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Original Article

Impact of long-term N-acetylcysteine use on cancer risk

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Abstract: Chronic obstructive pulmonary disease (COPD) patients face an increased risk of developing various malignancies due to shared risk factors and underlying systemic inflammation. N-acetylcysteine (NAC) has shown potential anticancer properties in preclinical studies, but clinical evidence in COPD patients is limited. We conducted a nationwide propensity score-matched cohort study using data from Taiwan's National Health Insurance Research Database to evaluate the anticancer effects of NAC in COPD patients. Patients diagnosed with COPD between 2008 and 2019 were included, and those with pre-existing cancer were excluded. NAC use was defined as consistent administration for most days with an average dose exceeding 28 cumulative defined daily doses (cDDDs) annually. Cox regression models were adjusted for various covariates was employed. PSM yielded 91,546 patients, evenly distributed between NAC and non-NAC groups. Multivariate Cox regression analysis revealed a lower cancer risk in patients with long-term NAC use compared to non-users (adjusted hazard ratio [aHR] 0.69, 95% confidence interval [CI] 0.66-0.72; P<0.001). Dose-dependent relationships were observed, with higher daily NAC intake associated with reduced cancer risk. Time-varying Cox regression analysis demonstrated significant reductions in the risk of specific cancers, including hepatocellular carcinoma, colorectal cancer, and breast cancer, among NAC users compared to non-users. Our study provides clinical evidence supporting the potential anticancer effects of NAC in COPD patients. These findings highlight the importance of exploring NAC as a chemopreventive agent in high-risk populations and inform clinical practice and future research endeavors.

Keywords: N-acetylcysteine, COPD, cancer risk, chemoprevention, dose-dependent

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory condition characterized by persistent airflow limitation, often accompanied by chronic inflammation and structural changes in the airways [1]. COPD patients face a heightened risk of developing various malignancies [2, 3], owing to shared risk factors such as smoking, environmental exposures, and underlying systemic inflammation [4]. Given the substantial COPD patient population globally, identifying safe, effective, and long-term pharmacological interventions for this susceptible group holds paramount importance. The association between COPD and increased cancer risk stems from multiple factors [2, 3, 5], including chronic inflammation, oxidative stress, impaired DNA repair mechanisms, and shared environmental exposures, all of which contribute to the pathogenesis of both diseases. Consequently, there is a pressing need to identify pharmacotherapeutic agents capable of mitigating cancer risk in COPD patients, thereby addressing an unmet medical need in this vulnerable population.

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N-acetylcysteine (NAC) has garnered attention for its potential anti-cancer and chemopreventive properties, based on findings from preclinical studies and limited clinical evidence [6-18]. As a commonly used antimucolytic agent in COPD management, NAC exhibits antioxidant, anti-inflammatory, and mucolytic properties, which may contribute to its potential anticancer effects [17-23]. Previous preclinical studies has suggested that NAC supplementation could modulate various pathways involved in carcinogenesis, including oxidative stress, inflammation, and cell proliferation, highlighting its potential as a chemopreventive agent [6-18]. Given its established role in respiratory care and its favorable safety profile, NAC presents a promising candidate for exploring its anticancer effects in COPD patients.

Despite the widespread use of NAC as an antimucolytic agent in COPD management [23], clinical studies evaluating its chemopreventive effects in this population are lacking. The potential of NAC to exert anticancer effects in COPD patients remains largely unexplored, underscoring the need for robust clinical evidence to guide therapeutic decision-making. To address this gap, we conducted a nationwide propensity score-matched (PSM) cohort study to evaluate the anticancer effects and dose-dependent relationships of NAC in COPD patients. By leveraging real-world data from a large cohort of COPD patients, we aim to provide comprehensive insights into the therapeutic potential of NAC as a chemopreventive agent in this high-risk population [2, 3, 5], thereby informing clinical practice and guiding future research endeavors.

Patients and methods

Data sources and study cohort

Data spanning from January 2008 to December 2019 were extracted from Taiwan's National Health Insurance Research Database (NHIRD), which houses the detailed claims data of National Health Insurance beneficiaries [24-27]. Encrypted for privacy, the NHIRD includes comprehensive outpatient and inpatient records, encompassing patient identification numbers, birth dates, sex, diagnostic codes based on the International Classification of Diseases (ICD-9-CM and ICD-10-CM), treatment details, medical expenditures, hospital admission and discharge dates, as well as mortality information [24-27]. Approval for the study protocols was obtained from the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Participant selection

Our study focused solely on individuals diagnosed with COPD between 2008 and 2019, with follow-up extending until December 31, 2022. To maintain data accuracy, patients with missing age-related information were excluded from the analysis. NAC use was precisely defined as consistent administration for most days, with an average dose exceeding 28 cumulative defined daily doses (cDDDs) annually. The index date was set as 3 years post the initial documented use of NAC therapy, exceeding the threshold of 28 cDDDs within one year. This 3-year period served as a washout period to prevent occult cancer preceding NAC use and to confirm any potential anti-cancer effects of NAC. Patients diagnosed with cancer within 3 years after initiating NAC therapy were excluded from the analysis to ensure that observed effects were not due to pre-existing cancer.

Patients with pre-existing cancer before the index date were excluded from the analysis. The case group consisted solely of COPD patients who received a minimum of 28 cDDDs of NAC annually, while the control group comprised individuals who did not receive NAC therapy but were prescribed at least one type of non-NAC antimucolytic agent throughout the entire follow-up period. This threshold of 28 cDDDs annually was chosen based on established pharmacoepidemiological practices. It aligns with prior literature where 28 cDDDs per year have been utilized as a standard to define long-term medication use in similar contexts [28-30].

We have included a detailed flowchart illustrating the study design and methodology, which is now provided as **Figure 1**.

Cancer cases were categorized into subgroups, including pancreatic, hepatocellular carcinoma, esophageal, head and neck, gastric, lung, colorectal, gynecological, breast, prostate, and other cancers. Cancer diagnoses were confirmed using the Taiwan Cancer Registry Database (TCRD) and significant illness card to

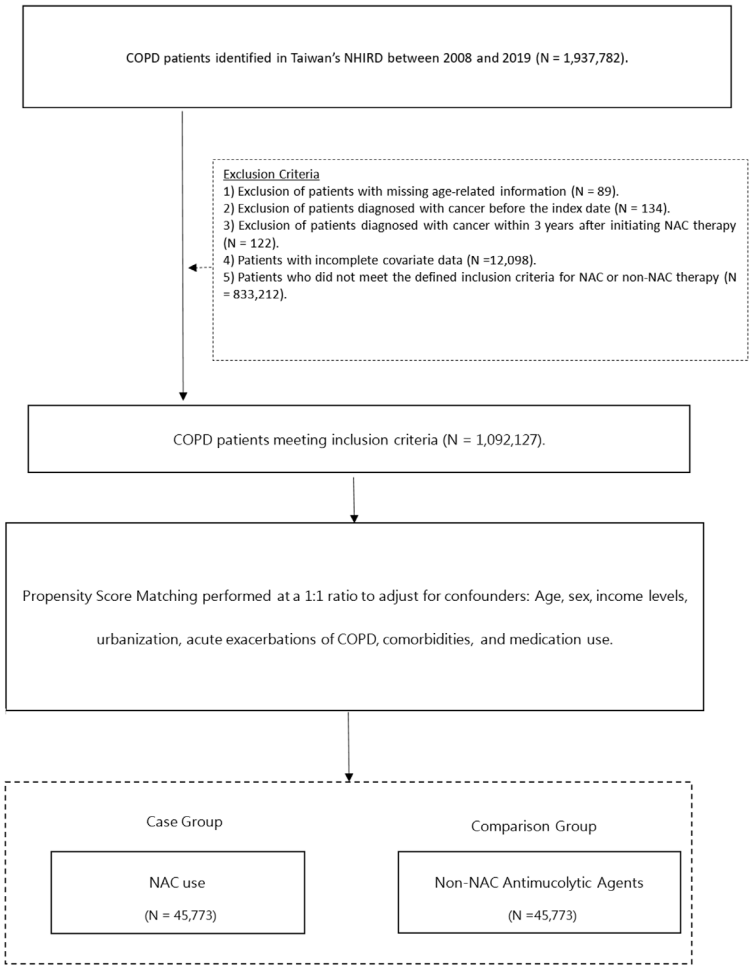

Figure 1. Study flow-chart.

ensure accurate identification of cases [24-27, 31, 32].

PSM and covariates

Following adjustment for confounders, we employed a Cox proportional hazards model to determine the time elapsed from the index date to cancer diagnosis in patients with and without NAC use. To minimize the influence of potential confounders when comparing cancer risk between the NAC and non-NAC use groups, participants underwent PSM at a 1:1 ratio using the greedy method with a caliper of 0.1 [33, 34]. Matching variables included age, sex, income levels, urbanization, acute exacerbations of COPD within one year (as a surrogate for COPD severity), Charlson comorbidity index (CCI) scores, diabetes, hypertension, hyperlipidemia, tuberculosis, asthma, upper respiratory tract infection, hepatitis B, hepatitis C, liver cirrhosis, inflammatory bowel disease, familial adenomatous polyposis, urinary tract infection, Parkinson's disease, child delivery, pneumonia, bronchitis, lung cystic fibrosis, gum and periodontal disease, gastric or duodenal ulcer, sleep disorder, alcohol-related liver disease, cigarette smoking, and medication use (statin, aspirin, and metformin) (**Table 1**). Repeat comorbidities were excluded from CCI scores to avoid repetitive adjustments in multivariate analysis. Comorbidities were ascertained based on ICD-9-CM or ICD-10-CM codes in the primary diagnosis of inpatient records or if there were ≥2 outpatient visits within 1 year. Pre-index date comorbidities were documented. Continuous variables were expressed as the mean ± standard deviation when appropriate. A Cox model was utilized to regress the variables associated with cancer risk in patients with and without NAC use, and a robust sandwich estimator was applied to address clustering within matched sets [35]. Multivariate Cox regression analysis was conducted to compute hazard ratios with 95% confidence intervals (CIs) to identify potential independent predictors of cancer risk.

Primary outcomes

The primary endpoints comprised hazard ratios (HRs) adjusted for the previously mentioned PSM variables to assess cancer risk.

NAC exposure

In our investigation, NAC prescriptions were meticulously coded using the Anatomical Therapeutic Chemical classification system, allowing precise retrieval of pharmaceutical claims data from the NHIRD. Additionally, we assessed the daily intensity of NAC use by calculating the average dose, obtained by dividing

Table 1. Comparative analysis of characteristics in COPD patients treated with N-acetylcysteine versus non-n-acetylcysteine antimucolytic agents after propensity score matching

	Non-NAC Antimucolytic Agents		NAC Use		ASMD
	N = 45,773		N = 45,773		
	N	%	N	%	
Age, years-old (mean ± SD)	56.19 ± 18.58		56.88 ± 18.42		
Age, median (IQR), years-old	58.00 (42.00, 71.00)		58.00 (42.00, 72.00)		
Age group, years					0.0120
18-49	15,847	34.62%	16,097	35.17%	
50-59	7,945	17.36%	7,869	17.19%	
60-69	8,527	18.63%	8,396	18.34%	
≥70	13,454	29.39%	13,411	29.30%	
Sex					0.0370
Female	24,002	52.44%	23,155	50.59%	
Male	21,771	47.56%	22,618	49.41%	
Income (NTD)					0.0170
Low income	290	0.63%	342	0.75%	
≤20,000	35,708	78.01%	35,659	77.90%	
20,001-30,000	3,902	8.52%	3,795	8.29%	
30,001-45,000	3,850	8.41%	3,907	8.54%	
>45,000	2,023	4.42%	2,070	4.52%	
Urbanization					0.0030
Rural	14,731	32.18%	14,664	32.04%	
Urban	31,042	67.82%	31,109	67.96%	
Acute exacerbations of COPD within one year	15,819	34.56%	16,008	34.97%	0.0422
CCI Scores					0.0015
0	14,834	32.41%	14,805	32.34%	
≥1	30,939	67.59%	30,968	67.66%	
Coexisting comorbidities					
Diabetes	8,591	18.77%	8,907	19.46%	0.0175
Hypertension	19,194	41.93%	19,033	41.58%	0.0071
Hyperlipidemia	9,913	21.66%	9,800	21.41%	0.0016
Tuberculosis	1,539	3.36%	1,779	3.89%	0.0284
Asthma	8,905	19.45%	8,723	19.06%	0.0099
Upper respiratory tract infection	35,455	77.46%	34,425	75.21%	0.0530
Hepatitis B	1,189	2.60%	1,267	2.77%	0.0105
Hepatitis C	758	1.66%	828	1.81%	0.0115
Liver Cirrhosis	815	1.78%	812	1.77%	0.0031
Inflammatory bowel disease	815	1.78%	812	1.77%	0.0008
Familial adenomatous polyposis	516	1.13%	580	1.27%	0.0129
Urinary tract infection	12,014	26.25%	12,276	26.82%	0.0129
Parkinson's disease	1,425	3.11%	1,675	3.66%	0.0304
Child delivery	1,502	3.28%	1,474	3.22%	0.0034
Pneumonia	8,919	19.49%	9,483	20.72%	0.0307
Bronchitis	23,366	51.05%	22,246	48.60%	0.0490
Cystic fibrosis	0	0.00%	0	0.00%	0.0000
Gum and periodontal disease	10,761	23.51%	10,801	23.60%	0.0169
Gastric or duodenal ulcer	7,726	16.88%	7,788	17.01%	0.0140
Sleep disorder	18,103	39.55%	18,003	39.33%	0.0024

Number of coexisting comorbidities					
0	10,045	21.93%	9,952	21.74%	0.0032
1	12,367	27.02%	12,468	27.23%	0.0051
2	11,200	24.46%	11,230	24.52%	0.0019
3	6,893	15.06%	7,003	15.29%	0.0063
≥4	5,268	11.52%	5,120	11.22%	0.0097
Alcohol-related liver disease	838	1.83%	964	2.11%	0.0201
Cigarette smoking	16,671	36.42%	16,687	36.46%	0.0008
Medication use					
Statins	4,154	9.08%	4,196	9.17%	0.0031
Metformin	3,911	8.54%	3,995	8.73%	0.0068
Aspirin	7,859	17.17%	8,048	17.58%	0.0108
NAC, cDDD					
Mean (SD)	0.00		167.52 ± 323.18		
Median (Q1, Q3)	0.00		62.40 (38.80, 138.05)		
NAC, cDDD					
Never use	45,773	100.00%	0	0.00%	
Q1	0	0.00%	11,522	25.17%	
Q2	0	0.00%	11,262	24.60%	
Q3	0	0.00%	11,531	25.19%	
Q4	0	0.00%	11,458	25.03%	
DDD					
Never use	45,773	100.00%	0	0.00%	
<1	0	0.00%	22,784	49.78%	
≥1	0	0.00%	22,989	50.22%	
Follow-up time (Years)					
Mean (SD) follow-up time, year	8.38 ± 4.74		7.57 ± 4.92		
Median (IQR) follow-up time, year	7.42 (3.26, 10.99)		6.75 (3.23, 11.67)		

Abbreviations: NAC: N-acetylcysteine; N: Number; SD: Standard Deviation; NTD: New Taiwan Dollar; ASMD: Absolute Standardized Mean Difference; COPD: Chronic Obstructive Pulmonary Disease; CCI: Charlson Comorbidity Index; Q: Quartile; cDDD: Cumulative Defined Daily Doses; DDD: Defined Daily Dose; IQR: Interquartile Range.

the defined daily dose (DDD) of NAC by the total number of prescription days. This method enabled differentiation between various levels of daily NAC use intensity, categorized as average doses below or above 1 DDD. Our aim was to identify the optimal intensity of NAC use for reducing cancer risk by determining the lowest hazard ratio associated with cancer concerning the DDD of NAC use. To explore potential dose-response relationships, patients were stratified into four subgroups based on quartiles of cDDD every year. All statistical models underwent adjustment for the aforementioned covariates, ensuring a rigorous analysis and comprehensive evaluation of the data.

Statistical analysis

To address potential confounding factors, our Cox regression models were adjusted for various covariates, including age, sex, income levels, urbanization, acute exacerbations of COPD within one year, CCI scores, diabetes, hypertension, hyperlipidemia, tuberculosis, asthma, upper respiratory tract infection, hepatitis B, hepatitis C, liver cirrhosis, inflammatory bowel disease, familial adenomatous polyposis, urinary tract infection, Parkinson's disease, child delivery, pneumonia, bronchitis, lung cystic fibrosis, gum and periodontal disease, gastric or duodenal ulcer, sleep disorder, alcohol-related liver disease, cigarette smoking, number of coexisting comorbidities, and medication use [36]. Additionally, to compare cancer incidence between NAC users and nonusers, we employed a time-dependent Cox hazards model, also adjusted for the mentioned covariates. To capture the dynamic nature of NAC prescriptions, we collected data on NAC use every 3 months,

Table 2. Incidence of cancer types in matched COPD patients receiving N-acetylcysteine versus non-N-acetylcysteine antimucolytic agents

	Cancer incidence				*P*-value
	Non-NAC Antimucolytic Agents		NAC Use		
	N = 45,773		N = 45,773		
	N	%	N	%	
Primary outcome					
All Cancers	6,032	13.18%	4,320	9.44%	<0.0001
Pancreatic cancer	145	0.32%	111	0.24%	<0.0001
Hepatocellular carcinoma	975	2.13%	599	1.31%	<0.0001
Esophageal cancer	132	0.29%	87	0.19%	0.0023
Head and neck cancer	401	0.88%	297	0.65%	<0.0001
Gastric cancer	306	0.67%	224	0.49%	0.0004
Lung cancer	1,049	2.29%	1,043	2.28%	0.8944
Colorectal cancer	1,141	2.49%	745	1.63%	<0.0001
Gynecological cancer	81	0.18%	49	0.11%	0.0050
Breast cancer	371	0.81%	206	0.45%	<0.0001
Prostate cancer	567	1.24%	349	0.76%	<0.0001
Others	2,107	4.60%	1,364	2.98%	<0.0001

Abbreviations: NAC: N-acetylcysteine; N: Number.

allowing precise characterization of NAC status as a time-dependent variable. To mitigate potential biases, event-free person-years before the first NAC prescription and follow-up periods without NAC use for at least 3 months were categorized as unexposed follow-up periods. Despite utilizing PSM to mitigate confounding effects, residual imbalances may persist due to the large sample size [37, 38]. Therefore, we complemented our analysis with time-varying multivariable Cox regression and competing risk of death analysis to adjust for the risk of cancer. The Kaplan-Meier estimator was utilized to calculate the cumulative incidence of cancer in propensity score-matched patients with or without NAC use, and the stratified log-rank test was applied to compare cancer incidence (stratified according to matched sets) [39].

Results

PSM and study cohort

PSM yielded 91,546 patients (45,773 in the NAC use group and 45,773 in the never NAC use group); their characteristics are detailed in **Table 1**. As a result of PSM, no significant between-group differences were observed in age, sex, income levels, urbanization, acute exacerbations of COPD within one year before the index date, CCI scores, diabetes, hypertension, hyperlipidemia, tuberculosis, asthma, upper respiratory tract infection, hepatitis B, hepatitis C, liver cirrhosis, inflammatory bowel disease, familial adenomatous polyposis, urinary tract infection, Parkinson's disease, child delivery, pneumonia, bronchitis, lung cystic fibrosis, gum and periodontal disease, gastric or duodenal ulcer, sleep disorder, alcohol-related liver disease, cigarette smoking, and medication use.

The crude incidence of cancer significantly differed between the NAC group and the never NAC use group (P<0.001; **Table 2**). The incidences of all cancers were 13.18% and 9.44% in the Non-NAC antimucolytic agents group and the NAC Use group, respectively. For the Non-NAC antimucolytic agents group compared to the NAC Use group, the incidences of specific cancers were as follows: pancreatic cancer, 0.32% versus 0.24% (P<0.0001); hepatocellular carcinoma, 2.13% versus 1.31% (P<0.0001); esophageal cancer, 0.29% versus 0.19% (P = 0.0023); head and neck cancers, 0.88% versus 0.65% (P<0.0001); gastric cancer, 0.67% versus 0.49% (P = 0.0004); lung cancer, 2.29% versus 2.28% (P = 0.8944); colorectal cancer, 2.49% versus 1.63% (P<0.0001); gynecological cancer, 0.18% versus 0.11% (P = 0.0050);

Table 3. Cancer risk in matched COPD patients treated with N-acetylcysteine across different daily intensity and cumulative doses

	Cancer risk					
	Crude HR (95% CI)	*P*-value	aHR* (95% CI)	*P*-value	aHR# (95% CI)	*P*-value
NAC (ref. Never-NAC use)	1.00	-	1.00	-	1.00	-
NAC use	0.70 (0.67, 0.72)	<0.0001	0.69 (0.66, 0.72)	<0.0001	0.64 (0.62, 0.67)	<0.0001
cDDD of NAC (ref. Never-NAC use)	1.00	-	1.00	-	1.00	-
Q1	0.74 (0.69, 0.79)	<0.0001	0.95 (0.89, 0.98)	0.0404	0.88 (0.83, 0.94)	0.0001
Q2	0.71 (0.67, 0.76)	<0.0001	0.83 (0.78, 0.89)	<0.0001	0.77 (0.72, 0.82)	<0.0001
Q3	0.71 (0.67, 0.76)	<0.0001	0.70 (0.66, 0.75)	<0.0001	0.64 (0.6, 0.68)	<0.0001
Q4	0.62 (0.58, 0.66)	<0.0001	0.45 (0.42, 0.48)	<0.0001	0.42 (0.39, 0.45)	<0.0001
P for trend		<0.0001		<0.0001		<0.0001
DDD of NAC (ref. Never-NAC use)	1.00	-	1.00	-	1.00	-
<1	0.75 (0.72, 0.79)	<0.0001	0.71 (0.66, 0.73)	<0.0001	0.67 (0.61, 0.69)	<0.0001
≥1	0.63 (0.6, 0.66)	<0.0001	0.69 (0.65, 0.72)	<0.0001	0.64 (0.61, 0.67)	<0.0001
P for trend		<0.0001		<0.0001		<0.0001

Abbreviations: NAC: N-acetylcysteine; ref.: Reference; HR: Hazard ratio; aHR: Adjusted hazard ratio; CI: Confidence interval; Q: Quartile; DDD: Defined daily dose; cDDD: Cumulative defined daily doses. *The time-varying Cox model, which treats NAC use as a dynamic variable, was adjusted to account for several factors. These include age, sex, income levels, urbanization, acute exacerbations of COPD within one year, CCI scores, coexisting comorbidities, number of coexisting comorbidities, alcohol-related liver disease, cigarette smoking, and medication use. #The Fine and Gray method was adapted to estimate the hazard of HCC considering competing risks from death.

breast cancer, 0.81% versus 0.45% (P< 0.0001); prostate cancer, 1.24% versus 0.76% (P<0.0001); and other cancers, 4.60% versus 2.98% (P<0.0001), respectively.

Cancer risk after multivariate cox regression analysis

The results of multivariate Cox regression analysis indicated that patients with long-term NAC use had a lower cancer risk (**Table 3**), with no significant differences observed in explanatory variables. In the multivariate Cox regression analysis, the aHRs (95% CIs) of cancer risk for the NAC group compared with the never NAC use group were 0.69 (0.66-0.72; P<0.001). This observation was supported by a significant log-rank test result (P<0.0001; **Figure 2**). Furthermore, Cox regression analysis revealed a dose-dependent decline in cancer risk associated with NAC usage. Examination of cDDDs of NAC per year displayed a consistent dose-response pattern, with progressively diminished aHRs across quartiles (0.45, 0.70, 0.83, and 0.95 for quartiles 4, 3, 2, and 1, respectively) relative to non-NAC users (P for trend <0.0001), as depicted in **Figure 3** (P<0.0001). These findings further support the notion of dose-dependent effects of NAC in mitigating cancer risk. We observed a proportional relationship between cumulative NAC dosage, measured by cDDD, and the aHRs for cancer, indicating decreased aHRs with higher cumulative NAC dosages (Supplementary Figure 1).

Individuals using 1 DDD or more and less than 1 DDD exhibited an aHR of 0.69 (95% CI: 0.65 to 0.72) and 0.71 (95% CI: 0.66-0.73), respectively, compared to those who never used NAC. The *P*-value for trend was less than 0.0001, indicating that higher daily NAC intake is associated with a more pronounced reduction in cancer risk. Additionally, our analysis unveiled a higher daily NAC intensity linked to lower aHRs for cancer (Supplementary Figure 2).

Cox regression model for cancer types in NAC-treated patients

In time-varying Cox regression analysis, the aHRs with 95% (CIs) for pancreatic cancer, hepatocellular carcinoma, esophageal cancer, head and neck cancers, gastric cancer, lung cancer, colorectal cancer, gynecological cancer, breast cancer, prostate cancer, and other cancers risk in the NAC group compared with the never NAC use group were 0.78 (0.61-0.99; P = 0.0451), 0.62 (0.56-0.68; P<0.0001), 0.66 (0.50-0.87; P = 0.0028), 0.74 (0.64-0.86; P<0.0001), 0.75 (0.63-0.89; P = 0.0013), 1.02 (0.93-1.11; P = 0.7257), 0.66 (0.60-0.72; P<0.0001), 0.61 (0.43-0.87; P = 0.0062), 0.56 (0.48-0.67; P<0.0001), 0.61 (0.53-0.69; P<0.0001), and 0.65 (0.61-0.70; P<0.0001),

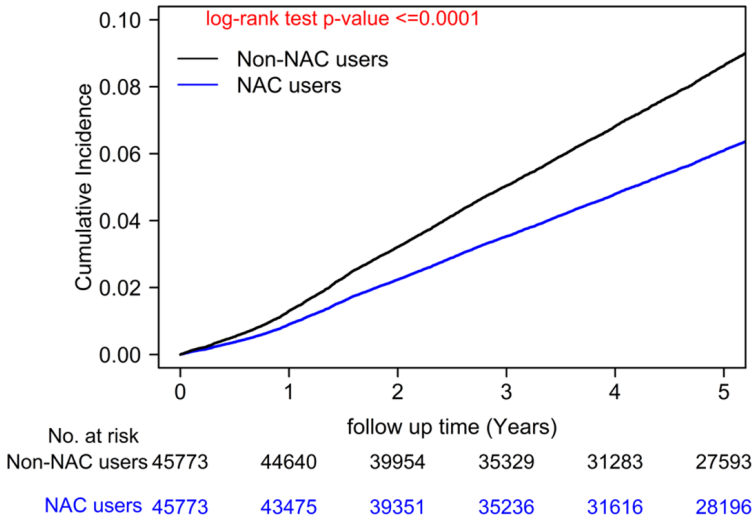

Figure 2. Kaplan-meier analysis of cumulative cancer incidence in patients with and without N-acetylcysteine treatment.

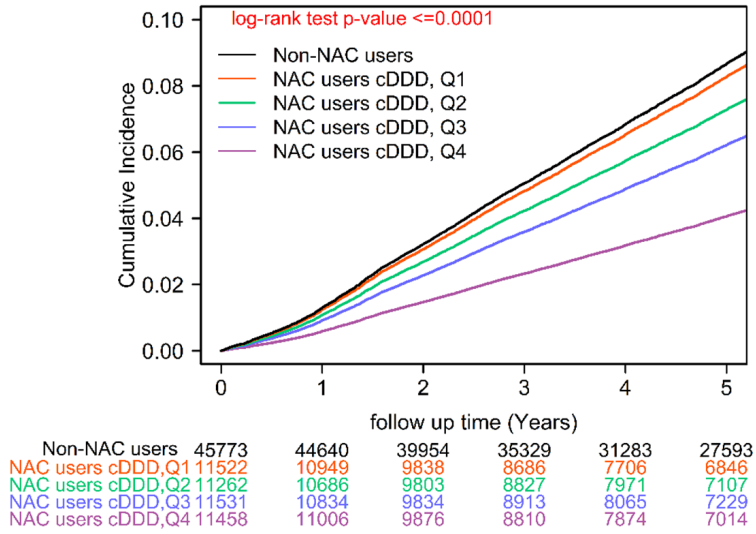

Figure 3. Kaplan-Meier curves for cumulative cancer incidence in patients treated with N-acetylcysteine, stratified by cDDD categories.

respectively (**Table 4**). The priority of the anti-cancer effects was observed for breast cancer, prostate cancer, gynecological cancer, hepatocellular carcinoma, other cancers, esophageal cancer, colorectal cancers, head and neck cancers, gastric cancer, and pancreatic cancer. Prophylactic NAC use appeared to have no anti-cancer effects for lung cancers compared with the never NAC use group. Additionally, we have included the Kaplan-Meier cumulative incidence curves for different cancer types as Supplementary Figure 3.

Discussion

NAC has emerged as a promising candidate for cancer chemoprevention, supported by preclinical evidence demonstrating its efficacy in various animal models [6-9]. Oral administration of NAC has been shown to prevent DNA alterations and suppress tumor development in rodents, indicating its potential to mitigate mutation and cancer through diverse mechanisms [10-16]. Ongoing clinical trials in the USA and Europe are evaluating NAC's chemopreventive properties, with preliminary results suggesting a reduction in polyp recurrence rates [17, 18]. However, the dual nature of antioxidants, with both anti-carcinogenic and potentially carcinogenic effects [17-20], underscores the need for rigorous evaluation of their efficacy and safety in clinical studies. Our study represents the largest clinical investigation to date, comprehensively assessing the chemopreventive effects of NAC across various cancer types, particularly among COPD patients - a high-risk population [2, 3]. Systematically analyzing the impact of NAC on cancer risk within the context of COPD, we leveraged Taiwan's NHIRD for a thorough examination of NAC's effects, including its comparison with non-NAC antimucolytic agents. This approach not only highlights NAC's specific benefits beyond its mucolytic action but also sheds light on potential mechanisms underlying its anti-cancer properties [23]. These findings offer valuable insights into the utility of NAC as a chemopreventive agent in high-risk populations, with implications for future research and clinical practice.

Our study benefits from several notable strengths, including the inclusion of a non-NAC

Table 4. Risk of different cancer types in matched COPD patients receiving treatment with or without N-acetylcysteine

		Cancer risk					
		Crude HR (95% CI)	*P*-value	aHR* (95% CI)	*P*-value	aHR# (95% CI)	*P*-value
All Cancers	NAC (ref. Never-NAC use)	0.70 (0.67, 0.72)	<0.0001	0.69 (0.66, 0.72)	<0.0001	0.64 (0.62, 0.67)	<0.0001
Pancreatic cancer	NAC (ref. Never-NAC use)	0.77 (0.6, 0.99)	0.0379	0.78 (0.61, 0.99)	0.0451	0.71 (0.56, 0.91)	0.0074
Hepatocellular carcinoma	NAC (ref. Never-NAC use)	0.62 (0.56, 0.68)	<0.0001	0.62 (0.56, 0.68)	<0.0001	0.57 (0.51, 0.63)	<0.0001
Esophageal cancer	NAC (ref. Never-NAC use)	0.66 (0.51, 0.87)	0.0031	0.66 (0.5, 0.87)	0.0028	0.62 (0.47, 0.82)	0.0006
Head and neck cancers	NAC (ref. Never-NAC use)	0.75 (0.64, 0.87)	0.0001	0.74 (0.64, 0.86)	<0.0001	0.70 (0.61, 0.82)	<0.0001
Gastric cancer	NAC (ref. Never-NAC use)	0.74 (0.62, 0.88)	0.0005	0.75 (0.63, 0.89)	0.0013	0.70 (0.59, 0.83)	<0.0001
Lung cancer	NAC (ref. Never-NAC use)	1.00 (0.92, 1.09)	1.0000	1.02 (0.93, 1.11)	0.7257	0.94 (0.86, 1.02)	0.1456
Colorectal cancer	NAC (ref. Never-NAC use)	0.65 (0.6, 0.72)	<0.0001	0.66 (0.6, 0.72)	<0.0001	0.61 (0.56, 0.67)	<0.0001
Breast cancer	NAC (ref. Never-NAC use)	0.56 (0.47, 0.66)	<0.0001	0.56 (0.48, 0.67)	<0.0001	0.55 (0.46, 0.65)	<0.0001
Prostate cancer	NAC (ref. Never-NAC use)	0.62 (0.54, 0.7)	<0.0001	0.61 (0.53, 0.69)	<0.0001	0.57 (0.50, 0.65)	<0.0001
Others	NAC (ref. Never-NAC use)	0.64 (0.6, 0.69)	<0.0001	0.65 (0.61, 0.7)	<0.0001	0.61 (0.57, 0.65)	<0.0001

Abbreviations: NAC: N-acetylcysteine; ref.: Reference; HR: Hazard ratio; aHR: Adjusted hazard ratio; CI: Confidence interval. *The time-varying Cox model, which treats NAC use as a dynamic variable, was adjusted to account for several factors. These include age, sex, income levels, urbanization, acute exacerbations of COPD within one year, CCI scores, coexisting comorbidities, number of coexisting comorbidities, alcohol-related liver disease, cigarette smoking, and medication use. #The Fine and Gray method was adapted to estimate the hazard of HCC considering competing risks from death.

antimucolytic group as a negative control [40]. This approach enhances the consistency in selecting patients receiving mucolytic therapy and helps mitigate potential selection bias. The primary function of a negative control is to replicate a condition that does not engage the hypothesized causal mechanism but is highly probable to involve similar sources of bias present in the initial association [40]. With all participants having COPD, they share a comparable baseline risk of cancer development, and the use of mucolytic agents indicates similar disease severity [40]. Additionally, we adjusted for COPD exacerbation severity within one year before the index date (**Table 1**), enhancing comparability between case and control groups. PSM was meticulously applied, ensuring comparability between NAC users and non-users and minimizing confounding bias in our observational research [33, 41]. This methodological rigor holds epidemiological value [33, 40, 41], elucidating causal relationships in complex real-world scenarios. Focusing on COPD patients, known for heightened cancer susceptibility [2, 3]. Amplifies our study's epidemiological relevance. By assessing NAC efficacy within this specific population, we bridge a crucial gap in the literature and offer insights with potential implications for public health interventions and clinical practice.

The anticancer effects of NAC are multifaceted, involving both direct and indirect mechanisms [6-16]. Its antioxidative properties play a critical role in reducing DNA damage, thus potentially preventing cancer initiation [42, 43]. Additionally, NAC's modulation of the immune response and its influence on apoptosis may further contribute to its protective effects against cancer progression [44]. The variation in its effectiveness across different cancer types suggests that these mechanisms may exert varying degrees of influence depending on the specific molecular and environmental factors driving carcinogenesis in different tissues [45, 46]. Consistent with previous findings, an animal model demonstrated that NAC's antioxidant activity, by diminishing ROS, DNA damage, and p53 expression, led to heightened proliferation of lung cancer cells [47]. Our study similarly corroborates these observations, revealing no discernible anticancer effects of NAC on lung cancer risk among COPD patients (**Table 4**) [47]. NAC exhibits diverse mechanisms underlying its chemopreventive effects [6-16]. Serving as a precursor of glutathione, NAC enhances intracellular antioxidant capacity, mitigating oxidative stress-induced DNA damage, a pivotal event in carcinogenesis [48]. Moreover, NAC possesses anti-inflammatory properties by suppressing pro-inflammatory cytokines and inhibiting NF-κB activation, thus attenuating inflammation-associated cancer development [21, 22]. Additionally, NAC modulates cellular signaling pathways crucial for cancer progression, such as the PI3K/Akt/mTOR and MAPK pathways, thereby inhibiting cell proliferation, survival, and metastasis [49]. Furthermore, NAC enhances DNA repair mech-

anisms, facilitating the removal of DNA lesions induced by oxidative stress and genotoxic agents, thus reducing the risk of mutations and cancer initiation [12]. Moreover, NAC modulates epigenetic regulation by restoring aberrant DNA methylation and histone modification patterns, leading to the suppression of oncogene expression and tumor growth [50]. Collectively, these multifaceted mechanisms underscore the potential of NAC as a promising chemopreventive agent, targeting various hallmarks of cancer [21, 22, 43-50]. Further research is warranted to fully elucidate the molecular mechanisms underlying NAC's chemopreventive properties and its clinical application in cancer prevention and therapy.

To date, our study represents the first comprehensive investigation into the anticancer effects of NAC, featuring an extended follow-up period. Moreover, it is the initial exploration of the daily intensity of NAC administration and the cumulative dosage over time (cDDD) to assess potential dose-dependent effects. Our findings suggest that long-term use of this medication exhibits anticancer efficacy, aligning with previous mechanistic studies [6-16, 21, 22, 43-50]. However, the optimal dosage, whether defined by daily density or cDDD, may necessitate further clinical trials for elucidation. The prioritization of anti-cancer effects, with notable efficacy in breast, prostate, and gynecological cancers, but not lung cancer, is particularly intriguing (**Tables 2**, **4** and Supplementary Figure 3). The lack of impact on lung cancer underscores the complexity of cancer prevention and highlights the need for targeted interventions that consider the specific risk factors and biological pathways involved in each cancer type.

The study benefits from several key strengths that contribute to its validity and reliability. Firstly, by leveraging Taiwan's NHIRD linked to TCRD, we accessed a comprehensive dataset that facilitated a thorough examination of patient characteristics and outcomes. The inclusion of a large study cohort spanning over a decade, with follow-up until 2022, ensured robust statistical power and the detection of significant associations. Moreover, the precise definition of NAC exposure minimized misclassification bias, while PSM effectively balanced potential confounders between NAC users and non-users. Rigorous statistical analyses, including time-varying Cox proportional hazards models and dose-response assessments, further strengthened the study's findings. The validation of cancer diagnoses using external databases enhanced the accuracy of cancer ascertainment. Additionally, the exploration of specific cancer types revealed prioritized anticancer effects for certain malignancies, offering valuable clinical insights. The extended follow-up period, averaging 8 years, along with a 3-year washout period, facilitated a thorough assessment of cancer risk over time, thereby capturing potential delayed effects of NAC exposure. Finally, the identification of cancer priority, particularly the absence of anti-cancer effects for lung cancers, underscores the study's contribution to understanding NAC's differential impact on various cancers and guides future research directions. These strengths collectively highlight the significance of the study in informing clinical practice and advancing our understanding of NAC's chemopreventive potential.

While the study boasts numerous strengths, several limitations warrant consideration. The retrospective design, though common in studies utilizing administrative databases, carries inherent biases that may impact the validity of findings. Despite efforts to address confounding through PSM, residual imbalances may persist, necessitating additional adjustment using COX regression. As an observational study, causality cannot be established, and the generalizability of results may be limited, particularly given the focus on COPD patients, which may restrict applicability to broader populations. Additionally, the assessment of NAC exposure solely based on prescription records may underestimate actual medication adherence, potentially attenuating the observed anticancer effects of NAC. While this limitation may affect the magnitude of the observed associations, it is unlikely to overturn the overall conclusions. Furthermore, the Taiwan NHIRD does not provide detailed data on dose consumption of alcohol intake or smoking, precluding the ability to match these important lifestyle factors with dose categories, such as no, light, or heavy smoking. This lack of detailed lifestyle data hampers the ability to account for important confounders, diminishing the study's explanatory power. These limitations under-

score the importance of cautious interpretation and highlight avenues for future research to address these shortcomings and further elucidate the role of NAC in cancer prevention.

Conclusions

Our investigation offers evidence supporting the potential chemopreventive effects of NAC in individuals with COPD. Moreover, our analysis reveals distinct anti-cancer benefits of NAC, particularly evident in breast, prostate, gynecological, and hepatocellular carcinomas. Notably, the dose-response analysis underscores a consistent trend wherein higher cumulative NAC dosages are associated with reduced cancer risk, emphasizing the importance of dosage optimization in clinical practice.

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Disclosure of conflict of interest

None.

Abbreviations

NAC, N-Acetylcysteine; COPD, Chronic Obstructive Pulmonary Disease; cDDD, Cumulative Defined Daily Doses; DDD, Defined Daily Dose; NHIRD, National Health Insurance Research Database; TCRD, Taiwan Cancer Registry Database; HR, Hazard Ratio; aHR, Adjusted Hazard Ratio; CI, Confidence Interval; PSM, Propensity Score Matching; ICD, International Classification of Diseases; CCI, Charlson Comorbidity Index.

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References

[1] Agarwal AK, Raja A and Brown BD. Chronic Obstructive Pulmonary Disease. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Avais Raja declares no relevant financial relationships with ineligible companies. Disclosure: Brandon Brown declares no relevant financial relationships with ineligible companies. 2024.

[2] Kornum JB, Svaerke C, Thomsen RW, Lange P and Sorensen HT. Chronic obstructive pulmonary disease and cancer risk: a Danish nationwide cohort study. Respir Med 2012; 106: 845-852.

[3] Ahn SV, Lee E, Park B, Jung JH, Park JE, Sheen SS, Park KJ, Hwang SC, Park JB, Park HS and Park JH. Cancer development in patients with COPD: a retrospective analysis of the National Health Insurance Service-National Sample Cohort in Korea. BMC Pulm Med 2020; 20: 170.

[4] Burke H and Wilkinson TMA. Unravelling the mechanisms driving multimorbidity in COPD to develop holistic approaches to patient-centred care. Eur Respir Rev 2021; 30: 210041.

[5] Parris BA, O'Farrell HE, Fong KM and Yang IA. Chronic obstructive pulmonary disease (COPD) and lung cancer: common pathways for pathogenesis. J Thorac Dis 2019; 11 Suppl 17: S2155-S2172.

[6] Kelloff GJ, Crowell JA, Boone CW, Steele VE, Lubet RA, Greenwald P, Alberts DS, Covey JM, Doody LA, Knapp GG, et al. Clinical development plan: N-Acetyl-l-cysteine. J Cell Biochem Suppl 1994; 20: 63-73.

[7] De Flora S, D'Agostini F, Izzotti A and Balansky R. Prevention by N-acetylcysteine of benzo[a] pyrene clastogenicity and DNA adducts in rats. Mutat Res 1991; 250: 87-93.

[8] Balansky R, Izzotti A, Scatolini L, D'Agostini F and De Flora S. Induction by carcinogens and chemoprevention by N-acetylcysteine of adducts to mitochondrial DNA in rat organs. Cancer Res 1996; 56: 1642-1647.

[9] De Flora S, Izzotti A, D'Agostini F and Cesarone CF. Antioxidant activity and other mechanisms of thiols involved in chemoprevention of mutation and cancer. Am J Med 1991; 91: 122S-130S.

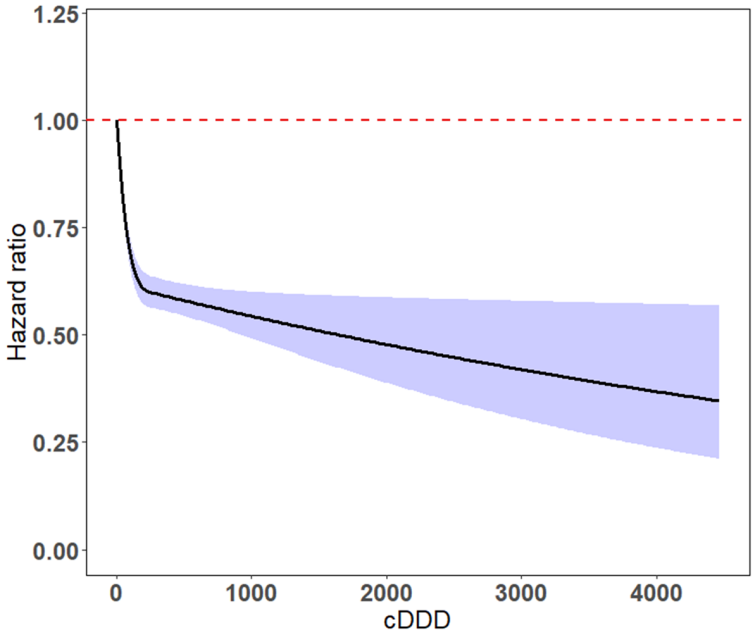
[10] Izzotti A, Bagnasco M, Camoirano A, Orlando M and De Flora S. DNA fragmentation, DNA-protein crosslinks, postlabeled nucleotidic modifications, and 8-hydroxy-2'-deoxyguanosine in the lung but not in the liver of rats receiving intratracheal instillations of chromium(VI). Chemoprevention by oral N-acetylcysteine. Mutat Res 1998; 400: 233-244.

[11] De Caro L, Ghizzi A, Costa R, Longo A, Ventresca GP and Lodola E. Pharmacokinetics and bioavailability of oral acetylcysteine in healthy volunteers. Arzneimittelforschung 1989; 39: 382-386.

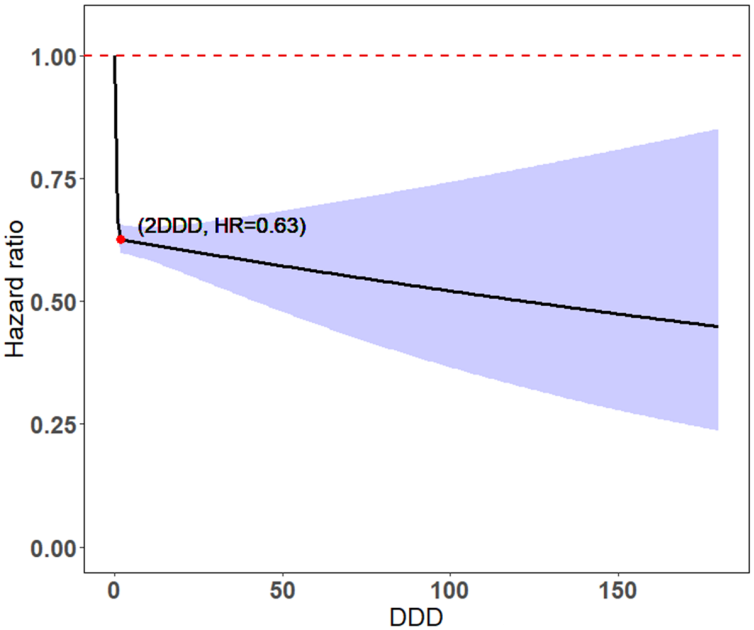
[12] De Flora S, Izzotti A, D'Agostini F and Balansky RM. Mechanisms of N-acetylcysteine in the prevention of DNA damage and cancer, with special reference to smoking-related endpoints. Carcinogenesis 2001; 22: 999-1013.

[13] De Flora S, D'Agostini F, Masiello L, Giunciuglio D and Albini A. Synergism between N-acetylcysteine and doxorubicin in the prevention of tumorigenicity and metastasis in murine models. Int J Cancer 1996; 67: 842-848.
[14] De Flora S and Ramel C. Mechanisms of inhibitors of mutagenesis and carcinogenesis. Classification and overview. Mutat Res 1988; 202: 285-306.
[15] De Flora S, Cesarone CF, Balansky RM, Albini A, D'Agostini F, Bennicelli C, Bagnasco M, Camoirano A, Scatolini L, Rovida A, et al. Chemopreventive properties and mechanisms of N-Acetylcysteine. The experimental background. J Cell Biochem Suppl 1995; 22: 33-41.
[16] Oikawa S, Yamada K, Yamashita N, Tada-Oikawa S and Kawanishi S. N-acetylcysteine, a cancer chemopreventive agent, causes oxidative damage to cellular and isolated DNA. Carcinogenesis 1999; 20: 1485-1490.
[17] Halliwell B, Murcia MA, Chirico S and Aruoma OI. Free radicals and antioxidants in food and in vivo: what they do and how they work. Crit Rev Food Sci Nutr 1995; 35: 7-20.
[18] Diplock AT, Rice-Evans CA and Burdon RH. Is there a significant role for lipid peroxidation in the causation of malignancy and for antioxidants in cancer prevention? Cancer Res 1994; 54 Suppl: 1952s-1956s.
[19] Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994; 330: 1029-1035.
[20] Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL Jr, Valanis B, Williams JH Jr, Barnhart S, Cherniack MG, Brodkin CA and Hammar S. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J Natl Cancer Inst 1996; 88: 1550-1559.
[21] Palacio JR, Markert UR and Martinez P. Anti-inflammatory properties of N-acetylcysteine on lipopolysaccharide-activated macrophages. Inflamm Res 2011; 60: 695-704.
[22] Naugler WE and Karin M. NF-kappaB and cancer-identifying targets and mechanisms. Curr Opin Genet Dev 2008; 18: 19-26.
[23] Sadowska AM, Verbraecken J, Darquennes K and De Backer WA. Role of N-acetylcysteine in the management of COPD. Int J Chron Obstruct Pulmon Dis 2006; 1: 425-434.
[24] Sun M, Chang CL, Lu CY, Zhang J and Wu SY. Effect of opioids on cancer survival in patients with chronic pain: a propensity score-matched population-based cohort study. Br J Anaesth 2022; 128: 708-717.
[25] Sun M, Chen WM, Wu SY and Zhang J. Dementia risk amongst older adults with hip fracture receiving general anaesthesia or regional anaesthesia: a propensity-score-matched population-based cohort study. Br J Anaesth 2023; 130: 305-313.
[26] Sun M, Lin JA, Chang CL, Wu SY and Zhang J. Association between long-term opioid use and cancer risk in patients with chronic pain: a propensity score-matched cohort study. Br J Anaesth 2022; 129: 84-91.
[27] Sun M, Chen WM, Wu SY and Zhang J. Metformin in elderly type 2 diabetes mellitus: dose-dependent dementia risk reduction. Brain 2023; 147: 1474-1482.
[28] Yu JM, Chang CL, Lin KC, Chen WM, Shia BC and Wu SY. Statin use during concurrent chemoradiotherapy for advanced nasopharyngeal cancer. J Natl Compr Canc Netw 2024; 22: e247046.
[29] Sun M, Wang X, Lu Z, Yang Y, Lv S, Miao M, Chen WM, Wu SY and Zhang J. Metformin use and risk of delirium in older adults with type 2 diabetes. Diabetes Care 2024; [Epub ahead of print].
[30] Sun M, Chen WM, Wu SY and Zhang J. Metformin in elderly type 2 diabetes mellitus: dose-dependent dementia risk reduction. Brain 2024; 147: 1474-1482.
[31] Chang CL, Lin KC, Chen WM, Shia BC and Wu SY. Comparative effectiveness of intensity-modulated proton therapy versus intensity-modulated radiotherapy for patients with inoperable esophageal squamous cell carcinoma undergoing curative-intent concurrent chemoradiotherapy. J Thorac Oncol 2024; 19: 818-828.
[32] Chen WM, Yu YH, Chen M, Shia BC and Wu SY. Correspondence: statin use during concurrent chemoradiotherapy with improved survival outcomes in esophageal squamous cell carcinoma. J Thorac Oncol 2023; 18: e107-e109.
[33] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150-161.
[34] Li Y and Li L. Propensity score analysis methods with balancing constraints: a Monte Carlo study. Stat Methods Med Res 2021; 30: 1119-1142.
[35] Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 2013; 32: 2837-2849.
[36] Robins JM, Hernan MA and Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000; 11: 550-560.

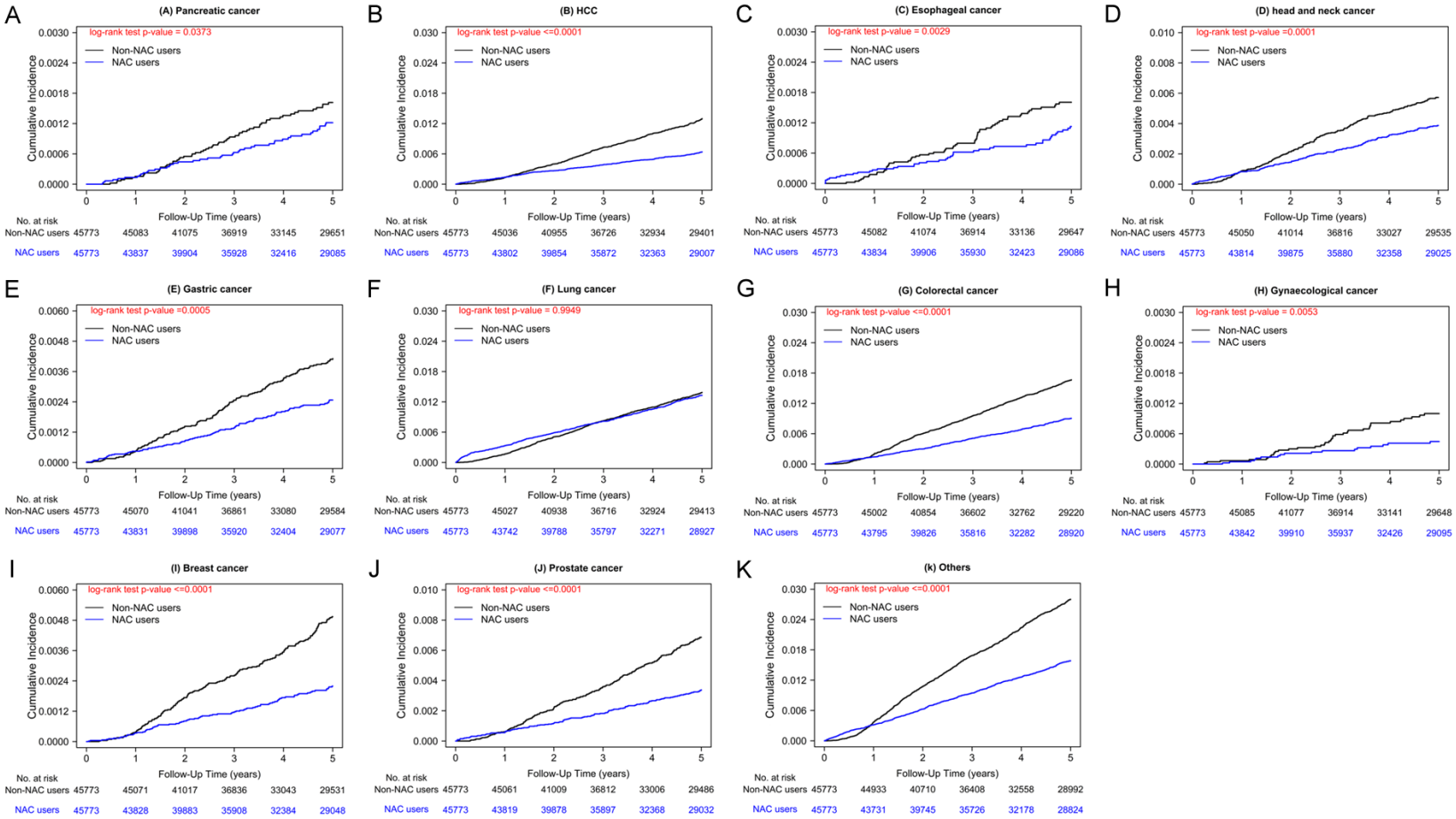
[37] Nguyen TL, Collins GS, Spence J, Daures JP, Devereaux PJ, Landais P and Le Manach Y. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol 2017; 17: 78.
[38] Zhang Z, Kim HJ, Lonjon G and Zhu Y; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. Ann Transl Med 2019; 7: 16.
[39] Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med 2014; 33: 1242-1258.
[40] Lipsitch M, Tchetgen Tchetgen E and Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010; 21: 383-388.
[41] Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. Stat Med 2010; 29: 2137-2148.
[42] Yedjou CG, Tchounwou CK, Haile S, Edwards F and Tchounwou PB. N-acetyl-cysteine protects against DNA damage associated with lead toxicity in HepG2 cells. Ethn Dis 2010; 20 Suppl 1: S1-101-103.
[43] Shih WL, Chang CD, Chen HT and Fan KK. Antioxidant activity and leukemia initiation prevention in vitro and in vivo by N-acetyl-L-cysteine. Oncol Lett 2018; 16: 2046-2052.
[44] Boubaker J, Ben Toumia I, Sassi A, Bzouich-Mokded I, Ghoul Mazgar S, Sioud F, Bedoui A, Safta Skhiri S, Ghedira K and Chekir-Ghedira L. Antitumoral potency by immunomodulation of chloroform extract from leaves of nitraria retusa, tunisian medicinal plant, via its major compounds beta-sitosterol and palmitic acid in BALB/c mice bearing induced tumor. Nutr Cancer 2018; 70: 650-662.
[45] Kwon Y. Possible beneficial effects of N-acetylcysteine for treatment of triple-negative breast cancer. Antioxidants (Basel) 2021; 10: 169.
[46] Kalyanaraman B. NAC, NAC, Knockin' on Heaven's door: interpreting the mechanism of action of N-acetylcysteine in tumor and immune cells. Redox Biol 2022; 57: 102497.
[47] Breau M, Houssaini A, Lipskaia L, Abid S, Born E, Marcos E, Czibik G, Attwe A, Beaulieu D, Palazzo A, Flaman JM, Bourachot B, Collin G, Tran Van Nhieu J, Bernard D, Mechta-Grigoriou F and Adnot S. The antioxidant N-acetylcysteine protects from lung emphysema but induces lung adenocarcinoma in mice. JCI Insight 2019; 4: e127647.
[48] Kerksick C and Willoughby D. The antioxidant role of glutathione and N-acetyl-cysteine supplements and exercise-induced oxidative stress. J Int Soc Sports Nutr 2005; 2: 38-44.
[49] Guo C, Yang M, Jing L, Wang J, Yu Y, Li Y, Duan J, Zhou X, Li Y and Sun Z. Amorphous silica nanoparticles trigger vascular endothelial cell injury through apoptosis and autophagy via reactive oxygen species-mediated MAPK/Bcl-2 and PI3K/Akt/mTOR signaling. Int J Nanomedicine 2016; 11: 5257-5276.
[50] Tortorella SM, Royce SG, Licciardi PV and Karagiannis TC. Dietary sulforaphane in cancer chemoprevention: the role of epigenetic regulation and HDAC inhibition. Antioxid Redox Signal 2015; 22: 1382-1424.



Supplementary Figure 1. Correlation between cumulative N-Acetylcysteine Doses (cDDDs) and cancer hazard ratio in patients.



Supplementary Figure 2. Correlation between N-Acetylcysteine Use Intensity (DDD) and cancer hazard ratio in patients.



Supplementary Figure 3. Kaplan-Meier analysis of cumulative incidence of various cancers in patients with and without N-acetylcysteine treatment. A. Pancreatic cancer. B. Hepatocellular carcinoma. C. Esophageal cancer. D. Head and neck cancers. E. Gastric cancer. F. Lung cancer. G. Colorectal cancer. H. Gynecological cancer. I. Breast cancer. J. Prostate cancer. K. Others.