 (12.86)	
3–4	212,030 (7.48)	3734 (4.55)		22,829 (5.57)	3731 (4.55)	
≥ 5	163,136 (5.76)	3773 (4.6)		20,752 (5.06)	3772 (4.6)	
Physical activity, times/week, n (%)			0.092			0.037
None	1575,891 (55.62)	51,592 (62.93)		245,844 (59.99)	51,587 (62.93)	
1–2	372,757 (13.16)	8903 (10.86)		46,832 (11.43)	8903 (10.86)	
3–4	315,369 (11.13)	7211 (8.8)		40,078 (9.78)	7211 (8.8)	
≥ 5	569,326 (20.09)	14,271 (17.41)		77,047 (18.8)	14,269 (17.41)	
Smoking status, n (%)			0.090			0.016
Never smoker	2003,332 (70.71)	62,234 (75.92)		307,621 (75.07)	62,232 (75.92)	
Past smoker	389,250 (13.74)	10,276 (12.54)		51,243 (12.5)	10,273 (12.53)	
Current smoker	440,761 (15.56)	9467 (11.55)		50,937 (12.43)	9465 (11.55)	
Body mass index, kg/m^2, mean (SD)	24.14 (3.38)	24.09 (3.16)	0.015	24.08 (3.18)	24.09 (3.16)	0.003
Systolic blood pressure, mmHg, mean (SD)	126.64 (16.05)	128.62 (16.39)	0.122	128.46 (16.31)	128.62 (16.39)	0.010
Fasting serum glucose, mg/dL, mean (SD)	102.09 (27.01)	103.98 (29.95)	0.066	106.8 (32.74)	103.98 (29.95)	0.090
Total cholesterol, mg/dL, mean (SD)	202.3 (43.91)	199.98 (45.13)	0.052	199.92 (46.68)	199.98 (45.13)	0.001
eGFR, mL/min/1.73m^2, mean (SD)	72.27 (23.38)	64.22 (23.19)	0.346	64.12 (21.79)	64.17 (22.3)	0.002
Hypertension, n (%)	1117,799 (39.45)	49,883 (60.85)	0.438	220,506 (53.81)	49,880 (60.85)	0.143
Diabetes, n (%)	359,735 (12.7)	15,876 (19.37)	0.183	99,980 (24.4)	15,874 (19.37)	0.122
Dyslipidemia, n (%)	580,349 (20.48)	23,981 (29.25)	0.204	106,905 (26.09)	23,977 (29.25)	0.071
Statin user, n (%)	710,477 (25.08)	33,225 (40.53)	0.334	140,339 (34.25)	33,221 (40.53)	0.130
NSAIDs user, n (%)	2616,443 (92.34)	78,770 (96.09)	0.161	389,179 (94.97)	78,763 (96.09)	0.054
Aspirin user, n (%)	781,322 (27.58)	44,206 (53.92)	0.557	169,524 (41.37)	44,201 (53.92)	0.253

Abbreviations; α-GPC, L-α-glycerylphosphorylcholine; SMD, standardized mean difference; eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation.

[a] Cumulative number of days with L-α-glycerylphosphorylcholine prescriptions between 2007 and 2010.

excluded for missing covariate data. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A two-sided P value < 0.05 was considered statistically significant.

2.6. Ethics approval

This study was approved by the Institutional Review Board of Seoul National University Hospital (E−2601–125–1710). Informed consent was waived due to data anonymization. The study was conducted in accordance with the Declaration of Helsinki and reported following the STROBE guidelines.

3. Results

3.1. Baseline Characteristics

Baseline characteristics of the study population before and after PS matching are presented in Table 1. Before matching, α-GPC users were older than non-users (mean age, 67.11 vs. 61.37 years). After 1:5 PS matching, 81,970 α-GPC users and 409,801 non-users were included, with the distributions of age, sex, household income, and CCI being identical between the two groups. After matching, SMDs for all PS matching variables (age group, sex, household income, CCI, and eGFR) were 0 or near 0, and most covariates showed SMDs below 0.1. In the matched cohort, women accounted for 62.72% of the α-GPC users. With respect to comorbidity burden, 46.56% of α-GPC users had a CCI score of ≥ 3, and 11.10% had a score of 0. Hypertension was more prevalent among α-GPC users than non-users (60.85% vs. 53.81%), and the prevalence of diabetes was higher among non-users than α-GPC users (24.40% vs. 19.37%). Mean eGFR was similar between α-GPC users and non-users in the matched cohort (64.17 vs. 64.12 mL/min/1.73 m^2).

3.2. Association between L-α-glycerylphosphorylcholine and risk of kidney cancer

The association between α-GPC use and kidney cancer risk is shown in Table 2. In the matched cohort, α-GPC use was not associated with risk of kidney cancer. During follow-up, 1570 kidney cancer events occurred among non-users over 4945,930 person-years (incidence rate, 0.32 per 1000 person-years), compared with 280 events among α-GPC users over 937,996 person-years (0.30 per 1000 person-years). In the age- and sex-adjusted model (Model 1), the aHR for kidney cancer among α-GPC users compared with non-users was 0.98 (95% CI, 0.86–1.11), and in the fully adjusted model (Model 2) it was similarly 0.95 (95% CI, 0.84–1.08). When stratified by cumulative prescription duration, neither < 180 days (185 events over 662,261 person-years; 0.28 per 1000 person-years; Model 2 aHR, 0.93 [95% CI, 0.80–1.08]) nor ≥ 180 days (95 events over 275,374 person-years; 0.34 per 1000 person-years; aHR, 1.01 [95% CI, 0.82–1.24]) was associated with kidney cancer risk. A sensitivity analysis including participants previously excluded for missing covariate data yielded consistent null results (Supplementary Table S1).

Sensitivity analyses applying lag periods of > 1, > 2, > 3, > 5, and > 7 years yielded results consistent with the main analysis (Table 3). Across all lag-time analyses, α-GPC use was not associated with kidney cancer risk, and no significant trends were observed according to cumulative prescription duration.

3.3. Subgroup analyses

Results of subgroup analyses stratified by sex, age group, household income, CCI, and eGFR are summarized in Supplementary Table S2. The association between α-GPC use and kidney cancer risk did not differ materially across subgroups. No significant interactions were observed for all subgroups (all P for interaction >0.05).

4. Discussion

The primary finding of this study is the null association between the use of α-GPC and the risk of developing kidney cancer. Contrary to our a priori hypothesis that supplemental α-GPC may lower kidney cancer risk considering the protective effects of dietary free choline, we observed no statistically significant associations, both before and after PS matching. Furthermore, the null findings remained consistent across sensitivity analyses incorporating 1–7-year lag periods, as well as across subgroup analyses stratified by age, sex, household income level, CCI, and eGFR levels.

Despite our a priori hypothesis of risk reduction of renal outcomes regarding choline, [5,8] the exogenous administration of α-GPC did not appear to decrease the risk of renal malignancy. The results from this study suggest that blood-brain barrier crossing α-GPC should only be used for its cognitive enhancement effects in neurological conditions such as Alzheimer's disease, and not necessarily for the prevention of kidney cancer. The safety profile of α-GPC, which is non-genotoxic in both preclinical and clinical models, [16,17] also support these results. It is notable that dietary free choline was associated with reduced RCC risk in prior studies, [10] while other choline-related nutrients from food were not; this distinction reinforces the complexity of the choline-kidney cancer relationship and the importance of distinguishing pharmaceutical from dietary exposure.

On one hand, α-GPC undergoes preferential metabolism by intestinal microbiota into trimethylamine N-oxide (TMAO) [18] – a metabolite

Table 2
Risk of kidney cancer among α-GPC users and non-users.

	Before the matching					After the matching				
	Non-user	**α-GPC User[a]**	**< 180 days**	**≥ 180 days**	**P for trend**	**Non-user**	**α-GPC User[a]**	**< 180 days**	**≥ 180 days**	**P for trend**
No. of participants, n	2833,343	81,977	57,428	24,549		409,801	81,970	57,422	24,548	
Events, n	10,355	280	185	95		1570	280	185	95	
Incidence rate, per 1000 PY	0.28	0.30	0.28	0.34		0.32	0.30	0.28	0.34	
aHR (95% Cl)										
Model 1[b]	**1.00 (Ref.)**	1.10 (0.98–1.25)	1.05 (0.91–1.22)	1.23 (0.99–1.50)	0.051	**1.00 (Ref.)**	0.98 (0.86–1.11)	0.93 (0.80–1.08)	1.07 (0.88–1.33)	0.947
Model 2[c]	**1.00 (Ref.)**	0.98 (0.87–1.10)	0.95 (0.82–1.10)	1.03 (0.84–1.26)	0.856	**1.00 (Ref.)**	0.95 (0.84–1.08)	0.93 (0.80–1.08)	1.01 (0.82–1.24)	0.648

Abbreviations: α-GPC, L-α-glycerylphosphorylcholine; aHR, adjusted hazard ratio; CI, confidence interval.
[a] Cumulative number of days with L-α-glycerylphosphorylcholine prescriptions between 2007 and 2010.
[b] Adjusted for age group, sex.
[c] Further adjusted household income, Charlson comorbidity index, smoking status, physical activity, alcohol consumption, body mass index, systolic blood pressure, total cholesterol, fasting serum glucose, hypertension, diabetes, dyslipidemia, statin, NSAIDs, aspirin, and eGFR on the basis of Model 1.

Table 3
Association between α-GPC use and kidney cancer risk with latent period in matched data.

	aHR (95% CI)				P for trend
	Non-user	α-GPC User[a]	< 180 days	≥ 180 days	
Lag time > 1 year					
Number of participants, n	404,532	80,512	56,418	24,094	
Events, n	1515	273	179	94	
Incidence rate, per 1000 PY	0.33	0.32	0.30	0.37	
aHR (95% CI)[b]	**1.00 (Ref.)**	0.96 (0.85–1.10)	0.93 (0.80–1.09)	1.03 (0.83–1.27)	0.792
Lag time > 2 year					
Number of participants, n	398,098	78,682	55,190	23,492	
Events, n	1463	261	172	89	
Incidence rate, per 1000 PY	0.35	0.34	0.31	0.39	
aHR (95% CI)[b]	**1.00 (Ref.)**	0.96 (0.84–1.09)	0.93 (0.79–1.09)	1.01 (0.82–1.26)	0.670
Lag time > 3 year					
Number of participants, n	391,232	76,713	53,838	22,875	
Events, n	1383	247	164	83	
Incidence rate, per 1000 PY	0.37	0.35	0.33	0.41	
aHR (95% CI)[b]	**1.00 (Ref.)**	0.96 (0.84–1.10)	0.94 (0.80–1.11)	1.00 (0.80–1.25)	0.700
Lag time > 5 year					
Number of participants, n	375,635	72,394	50,960	21,434	
Events, n	1218	216	144	72	
Incidence rate, per 1000 PY	0.41	0.39	0.37	0.45	
aHR (95% CI)[b]	**1.00 (Ref.)**	0.96 (0.83–1.11)	0.94 (0.79–1.12)	0.97 (0.79–1.27)	0.707
Lag time > 7 year					
Number of participants, n	357,826	67,692	47,809	19,883	
Events, n	989	182	125	57	
Incidence rate, per 1000 PY	0.44	0.44	0.43	0.48	
aHR (95% CI)[b]	**1.00 (Ref.)**	1.00 (0.86–1.18)	1.01 (0.84–1.22)	0.99 (0.76–1.30)	0.995

Abbreviations: α-GPC, L-α-glycerylphosphorylcholine; aHR, adjusted hazard ratio; CI, confidence interval.
[a] Cumulative number of days with L-α-glycerylphosphorylcholine prescriptions between 2007 and 2010.
[b] Adjusted for age group, sex, household income, Charlson comorbidity index, smoking status, physical activity, alcohol consumption, body mass index, systolic blood pressure, total cholesterol, fasting serum glucose, hypertension, diabetes, dyslipidemia, statin, NSAIDs, aspirin, and eGFR.

implicated in atherosclerosis, chronic kidney disease (CKD), and several malignancies. [1,11] A randomized controlled trial demonstrated that supplemental choline bitartrate raised fasting plasma TMAO levels higher than equivalent dietary choline from foods such as eggs, [14] indicating that pharmaceutical forms of choline generate greater TMAO exposure than dietary sources. Renal tubular epithelial cells, which highly express organic cation transporters involved in choline compound handling, represent a plausible site for TMAO-accumulation and toxicity. [19,20] Given that approximately 95% of circulating TMAO is renally excreted, [21] prolonged tubular exposure could trigger chronic tubulointerstitial inflammation, potentially via NLRP3 inflammasome activation [22] and TNF-α-mediated fibrotic signalling, [21,23] which may in turn engender oxidative stress and epigenetic dysregulation [24]—collectively fostering a microenvironment potentially conducive to renal carcinogenesis. However, the association between TMAO and disease is frequently confounded by renal function, gut microbiome composition, and FMO3 genotype, demanding careful interpretation. [11] The null finding for kidney cancer may reflect insufficient TMAO accumulation in this population, organ-specific differences in TMAO toxicity, or the protective role of adequate renal function in TMAO clearance.

Human epidemiologic evidence examining supplemental α-GPC exposure and kidney cancer remains limited. Our study was designed to control for potential confounders including BMI, systolic blood pressure, total cholesterol, NSAIDs use, aspirin use, and eGFR, and observed no significant association between α-GPC exposure and kidney cancer risk. These findings suggest that orally administered α-GPC may differ from dietary choline in its biological effects, possibly reflecting differences in metabolic pathways and host-related factors. Further well-designed clinical and population-based studies are needed to better characterize the long-term oncologic safety of α-GPC.

Strengths of this study include its focus on a specific cholinergic agent, distinguishing it from broader dietary choline studies that are often confounded by high-protein and high-fat diets. Rigorous exclusion of ESRD patients minimized confounding regarding the potential association between renal cancer and underlying kidney disease. Exact 1:5 PS matching maximized comparability between exposed and non-exposed groups. Washout periods were implemented to mitigate reverse causality. The use of a nationwide database covering ~97% of the Korean population with long-term follow-up through 2024 provides a large, representative sample with robust outcome ascertainment.

5. Limitations

This study has certain limitations. First, dietary habits, FMO3 genotype, and gut microbiome composition were not available in the NHIS database, representing potential residual confounding. Second, prescription records do not guarantee actual medication intake, and cumulative prescription days may not accurately represent the actual dose of α-GPC received. Third, participants with missing covariate data were excluded, which could introduce selection bias if missing data were not missing at random. To address this, we conducted a sensitivity analysis using the full cohort that included participants with missing covariate data (Supplementary Table S1), which yielded consistent null results. Fourth, the study population was limited to Korean adults aged ≥ 50, limiting generalizability to other ethnic or geographic populations. Future longitudinal studies should continue to monitor the long-term safety and effects of α-GPC on cancer outcomes, [25,26] particularly in patients with pre-existing metabolic conditions like type 2 diabetes, where choline metabolism may be further altered. [27]

6. Conclusions

In this large nationwide cohort study, α-GPC use was not associated with a reduced risk of incident kidney cancer across primary, extended-lag, and subgroup analyses. Consequently, clinicians and consumers are not recommended to use α-GPC as a preventative agent for kidney cancer. Further studies across diverse ethnic populations and with longer lag periods are needed to confirm these findings.

CRediT authorship contribution statement

Sun Jae Park: Writing – review & editing, Methodology. **Gyeongsil Lee:** Writing – review & editing, Methodology, Conceptualization. **Hyun-Young Shin:** Writing – review & editing, Methodology. **Sang Min Park:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Young Jun Park:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Jiwon Yu:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Seogsong Jeong:** Methodology, Writing – review & editing. **Ju Hyun Kang:** Writing – review & editing, Validation, Methodology.

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Declaration of Competing Interest

The authors report no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2026.103152.

Data Availability

The original and processed data in this cohort study are only accessible to qualified researchers in permitted security facilities for a certain period since the used database was based on records of national insurance. Thus, the raw data cannot be shared openly. However, access to the code used in this study can be shared for noncommercial and academic purposes.

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