European Journal of Nutrition (2023) 62:879–889
https://doi.org/10.1007/s00394-022-03044-1

ORIGINAL CONTRIBUTION

Associations of dietary supplement use with all-cause and cause-specific mortality in patients diagnosed with cancer: a large prospective cohort study in the UK Biobank

Chun Sing Lam[1] · Ho Kee Koon[2] · Herbert Ho-Fung Loong[3] · Vincent Chi-Ho Chung[2,4] · Yin Ting Cheung[1]

Received: 11 August 2022 / Accepted: 20 October 2022 / Published online: 1 November 2022

Abstract

Purpose Despite the increasing popularity of supplement use among the cancer community, the current evidence on its effect on mortality in large studies is inconclusive. This study examined the association of dietary supplement use with mortality risk in a large population-based cohort.

Methods This prospective cohort study analyzed data from the UK Biobank on participants who were diagnosed with cancer before July 31, 2019 and self-reported whether they had regular intake of dietary supplements (vitamins, minerals, or non-vitamin non-mineral [NVNM] supplements) after cancer diagnosis. The associations between the use of supplements with mortality were analyzed using Cox proportional hazards models, adjusting for confounders (sociodemographic factors, lifestyle and comorbidities).

Results This analysis included 30,239 participants (mean age: 60.0 years; 61.9% female). Over half (57.8%) were supplement users. At a median follow-up of 11.9 years, 5577 all-cause deaths were registered. A marginal protective effect of supplement use on the risk of all-cause (adjusted hazard ratio [aHR] = 0.95, 95% CI = 0.90–0.99) and cancer (aHR = 0.89, 95% CI = 0.83–0.95) mortality were found, but not the risk of mortality due to other causes. In subgroup analyses, only NVNM dietary supplements were significantly associated with a lower risk of all-cause mortality (aHR = 0.88, 95% CI = 0.83–0.93). Both vitamins (aHR = 0.93, 95% CI = 0.87–0.99) and NVNM dietary supplements (aHR = 0.88, 95% CI = 0.82–0.94) were associated with a modest decrease in cancer mortality which were marginally significant.

Conclusions This is one of the largest cohort studies that identified the associations of dietary supplements with survival in the cancer population. However, the associations are small and should be interpreted cautiously due to the variations among different supplements and the small effect size. Future studies should investigate the effect of individual supplements, particularly NVNM supplements, on improving other cancer-related outcomes.

Keywords Supplements · Vitamin · Mineral · Mortality · Cancer · UK Biobank

Introduction

The global cancer burden is expected to grow exponentially by 50% over the next two decades [1]. The resulting needs arising from the booming population of cancer patients and survivors demand greater attention. Patients and survivors of cancer who are treated with conventional therapies often experience treatment-related toxicities and chronic symptoms [2]. The use of traditional, complementary, and integrative medicines (TCIM) is becoming common among patients with cancer to improve cancer outcomes, manage the complications of therapies and cancer-related symptoms, and address their holistic needs [3]. A recent systematic review reported that approximately half of cancer patients

Vincent Chi-Ho Chung and Yin Ting Cheung have contributed equally and are the co-senior authors.

✉ Yin Ting Cheung
yinting.cheung@cuhk.edu.hk

1 School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

2 School of Chinese Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

3 Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

4 Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

worldwide used TCIM in 2018, demonstrating a significant increase in use from 25% prior to 1990 [3]. Of the TCIM modalities, dietary supplements are the most commonly used by patients with cancer in the US (36–81%) [4, 5] and the UK (41%)[6].

Dietary supplements refer to products taken orally that contain "dietary ingredients" (such as vitamins, minerals, herbs, amino acids) that are intended to supplement the diet and are marketed for use in dosage form [7, 8]. Evidence for the association between the use of dietary supplements and cancer-related outcomes, such as overall survival and mortality, is conflicting and inconclusive [9–13]. There are also concerns about the generalizability of the findings of previous studies and reviews, as many have focused on vitamins and mineral supplements and have paid less attention to the effects of herbal and other supplements [9, 13–15]. Moreover, most studies have been conducted in patients with breast cancer only, which may not be generalizable to other cancer types [11–13, 16, 17]. Furthermore, previous studies usually focused on the effects of a single supplement [9, 18]. While these studies provide more precise estimates for the efficacy/effectiveness of individual supplements, they may not address real-world scenarios and practice settings, where dietary supplement users tend to take combinations of supplements or multi-ingredient products [5, 11, 19].

With the overarching aim of mimicking real-life clinical scenarios, where patients may take multiple types/classes of supplements, this study examined the association between the overall use of dietary supplements by patients diagnosed with cancer and the risk of mortality (all-cause and cause-specific mortality) in a large population-based cohort in the UK. In addition, the study explored the associations between the use of different classes of supplements (vitamins, minerals, and non-vitamin non-mineral [NVNM] dietary supplements) and the risk of mortality.

Methods

This study was registered with the UK Biobank (ref.: 74158), and is reported according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [20].

Study population

The UK Biobank is a large population-based cohort of approximately 500,000 participants in the UK. It facilitates investigation of a wide range of complex diseases of middle and old age [21]. The UK Biobank study first recruited participants aged 40–69 across the UK from 2006 to 2010 and has since conducted repeated assessments. The methods used have been reported in detail elsewhere [21].

In this study, participants were excluded if (1) they had not been diagnosed with malignant cancer at any time from prior to baseline recruitment to subsequent follow-up visits or (2) they were not recruited in subsequent visits after their cancer diagnosis to provide responses to questions related to the use of dietary supplements.

Cancer ascertainment

UK Biobank is linked to national cancer registries (Health and Social Care Information Centre and the National Health Service Central Register) [22]. Cancer diagnoses were coded according to the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10). We included only malignant neoplasms (ICD-9: 140–208; ICD-10: C00–C97), except non-melanoma skin cancer (ICD-9: 173; ICD-10: C44), that had been diagnosed on or before July 31, 2019 (the censoring date of the cancer registry when the data set was acquired).

Ascertainment of the use of supplements

The participants were asked "Do you regularly take any of the following?" and they were provided with a list of supplements in a touchscreen questionnaire. If the participants forgot to record any answers or took supplements that were not listed, they were able to provide the missing details during a verbal interview. The type of supplements that were considered in this study included vitamins; minerals; and NVNM dietary supplements, such as herbs and amino acids. The ingredients that were classified as supplements are listed in Supplementary Table 1.

Supplement users were defined as those who selected any of the supplements mentioned in the touchscreen questionnaire or listed any supplements at the interview stage during any of the assessments (baseline or follow-up) after the date of their cancer diagnosis. Participants who did not provide answers to the questions (did not select any of the supplements or indicated "None of the above") in the touchscreen questionnaire and did not state the use of any supplements during their verbal interviews were excluded.

Ascertainment of mortality outcomes

The UK Biobank obtained comprehensive mortality data (date and cause of death) from the Information Centre (England and Wales) and the National Health Service Central Register Scotland [21]. ICD-10 codes were used in the death records to identify the causes of death. In the current study, all-cause and specific mortality due to cancer (C00–C97), cardiovascular diseases (CVD, I00–I99), respiratory diseases

(J09–J98), digestive diseases (K20–K93), and nervous system diseases (G00–G99) were analyzed. The participants were followed up from the date of recruitment (2006–2010) until the date of death or the end of the follow-up period (March 23, 2021 or earlier if they were lost to follow-up), whichever occurred first.

Assessment of confounders

Potential confounders commonly associated with the use of dietary supplements were selected a priori based on data from the literature [3, 6, 23–26]. These included sociodemographic information (sex, age, Townsend Deprivation Index score, and educational level) and lifestyle behaviors (smoking status, alcohol consumption, physical activity, fruit and vegetable intake, and body mass index [BMI]), which were collected from the baseline touchscreen questionnaire. Clinical confounders included cancer types, age at cancer diagnosis and comorbidities [24, 26]. The Charlson Comorbidity Index (CCI) was used to quantify the comorbidity burden of the participants prior to their cancer diagnosis [27]. The details of the confounders are presented in Supplementary Table 1.

Statistical analyses

Descriptive statistics were used to summarize the pattern of supplement use among cancer patients in the cohort and the baseline characteristics of the participants. Multiple imputation with chained equations was used to deal with missing values and reduce inferential bias [28]. All of the factors included in the multivariate model were included in the imputation model. As the proportion of missing data was small (< 5%) for all of the covariates, five imputed data sets were deemed sufficient [29]. Logistic regression analysis was performed to verify the significant associations between the pre-identified confounders listed in the previous section (Supplementary Table 2).

Associations between the use of dietary supplements and the risk of all-cause and cause-specific mortality were analyzed using Cox proportional hazards models. Three models were run, including a crude model (Model 1); a model adjusted for age and sex (Model 2); and a model fully adjusted for factors identified a priori, including age, sex, socioeconomic factors, lifestyle factors, cancer types, age at cancer diagnosis, and CCI score (Model 3). Index date was defined as the date of primary cancer diagnosis. A competing risk analysis was performed to measure the associations between supplement use and cancer mortality, while considering death due to causes other than cancer as competing risks. Subgroup analyses were performed for different classes of supplements (vitamins, minerals, and NVNM dietary supplements) and their combinations. Stratified analyses were performed to assess the potential modifying effects of factors identified earlier, using the pre-determined groupings presented in Supplementary Table 1.

Three sensitivity analyses were performed. First, all of the analyses described above were repeated using the non-imputed data set. Second, the association between supplement use and the risk of cancer mortality were analyzed without considering competing risks. Third, the analyses were repeated after excluding all patients diagnosed with cancer before 2006 (the initial year of recruitment for the UK Biobank cohort), to reduce the possibility of survival bias. All of the statistical analyses were performed using R, version 4.0.3. A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Of the 502,412 total participants in the cohort, participants were excluded if (1) they had not been diagnosed with malignant cancer at any time from prior to baseline recruitment to subsequent follow-up visits (n = 446,233) or (2) they were not recruited in subsequent visits after their cancer diagnosis and, therefore, had not provided answers to questions related to the use of dietary supplements (n = 25,940). Finally, 30,239 participants were included in the analysis (Supplementary Fig. 1).

The mean age of the participants upon cohort entry was 60.0 (SD = 7.0) years, and 61.9% of them were female (Table 1). The mean age at first cancer diagnosis was 52.8 (SD = 10.3 years). More than half (n = 17,464, 57.8%) of the participants reported the use of supplements after their cancer diagnosis. Most supplement users reported the use of dietary supplements (non-vitamin, non-mineral and non-herbal) (n = 12,460, 41.2%), followed by vitamins (n = 12,043, 39.8%) (Fig. 1). Fish oil (n = 10,234, 33.8%) and multivitamins (n = 6959, 23.0%) were the most commonly used individual supplements. Around 70% of the supplement users (n = 11,991/17,464) took more than one supplements, and more than half (n = 10,222/17464, 58.5%) of them used multiple categories of supplements. The top three combinations are multivitamins–fish oil (n = 4324, 14.3%), glucosamine–fish oil (n = 3999, 13.2%) and vitamin D–calcium (n = 2991, 9.9%).

Compared with non-users, those who reported supplement use were more likely to be female, have a higher socioeconomic status, and be more educated (Supplementary Table 2). Supplement users generally had a healthier lifestyle, as they were less likely to be obese or current smokers, were more physically active, and had higher fruit and vegetable intake. They also tended to have higher comorbidity

Table 1 Baseline characteristics of eligible participants ($N = 30,239$)

	Overall ($n = 30,239$)	%	Supplement user ($n = 17,464$)	%	Non-user ($n = 12,775$)	%	*P*
Sociodemographics							
Sex							**< 0.001**
Male	11,523	38.1	5828	33.4	5695	44.6	
Female	18,716	61.9	11,636	66.6	7080	55.4	
Age attending assessment centres (Mean ± SD)	60.0	± 7.0	60.6	± 6.6	59.2	± 7.3	**< 0.001**
Townsend deprivation index (Mean ± SD)	− 1.5	± 3.0	− 1.5	± 3.0	− 1.3	± 3.1	**< 0.001**
Annual household income (£)							
< 18 000	7230	23.9	4174	23.9	3056	23.9	0.66
≥ 18 000	18,145	60.0	10,418	59.7	7727	60.5	
Missing	4864	16.1	2872	16.4	1992	15.6	
Ethnic background							0.40
White	29,247	96.7	16,859	96.5	12,388	97.0	
Asian	311	1.0	190	1.1	121	0.9	
Black	300	1.0	185	1.1	115	0.9	
Mixed	136	0.4	83	0.5	53	0.4	
Others	168	0.6	96	0.5	72	0.6	
Missing	77	0.3	51	0.3	26	0.2	
Education							**0.04**
College or university degree	9206	30.4	5393	30.9	3813	29.9	
Below degree	20,672	68.4	11,842	67.8	8830	69.1	
Missing	361	1.2	229	1.3	132	1.0	
Lifestyle							
BMI (Mean ± SD)	27.4	± 4.8	27.2	± 4.7	27.8	± 4.9	**< 0.001**
Smoking status							**< 0.001**
Never	15,466	51.2	9124	52.2	6342	49.6	
Former	11,924	39.4	6931	39.7	4993	39.1	
Current	2701	8.9	1327	7.6	1374	10.8	
Missing	148	0.5	82	0.5	66	0.5	
Alcohol consumption							0.50
Never	1339	4.4	762	4.4	577	4.5	
Former	1294	4.3	765	4.4	529	4.2	
Current	27,572	91.2	15,917	91.1	11,655	91.2	
Missing	34	0.1	20	0.1	14	0.1	
Physical activities (min/week)							**< 0.001**
≥ 150	20,065	66.3	11,916	68.2	8149	63.8	
< 150	9425	31.2	5153	29.5	4272	33.4	
Missing	749	2.5	395	2.3	354	2.8	
Fruit intake (servings/day)							**< 0.001**
< 2.0	7524	24.9	3550	20.3	3974	31.1	
2.0–3.9	12,434	41.1	7222	41.4	5212	40.8	
4.0–5.9	6285	20.8	3985	22.8	2300	18.0	
≥ 6.0	3941	13.0	2683	15.4	1258	9.9	
Missing	55	0.2	24	0.1	31	0.2	
Vegetable intake (servings/day)							**< 0.001**
< 2.0	1634	5.4	768	4.4	866	6.8	
2.0–3.9	8227	27.2	4583	26.2	3644	28.5	
4.0–5.9	10,575	35.0	6179	35.4	4396	34.4	
≥ 6.0	9639	31.9	5855	33.5	3784	29.6	
Missing	164	0.5	79	0.5	85	0.7	

Table 1 (continued)

	Overall ($n=30,239$)	%	Supplement user ($n=17,464$)	%	Non-user ($n=12,775$)	%	*P*
Clinical							
Cancer diagnosis[a]							
Breast	10,267	34.0	6608	37.8	3659	28.6	**< 0.001**[a]
Male genital organs	4882	16.1	2609	14.9	2273	17.8	**< 0.001**[a]
Digestive organs	3386	11.2	1794	10.3	1592	12.5	**< 0.001**[a]
Female genital organs	2876	9.5	1702	9.8	1174	9.2	0.15 [a]
Primary, of lymphoid, haematopoietic and related tissue	2459	8.1	1298	7.4	1161	9.1	**< 0.001**[a]
Malignant melanoma of skin	2454	8.1	1401	8.0	1053	8.2	0.59 [a]
Age at first cancer diagnosis (Mean ± SD)	52.8	± 10.3	53.3	± 10.1	52.2	± 10.6	**< 0.001**
Baseline comorbidities							**0.008**
Yes	16,930	56.0	9892	56.6	7038	55.1	
No	13,309	44.0	7572	43.4	5737	44.9	
Charlson comorbidity scores (Median [range] ± IQR)	2 [2–13]	± 0	2 [2–13]	± 0	2 [2–11]	± 0	**< 0.001**

[a]The top six cancer diagnoses are listed here

[b]False discovery rate-adjusted *P* values for multiple testing

Bold values indicate the statistical significance $P < 0.05$

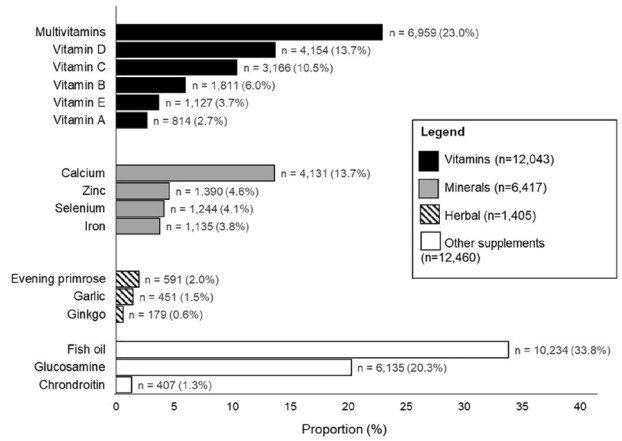

Fig. 1 Pattern of supplement use among cancer patients in the UK Biobank cohort ($n=30,239$)

burden, were older at cancer diagnosis, and diagnosed with cancers that have poorer average prognosis.

Associations of supplement use with all-cause mortality and cause-specific mortality

At a median follow-up of 11.9 years (IQR = 10.2–13.6 years), 5577 all-cause deaths were registered. Cause-specific mortality included 4208 cancer-related deaths, 516 CVD-related deaths, 213 respiratory disease-related deaths, 145 digestive disease-related deaths, and 126 nervous system disease-related deaths. In all three models (crude, age and sex-adjusted, and multivariate), significant inverse associations were found between supplement use and the risk of all-cause and cancer-related mortality (Table 2). The adjusted hazard ratios (aHRs) associated with supplement use were 0.95 (95% confidence interval [CI] = 0.90–0.99, $p=0.04$) for all-cause mortality and 0.89 (95% CI = 0.83–0.95, $p<0.001$) for cancer-related mortality. No significant associations were observed between supplement use and the risk of cause-specific mortality due to CVD, respiratory, digestive, or nervous system diseases.

Subgroup analyses were performed to analyze the associations of different classes of supplements and their combinations with all-cause and cause-specific mortality (Table 3 and Supplementary Table 3). For all-cause mortality, Only NVNM dietary supplements were significantly associated with a lower risk of all-cause mortality (aHR = 0.88, 95% CI = 0.83–0.93, $p<0.001$) in the multivariate model. The use of both vitamins (aHR = 0.93, 95% CI = 0.87–0.99, $p=0.04$) and NVNM dietary supplements (aHR = 0.88, 95% CI = 0.82–0.94, $p<0.001$), was associated with a small decrease in the risk of cancer-related mortality. The combined use of vitamins with NVNM supplements and all three types of supplements were associated with a lower risk of all-cause and cancer-related mortality (aHR = 0.85–0.91, all $p<0.05$). Notably, mineral supplements were found to be associated with an increased risk of mortality due to respiratory (aHR = 1.53, 95% CI = 1.12–2.11, $p=0.008$) and digestive diseases (aHR = 1.56, 95% CI = 1.06–2.31, $p=0.03$), and similar findings were observed for the combined use of vitamins and minerals (aHR = 1.57–1.64, all $p<0.03$).

Stratified analyses were conducted and significant interactions were found between supplement use and sex on the risk of all-cause mortality and cancer-related mortality ($p=0.02$)

Table 2 Association of supplement use with risk of overall and cause-specific mortality

	Death among users	Death among non-users	Model 1 (Crude)	*p* value	Model 2[a]	*p* value	Model 3[a]	*p* value
	N (%)	*N* (%)	Hazard ratio (95% CI)		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
All-cause mortality	3104 (17.8)	2473 (19.4)	0.89 (0.84–0.94)	**< 0.001**	0.91 (0.86–0.96)	**< 0.001**	0.95 (0.90–0.99)	**0.04**
Cancer mortality[b]	2290 (13.1)	1918 (15.0)	0.85 (0.80–0.90)	**< 0.001**	0.87 (0.81–0.92)	**< 0.001**	0.89 (0.83–0.95)	**< 0.001**
CVD mortality	294 (1.7)	222 (1.7)	0.93 (0.78–1.11)	0.43	0.96 (0.81–1.15)	0.67	1.07 (0.89–1.27)	0.48
Respiratory disease mortality	124 (0.7)	89 (0.7)	0.98 (0.75–1.29)	0.89	0.96 (0.73–1.27)	0.77	1.11 (0.84–1.47)	0.47
Digestive disease mortality	89 (0.5)	56 (0.4)	1.12 (0.80–1.57)	0.51	1.18 (0.84–1.66)	0.34	1.30 (0.92–1.84)	0.13
Nervous system disease mortality	82 (0.5)	44 (0.3)	1.31 (0.90–1.89)	0.16	1.25 (0.86–1.81)	0.24	1.22 (0.84–1.78)	0.29

[a]Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, socio-economic (Townsend deprivation index score and education level), lifestyle behaviors (BMI, fruit and vegetable consumption, smoking and alcohol status, physical activity), age at cancer diagnosis, Charlson Comorbidity Index, cancer types

[b]Competing risk analysis considering death due to causes other than cancer as competing risks

Bold values indicate the statistical significance $P < 0.05$

(Supplementary Fig. 2). The associations between supplement use and a lower risk of mortality were observed among female patients, but not male patients. No significant interaction effects were observed between supplement use and other sociodemographic, lifestyle, or clinical factors on the risks of all-cause or cancer-related mortality, indicating that the observed associations were not significantly modified by other specific risk factors.

Sensitivity analyses

The results of our sensitivity analyses of the associations between the overall use of dietary supplements and all-cause and cause-specific mortality were mostly consistent with the results of the main analyses (Supplementary Table 4). Significant inverse associations between supplement use and all-cause and cancer-related mortality were still observed when we analyzed the non-imputed data set. However, the associations between supplement use and all-cause mortality were not observed after excluding participants who were diagnosed with cancer before 2006.

For the subgroup sensitivity analyses that only included patients diagnosed with cancer after 2006, the use of mineral supplements was associated with a lower risk of all-cause mortality (aHR = 0.90, 95% CI = 0.85–1.00, $p < 0.05$) and cancer-related mortality (aHR = 0.85, 95% CI = 0.75–0.96, $p = 0.01$) but the associations were borderline significant (Supplementary Tables 5 and 6). Similarly, the associations between NVNM supplement use and mortality were insignificant in this sensitivity analysis. All the combinations were associated with a lower risk of all-cause and cancer-related mortality ($p < 0.05$). No significant associations were observed between supplement use and other types of cause-specific mortality.

Discussion

This is one of the largest prospective cohort studies to investigate the association between supplement use and the risk of mortality in cancer patients. The large sample and the availability of well-defined mortality data from UK Biobank enabled analyses that considered a wide range of potential confounders and different categories of supplements. Previous studies have mainly focused on the effect of individual supplements; however, in our study, we found that more than half of the participants consumed more than one classes of supplements. Hence, this warranted our approach to analyze supplements as a whole and by categories rather than by individual supplements. It provided a broader picture of how supplements use as a growing phenomenon among patients with cancer can impact their mortality outcomes. We found that the use of supplements was associated with a modest reduction in the risk of all-cause mortality and cancer-related mortality, after adjusting for clinically relevant confounders. Of the three types of supplements analyzed, the use of NVNM dietary supplements was associated with a lower risk of all-cause and cancer-related mortality, while vitamin use was associated with a marginally lower risk of cancer-related mortality. Our findings should be

Table 3 Subgroup analyses of association of supplement use with risk of overall and cause-specific mortality

	Death among users	Death among non-users	Model 1 (Crude)		Model 2[a]		Model 3[a]	
	N (%)	*N* (%)	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Vitamins								
All-cause mortality	2134 (17.7)	3443 (18.9)	0.94 (0.89–0.99)	**0.02**	1.01 (0.95–1.06)	0.78	0.99 (0.93–1.04)	0.63
Cancer mortality[b]	1578 (13.1)	2630 (14.5)	0.91 (0.85–0.97)	**0.002**	0.96 (0.90–1.02)	0.18	0.93 (0.87–0.99)	**0.04**
CVD mortality	195 (1.6)	321 (1.8)	0.92 (0.77–1.10)	0.36	1.05 (0.88–1.25)	0.61	1.08 (0.90–1.29)	0.43
Respiratory disease mortality	88 (0.7)	125 (0.7)	1.07 (0.81–1.40)	0.64	1.16 (0.88–1.53)	0.30	1.20 (0.91–1.59)	0.20
Digestive disease mortality	63 (0.5)	82 (0.5)	1.17 (0.84–1.62)	0.36	1.32 (0.94–1.84)	0.10	1.32 (0.94–1.85)	0.10
Nervous system disease mortality	51 (0.4)	75 (0.4)	1.03 (0.72–1.48)	0.85	1.11 (0.77–1.60)	0.56	1.06 (0.74–1.53)	0.75
Minerals								
All-cause mortality	1152 (18.0)	4425 (18.6)	0.94 (0.88–1.01)	0.08	1.05 (0.99–1.13)	0.12	1.06 (0.99–1.13)	0.11
Cancer mortality[b]	840 (13.1)	3368 (14.1)	0.90 (0.84–0.97)	**0.008**	0.98 (0.91–1.06)	0.67	0.97 (0.90–1.05)	0.46
CVD mortality	99 (1.5)	417 (1.8)	0.87 (0.70–1.08)	0.20	1.09 (0.87–1.36)	0.46	1.12 (0.89–1.40)	0.34
Respiratory disease mortality	56 (0.9)	157 (0.7)	1.30 (0.95–1.76)	0.10	1.51 (1.10–2.07)	**0.01**	1.53 (1.12–2.11)	**0.008**
Digestive disease mortality	37 (0.6)	108 (0.5)	1.25 (0.86–1.82)	0.24	1.55 (1.06–2.28)	**0.03**	1.56 (1.06–2.31)	**0.03**
Nervous system disease mortality	28 (0.2)	98 (0.4)	1.04 (0.68–1.59)	0.85	1.19 (0.77–1.84)	0.42	1.13 (0.73–1.74)	0.59
Other dietary supplements (non-vitamin non-mineral)								
All-cause mortality	2147 (16.9)	3430 (19.6)	0.81 (0.77–0.85)	**< 0.001**	0.78 (0.74–0.82)	**< 0.001**	0.88 (0.83–0.93)	**< 0.001**
Cancer mortality[b]	1603 (12.6)	2605 (14.9)	0.80 (0.76–0.86)	**< 0.001**	0.79 (0.74–0.84)	**< 0.001**	0.88 (0.82–0.94)	**< 0.001**
CVD mortality	203 (1.6)	313 (1.8)	0.82 (0.68–0.97)	**0.02**	0.76 (0.63–0.91)	**0.002**	0.93 (0.77–1.11)	0.41
Respiratory disease mortality	81 (0.6)	132 (0.8)	0.77 (0.58–1.02)	0.07	0.69 (0.52–0.91)	**0.009**	0.87 (0.65–1.16)	0.33
Digestive disease mortality	51 (0.4)	94 (0.5)	0.68 (0.48–0.96)	**0.03**	0.65 (0.46–0.92)	**0.02**	0.83 (0.58–1.18)	0.30
Nervous system disease mortality	65 (0.5)	61 (0.3)	1.32 (0.93–1.88)	0.12	1.15 (0.80–1.64)	0.44	1.15 (0.80–1.64)	0.44

[a]Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, socio-economic (Townsend deprivation index score and education level), lifestyle behaviors (BMI, fruit and vegetable consumption, smoking and alcohol status, physical activity), age at cancer diagnosis, Charlson Comorbidity Index, cancer types

[b]Competing risk analysis considering death due to causes other than cancer as competing risks

Bold values indicate the statistical significance $P < 0.05$

interpreted cautiously considering the small effect sizes. Moreover, the associations were small and could be due to other unmeasured confounders not able to be addressed in this study besides supplement usage. Nevertheless, these results derived from real-world data have significant implications for the development of future research priorities for evaluating the role of supplements in cancer care. This will subsequently lead to refinement of guidelines and recommendations for the evidence-informed use of supplements by cancer patients.

Our finding that vitamin and NVNM dietary supplement use reduced mortality was consistent with previous results. For example, a study of four cohorts of breast cancer survivors revealed the potential protective effects of vitamin C and E and multivitamins against the risk of death [17], while recent reviews and meta-analysis suggested the potential role of vitamin D in increasing cancer survival rates [9, 10, 30, 31]. Our findings suggested a consistent association between NVNM dietary supplement use and reduced mortality. However, evidence for the benefits of NVNM dietary supplements is relatively limited compared with that of vitamins. A meta-analysis showed that omega-3 supplementation increased overall survival in pancreatic cancer patients [32], while preliminary evidence showed some survival benefits in patients taking fish oil supplements [33, 34]. Overall, our study supported the finding of these studies that vitamins and NVNM dietary supplements may confer survival benefits to cancer patients in general. Future studies should continue to explore the potential benefits of these supplements, especially NVNM supplements, in cancer patients and survivors.

There are multiple potential mechanisms, whereby these supplements have a protective effect against cancer-related mortality. First, while inflammation is involved in the pathophysiology of cancer [35, 36], elevated concentrations of inflammatory markers, such as C-reaction protein, have been shown to be associated with an increase in all-cause mortality and cancer-related mortality [37, 38]. Many vitamins and NVNM supplements, such as vitamin D [39], coenzyme Q10 [40], fish oil [34, 41], and glucosamine [41, 42], have anti-inflammatory effects. Another potential mechanism is the alteration of metabolism. For example, omega-3 may help correct cancer cachexia, which is a common syndrome that is inversely associated with cancer survival [32, 43]. Further clinical or epidemiological studies are needed to confirm other potential mechanisms, such as antioxidative effects of various supplements via modulating intracellular signaling pathways of cancer cells and the microenvironment [44, 45], as well as to explore in depth the potential benefits of supplements for clinical outcomes that affect mortality and the quality of life of patients diagnosed with cancer, and whether specific groups of patients may benefit more from dietary supplementation.

Nevertheless, our findings regarding mineral supplement use and mortality remained inconclusive. Our main analysis suggested that minerals may lead to higher rates of mortality among cancer patients, whereas the sensitivity analysis suggested otherwise. This discrepancy may be attributable to differences in treatment efficacy, as patients diagnosed with cancer before 2006 may have received less effective cancer treatment, leading to an increase in susceptibility to late effects and a higher risk of mortality. As treatment data were not available for this cohort, we were unable to explore its confounding effects. Therefore, our results should be interpreted cautiously in view of changes in cancer treatment strategies over time and the consequent potential for survival bias. Future data enhancements (such as the availability of information about cancer treatment) in the UK Biobank may enable more comprehensive analyses of the effect of dietary supplementation on mortality [46].

Our findings obtained from real-world data may help to optimize current policies and recommendations for the use of TCIM in cancer patients, particularly in low- and middle-income countries, where TCIM modalities play an important role in primary health care [47]. Our finding that vitamins and NVNM dietary supplements may have potential protective effects may guide the future recommendation of such low-cost and easily accessible supplements to improve cancer outcomes globally, after validation of its effectiveness and safety in randomized trials on specific supplements. International collaboration and effectively implemented multinational randomized trials and large-scale observational studies are needed to generate high-quality evidence on the effectiveness and safety of supplements. If these supplementations are found to be effective and safety, their usage in routine cancer care would benefit patients worldwide.

Despite using a large sample and a prospective observational design with well-characterized mortality outcomes, this study has some potential limitations. First, the use of dietary supplements after the cancer diagnosis was entirely self-reported, potentially leading to recall inaccuracies during the verbal interviews and introducing immortal time bias [48]. There may be time periods between patients being diagnosed with cancer and the questionnaire assessments or interviews that could be misclassified as users or non-users. Therefore, our results may have to be interpreted cautiously. Second, there were a range of supplements included in the study which have different pharmacological effects. The small associations found in the study may, therefore, be due to other confounders not addressed instead of supplements alone. Besides cancer treatment data, some information, including cancer staging, indications for supplement use, and the use of other TCIM, is also not available. The stage of cancer may affect the cancer prognosis and mortality rate, while may also influence the decision on supplement use. Future studies can include these questions to

obtain a more complete picture of supplement or TCIM use among cancer patients. Furthermore, the UK Biobank study is known to have a low participation rate and a selection bias toward healthy volunteers with relatively low mortality rates and healthy lifestyles [49]. All of the participants provided information on supplement use at baseline but to avoid potential misclassification, we only included patients who also reported their supplement use status after their cancer diagnoses in this analysis. This has led to the exclusion of a considerable number of subjects from our analysis as only half of participants who completed baseline assessment were invited or recruited in the repeated assessment visit or subsequent studies by the UK Biobank. However, many studies have shown that this cohort may still provide valid inferences of risk factors and exposure-disease associations that are generalizable [49, 50]. To further increase the generalizability of the findings, they should be further validated in other large cohorts, with data on overall supplement use rather than just data for a few individual supplements.

Conclusions

More than half of the participants in the UK Biobank cohort reported using supplements after their cancer diagnosis, reflecting the popularity of supplement use among the adult cancer population. The use of supplements was associated with a small reduction in the risk of all-cause mortality and cancer-related mortality, after adjusting for clinically relevant factors. However, these associations should be interpreted cautiously due to the variations among supplements and the small effect size, and therefore, the effects may be not due to supplements alone but other unmeasured confounders. These findings warrant future research, including multinational randomized trials and large-scale observational studies, to investigate the potential of specific supplements, particularly NVNM supplements, in improving clinical outcomes that affect mortality and other key outcomes in patients with cancer, thereby guiding the integration of dietary supplements into routine cancer care in the future.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00394-022-03044-1.

Acknowledgements research has been conducted using the UK Biobank Resource under Application Number 74158.

Author contributions CSL: conceptualization; formal analysis; investigation; methodology; writing—original draft; writing—review and editing. HKK: conceptualization; investigation; methodology; writing—original draft; writing—review and editing. HH-FL: conceptualization; methodology; writing—review and editing. VC-HC: conceptualization; methodology; supervision; writing—review and editing. YTC: conceptualization; formal analysis; investigation; methodology; supervision; writing—original draft; writing—review and editing.

Funding No funding was received for conducting this study.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical approval This study was approved by the Survey and Behavioral Research Ethics Committee of the Chinese University of Hong Kong (Reference no. SBRE-21-0310).

Informed consent All participants provided written informed consent.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3):209–249
2. Stein KD, Syrjala KL, Andrykowski MA (2008) Physical and psychological long-term and late effects of cancer. Cancer 112(S11):2577–2592
3. Keene MR, Heslop IM, Sabesan SS, Glass BD (2019) Complementary and alternative medicine use in cancer: a systematic review. Complement Ther Clin Pract 35:33–47
4. Posadzki P, Watson L, Alotaibi A, Ernst E (2012) Prevalence of complementary and alternative medicine-use by UK cancer patients: a systematic review of surveys. J Integr Oncol 1:1
5. Sanford NN, Sher DJ, Ahn C, Aizer AA, Mahal BA (2019) Prevalence and nondisclosure of complementary and alternative medicine use in patients with cancer and cancer survivors in the United States. JAMA Oncol 5(5):735–737
6. Velicer CM, Ulrich CM (2008) Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. J Clin Oncol 26(4):665–673
7. European Food Safety Authority (2018) Food supplements. https://www.efsa.europa.eu/en/topics/topic/food-supplements. Accessed 13 Apr 2022
8. National Institutes of Health (2018) Dietary supplement health and education Act of 1994 Public Law 103–417. https://ods.od.nih.gov/About/DSHEA_Wording.aspx. Accessed 13 Apr 2022
9. Kanellopoulou A, Riza E, Samoli E, Benetou V (2021) Dietary supplement use after cancer diagnosis in relation to total mortality, cancer mortality and recurrence: a systematic review and meta-analysis. Nutr Cancer 73(1):16–30
10. Griffin N, Dowling M (2018) Vitamin D supplementation and clinical outcomes in cancer survivorship. Br J Nurs 27(19):1121–1128
11. Greenlee H, Kwan ML, Kushi LH, Song J, Castillo A, Weltzien E, Quesenberry CP Jr, Caan BJ (2012) Antioxidant supplement use after breast cancer diagnosis and mortality in the life after cancer epidemiology (LACE) cohort. Cancer 118(8):2048–2058
12. Harris HR, Orsini N, Wolk A (2014) Vitamin C and survival among women with breast cancer: a meta-analysis. Eur J Cancer 50(7):1223–1231
13. Ambrosone CB, Zirpoli GR, Hutson AD, McCann WE, McCann SE, Barlow WE, Kelly KM, Cannioto R, Sucheston-Campbell LE, Hershman DL (2020) Dietary supplement use during chemotherapy and survival outcomes of patients with breast cancer enrolled in a cooperative group clinical trial (SWOG S0221). J Clin Oncol 38(8):804
14. Davies AA, Davey Smith G, Harbord R, Bekkering GE, Sterne JA, Beynon R, Thomas S (2006) Nutritional interventions and

outcome in patients with cancer or preinvasive lesions: systematic review. J Natl Cancer Inst 98(14):961–973
15. Hamer J, Warner E (2017) Lifestyle modifications for patients with breast cancer to improve prognosis and optimize overall health. CMAJ 189(7):E268–E274
16. He J, Gu Y, Zhang S (2018) Vitamin A and breast cancer survival: A systematic review and meta-analysis. Clin Breast Cancer 18(6):e1389–e1400
17. Poole EM, Shu X, Caan BJ, Flatt SW, Holmes MD, Lu W, Kwan ML, Nechuta SJ, Pierce JP, Chen WY (2013) Postdiagnosis supplement use and breast cancer prognosis in the after breast cancer pooling project. Breast Cancer Res Treat 139(2):529–537
18. Miller MF, Bellizzi KM, Sufian M, Ambs AH, Goldstein MS, Ballard-Barbash R (2008) Dietary supplement use in individuals living with cancer and other chronic conditions: a population-based study. J Am Diet Assoc 108(3):483–494
19. Norman HA, Butrum RR, Feldman E, Heber D, Nixon D, Picciano MF, Rivlin R, Simopoulos A, Wargovich MJ, Weisburger EK (2003) The role of dietary supplements during cancer therapy. J Nutr 133(11):3794S-3799S
20. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ 85:867–872
21. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M (2015) UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 12(3):e1001779
22. UK Biobank (2014) Cancer data: a report on the number of prevalent and incident cases. https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/cancerpi.pdf. Accessed 13 Apr 2022
23. Judson PL, Abdallah R, Xiong Y, Ebbert J, Lancaster JM (2017) Complementary and alternative medicine use in individuals presenting for care at a comprehensive cancer center. Integr Cancer Ther 16(1):96–103
24. Bours MJ, Beijer S, Winkels RM, Van Duijnhoven FJ, Mols F, Breedveld-Peters JJ, Kampman E, Weijenberg MP, Van De Poll-Franse LV (2015) Dietary changes and dietary supplement use, and underlying motives for these habits reported by colorectal cancer survivors of the patient reported outcomes following initial treatment and long-term evaluation of survivorship (PROFILES) registry. Br J Nutr 114(2):286–296
25. Molassiotis A, Fernadez-Ortega P, Pud D, Ozden G, Scott JA, Panteli V, Margulies A, Browall M, Magri M, Selvekerova S (2005) Use of complementary and alternative medicine in cancer patients: a European survey. Ann Oncol 16(4):655–663
26. John GM, Hershman DL, Falci L, Shi Z, Tsai W-Y, Greenlee H (2016) Complementary and alternative medicine use among US cancer survivors. J Cancer Surviv 10(5):850–864
27. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
28. Van Buuren S, Groothuis-Oudshoorn K (2011) Mice: multivariate imputation by chained equations in R. J Stat Softw 45:1–67
29. Azur MJ, Stuart EA, Frangakis C, Leaf PJ (2011) Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 20(1):40–49
30. Gnagnarella P, Muzio V, Caini S, Raimondi S, Martinoli C, Chiocca S, Miccolo C, Bossi P, Cortinovis D, Chiaradonna F (2021) Vitamin D supplementation and cancer mortality: narrative review of observational studies and clinical trials. Nutrients 13(9):3285
31. Keum N, Giovannucci E (2014) Vitamin D supplements and cancer incidence and mortality: a meta-analysis. Br J Cancer 111(5):976–980
32. Ma Y-J, Yu J, Xiao J, Cao B-W (2015) The consumption of omega-3 polyunsaturated fatty acids improves clinical outcomes and prognosis in pancreatic cancer patients: a systematic evaluation. Nutr Cancer 67(1):112–118
33. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC (2011) Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. Cancer 117(16):3774–3780
34. Chagas TR, Borges D, de Oliveira PF, Mocellin MC, Barbosa AM, Camargo C, Del Moral J, Poli A, Calder P, Trindade E (2017) Oral fish oil positively influences nutritional-inflammatory risk in patients with haematological malignancies during chemotherapy with an impact on long-term survival: a randomized clinical trial. J Hum Nutr Diet 30(6):681–692
35. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA (2013) Inflammation-induced cancer: crosstalk between tumors, immune cells and microorganisms. Nat Rev Cancer 13(11):759–771
36. Tabas I, Glass CK (2013) Anti-inflammatory therapy in chronic disease: challenges and opportunities. Science 339(6116):166–172
37. Goyal A, Terry MB, Jin Z, Siegel AB (2014) C-reactive protein and colorectal cancer mortality in US adults. Cancer Epidemiol Biomark Prev 23(8):1609–1618
38. Zuo H, Ueland PM, Ulvik A, Eussen SJ, Vollset SE, Nygård O, Midttun Ø, Theofylaktopoulou D, Meyer K, Tell GS (2016) Plasma biomarkers of inflammation, the kynurenine pathway, and risks of all-cause, cancer, and cardiovascular disease mortality: the Hordaland health study. Am J Epidemiol 183(4):249–258
39. van Harten-Gerritsen AS, Balvers MG, Witkamp RF, Kampman E, van Duijnhoven FJ (2015) Vitamin D, inflammation, and colorectal cancer progression: a review of mechanistic studies and future directions for epidemiological studies. Cancer Epidemiol Biomarkers Prev 24(12):1820–1828
40. Alimohammadi M, Rahimi A, Faramarzi F, Golpour M, Jafari-Shakib R, Alizadeh-Navaei R, Rafiei A (2021) Effects of coenzyme Q10 supplementation on inflammation, angiogenesis, and oxidative stress in breast cancer patients: a systematic review and meta-analysis of randomized controlled-trials. Inflammopharmacology 29(3):579–593
41. Kantor ED, Lampe JW, Vaughan TL, Peters U, Rehm CD, White E (2012) Association between use of specialty dietary supplements and C-reactive protein concentrations. Am J Epidemiol 176(11):1002–1013
42. Kantor ED, Lampe JW, Navarro SL, Song X, Milne GL, White E (2014) Associations between glucosamine and chondroitin supplement use and biomarkers of systemic inflammation. J Altern Complement Med 20(6):479–485
43. Dimitriu C, Martignoni M, Bachmann J, Fröhlich B, Tintărescu G, Buliga T, Lică I, Constantinescu G, Beuran M, Friess H (2005) Clinical impact of cachexia on survival and outcome of cancer patients. Rom J Intern Med 43(3–4):173–185
44. Alok S, Jain SK, Verma A, Kumar M, Mahor A, Sabharwal M (2014) Herbal antioxidant in clinical practice: a review. Asian Pac J Trop Biomed 4(1):78–84
45. Pawlowska E, Szczepanska J, Blasiak J (2019) Pro-and antioxidant effects of vitamin C in cancer in correspondence to its dietary and pharmacological concentrations. Oxid Med Cell Longev 2019:1–18
46. UK Biobank (2022) Provisional timeline for future data releases. https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/future-data-release-timelines. Accessed 13 Apr 2022
47. Mao JJ, Pillai GG, Andrade CJ, Ligibel JA, Basu P, Cohen L, Khan IA, Mustian KM, Puthiyedath R, Dhiman KS (2022)

Integrative oncology: addressing the global challenges of cancer prevention and treatment. CA Cancer J Clin 72(2):144–164
48. Yadav K, Lewis RJ (2021) Immortal time bias in observational studies. JAMA 325(7):686–687
49. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE (2017) Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 186(9):1026–1034
50. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S (2020) Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ 368:m131