Nutrition Journal

RESEARCH

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Adherence to a low-fat dietary pattern reduces head and neck cancer risk: evidence from the PLCO trial

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Abstract

Purpose Low-fat dietary (LFD) pattern refers to a dietary structure with reduced fat intake. The aim was to investigate the association between LFD pattern and risk of head and neck cancer (HNC).

Methods Data were derived from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. LFD score was used to assess adherence to an LFD pattern, with higher scores indicating greater adherence. Cox regression was used to evaluate the association between LFD score and risk of HNC and its subtypes. To visualize the trend in risk of HNC and its subtypes with changing LFD score, restricted cubic spline plots were utilized. A series of subgroup analyses were conducted to identify potential confounders. Sensitivity analyses were performed to assess the robustness of the results.

Results Among 98,459 participants of PLCO trial, 268 cases with HNC were identified during an average of 8.8 years of follow-up. In the fully adjusted model, participants in the highest compared with the lowest quartiles of LFD score had a lower risk of HNC ($HR_{Q4\ vs.\ Q1}$: 0.60; 95% CI: 0.40–0.90; *P* for trend = 0.026) and larynx cancer ($HR_{Q4\ vs.\ Q1}$: 0.46; 95% CI: 0.22–0.96; *P* for trend = 0.039). The restricted cubic spline plots demonstrated a linear dose-response relationship between the LFD score and the risk of HNC and its subtypes (all *P* for nonlinearity > 0.05). The primary association remained robust in the sensitivity analysis.

Conclusion Our findings suggest that adherence to an LFD pattern may lower the risk of HNC in the US population.

Keywords Low-fat diet, Head and neck cancer, Epidemiology, Cohort studies, Dietary pattern

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Introduction

Head and neck cancer (HNC), including cancers of the oral cavity, pharynx, and larynx, is the sixth most common cancer worldwide [1]. In 2018, there were an estimated 890,000 new cases and 450,000 deaths from HNC globally [1]. Known risk factors for HNC include tobacco use, alcohol consumption, human papillomavirus (HPV) infection, and genetic factors [2]. However, these established factors do not fully account for the observed patterns in HNC occurrence [3]. Therefore, identifying novel modifiable risk factors is important for the prevention of this malignancy. Dietary pattern has emerged as a potential risk factor for HNC in recent years [4–9]. Dietary patterns take into account the synergistic interactions between different food components and can provide more rational dietary guidance compared to individual foods or nutrients. Current studies have evaluated the associations between different dietary patterns, such as Western and prudent/healthy patterns, and HNC risk, with inconsistent results [10–12].

The occurrence and development of cancer are inseparable from metabolism. Changes in glucose metabolism are critical to the growth and progression of cancer [13], and mainly involve four aspects: tricarboxylic acid cycle, glycolysis, gluconeogenesis, and glycogen synthesis [14]. Accumulated studies have described deregulated levels of enzymes and molecules related to lipid metabolism in HNC, e.g., elevated fatty acids [15], fatty acid binding protein and fatty acid synthase [16, 17]. Unhealthy dietary patterns disrupt lipid and glucose metabolism and play an important role in HNC. Consumption of fried foods, high-fat and processed meats, and sweets has been associated with an increased risk of throat cancer [8, 18, 19]. So, is it possible to choose a dietary pattern to reduce the risk of head and neck squamous cell carcinoma?

The low-fat dietary (LFD) pattern refers to a dietary structure with reduced fat intake, where a greater proportion of energy intake is derived from carbohydrates and protein. It is commonly used for weight control, reducing cardiovascular disease risk, and dietary management of diabetes. However, obesity and high intake of animal fat are associated with HNC. This pattern represents a prudent dietary choice that may protect against HNC by modulating metabolism, oxidative stress, and insulin resistance [20]. Only one case-control study has examined the LFD pattern scores in association with HNC risk, and reported no significant relationship [21]. However, no prospective cohort studies have specifically investigated the LFD pattern in relation to HNC risk.

In the present study, we aimed to prospectively examine the association between LFD score, incorporating intakes of carbohydrates, fat, and protein, and the risk of HNC. We conducted this prospective study utilizing data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Methods and methods

Study population and exclusion criteria

To determine whether screening tests could reduce colorectal, lung, prostate and ovarian cancer-related mortality, the National Cancer Institute (NCI) of USA conducted a randomized controlled trial named Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. The design and methodology of this trial have been previously reported [22]. They recruited close to 155,000 volunteers aged 55–74 years from 10 centers between November 1993 and July 2001. Cancer diagnosis data up to December 2009 were collected. Demographic and medical history data for all participants were collected via baseline questionnaire (BQ). In addition, dietary data were collected using dietary history questionnaire (DHQ) and supplemental questionnaires (SQX). DHQ collects dietary information from participants based on the 137-item Food Frequency Questionnaire (FFQ). Multiple studies have confirmed that FFQ is a good nutritional assessment model [23, 24]. SQX is used to supplement some data not collected by BQ. The institutional review boards at each PLCO study center and the NCI provided ethical approval for the study protocols. Informed consent in writing was collected from all participants prior to their enrollment. For this analysis, we used the NCI-approved public dataset (project ID: PLCO-1335). Therefore, inclusion of human participants did not require ethical approval.

Exclusion criteria was as follows: (1) Failure to return BQ; (2) Participants with invalid DHQ (including the missing DHQ response items exceed 8 or more, extreme caloric intake assessed by DHQ (first and last percentiles) and DHQ completion date not available before death); (3) Participants with a cancer diagnosis before completing the DHQ; (4) Participants with an occurred outcome events between randomization to DHQ completion (who developed HNC, died, or were lost to follow-up in the period); (5) Participants with potentially unreliable dietary intake (including females with "<600 or >3500 kcal/day" and males with "<800 or >4200 kcal/day") [25].

Construction and evaluation of LFD score

We calculated LFD score according to previously reported standards [26, 27]. In brief, participants were stratified into 11 tiers (Supplementary Table 1) based on percentage of energy derived from constant macronutrients including fat, carbohydrate and protein consumption. For fat, participants in the lowest tier were assigned 10 points and those in the highest tier were assigned 0 points. For protein and carbohydrate, the order of tiers

was reversed. We then summed scores for the three constant macronutrients to calculate LFD score for all participants, ranging from 0 to 30. Thus, higher LFD score indicate better adherence to LFD pattern. Specifically, we extracted the percent energy from the three macronutrients (protein, fat and carbohydrate) using data obtained from the DHQ. The derivation of nutrient values utilized DietCalc software, the USDA National Nutrient Database for Standard Reference, and the Nutrition Data System. The raw responses from DHQ were processed into analyzable variables such as daily food frequency, pyramid servings, and gram intake. The reliability of DHQ to assess participants' dietary and nutrition data has been reported elsewhere [23, 28].

Diagnosis of HNC

In the PLCO cancer screening trial, diagnosis of HNC was primarily dependent on annual study update questionnaires mailed to living participants. The PLCO trial confirmed diagnoses of HNC through medical record abstraction (MRA) of participants suspected by the trial to have HNC. Note that if the MRA process does not find records indicating cancer diagnosis, even if a source such as a death certificate indicates cancer, the cancer is not considered confirmed. For patients diagnosed with primary HNC, additional information regarding diagnostic procedures, cancer staging, grading, histopathological type, and initial cancer therapy was recorded by the participants' physicians. We extracted information on diagnosis date, type (e.g., HNC, oral cavity and pharynx cancer, and larynx cancer), and ICD-O-2 codes from the PLCO data. The endpoint was incidence of HNC and its subtypes (oral cavity and pharynx cancer, and larynx cancer).

Dealing with covariates

We obtained participants' baseline covariates including sex (male, female), education level (less than college, college graduate, postgraduate), trial group (intervention, control), height, race (non-Hispanic White, non-Hispanic Black, Hispanic, and other race/ethnicity), weight, smoking status (never, current or former), history of hypertension (no, yes), aspirin use (no, yes), history of diabetes (no, yes) and family history of HNC (no, yes, possibly) from the BQ. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Additionally, the DHQ was used to collect participants' age, alcohol intake (no, yes), intake of dietary cholesterol, pyramid food servings (grain, total fruit, vegetable, dairy), saturated fatty acids, mono-unsaturated fatty acids, poly-unsaturated fatty acids, fish and other seafood, eggs, total dietary fiber from diet, discretionary fat, red processed meat, cakes, cookies, pies, and pastries, sugars and sweets, total lean meat, added sugars, alcohol, energy intake in diet, and consumption of total carbohydrate, fat, and protein. Total minutes of moderate to vigorous physical activity per week was obtained from the SQX as physical activity.

Statistical analysis

Data were assessed for missingness prior to analysis. Missingness ranging from 0 to 26% was observed for covariates in the BQ and DHQ. For variables missing < 5% of data, continuous variables such as BMI were imputed using median replacement, while categorical variables including education, family cancer history, regular aspirin use, and diabetes were imputed using mode substitution. For physical activity data missing > 25% in the Supplementary Questionnaire (SQX), multiple imputation was performed using chained equations to generate five complete datasets. Details of missingness and imputation for each variable are presented in Supplementary Table 2. Logistic regression models were fitted on each imputed dataset and results were pooled using Rubin's rules. Imputation procedures were performed in R version 4.3.1.

Cox proportional hazards regression models were utilized to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to investigate potential associations between LFD score and risk of HNC incidence. Models were adjusted for potential confounders and used follow-up time as the time metric. Participants were categorized into quartiles based on LFD score (Quartile 1, Quartile 2, Quartile 3 and Quartile 4), with the lowest scoring quartile (Quartile 1) serving as the reference group. Person-years were quantified according to follow-up time for each quartile. The Schoenfeld residuals method was utilized to evaluate the time-invariance of the LFD score. Trend analysis for HNC risk across increasing LFD score quartiles was conducted using Cox regression models, with median values for each quartile assigned to all participants within that quartile and treated as a continuous variable. To control for potential confounding, two multivariable Cox regression models were utilized in the analyses. Model 1 was adjusted for participants' age, race, and sex. Model 2 was further adjusted for education, trial group, energy intake from diet, family history of HNC, smoking pack-years, alcohol intake, BMI, aspirin use, physical activity, and diabetes history.

We used restricted cubic spline (RCS) regression with knots located the 10th, 50th, and 90th percentiles to accurately describe the risk of HNC across the entire range of LFD score. It is noted that the number of knots was selected based on the Akaike's information criterion (AIC) and the Bayesian information criterion (BIC), with the lowest AIC and BIC values indicating the best-fitted model. When AIC results were inconsistent with those from BIC, BIC results were used for knot selection, as

BIC is more conservative than AIC [29]. The median of the first quartile of LFD score was set as the reference value. The $p_{\text{nonlinearity}}$ was also determined by testing the null hypothesis. If the p value is less than 0.05, it means that the nonlinear effect of the model is significant. Furthermore, the above methodology was employed to assess the association between LFD score and the incidence rate of HNC subtypes, including oral cavity and pharynx cancer and larynx cancer.

Stratified analyses were conducted to evaluate potential effect modification by age (≤65, >65 years), sex, BMI (≤30, >30 kg/m^2), smoking (never, former, current), alcohol intake (yes/no), and diabetes history (yes/no) on the relationship between LFD score and HNC risk. Multiplicative interaction was assessed using likelihood ratio tests comparing Cox models with and without cross-product interaction terms.

Sensitivity analyses were performed to evaluate the robustness of findings: (1) Repeated analysis in participants with non-missing data; (2) Excluded participants with family history of HNC; (3) Excluded participants with a history of diabetes. and (4) Excluded cases observed within the first 2 and 4 years of follow-up to address the concern of reverse causality.

Baseline characteristics of the study population are presented as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. All statistical tests were two-sided and performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria); P values < 0.05 were considered statistically significant.

Results

Screening of the study population

Our aim was to analyze the association between LFD patterns and risk of HNC. Therefore, based on the five exclusion criteria mentioned in the methods, the numbers of participants excluded for each criterion were as follows: (1) n=4,918; (2) n=38,462; (3) n=9,684; (4) n=68; (5) n=3,296. Finally, our study included 98,459 participants (Fig. 1). In Cox proportional hazards regression analysis, follow-up time was defined as the interval between completion of the DHQ at baseline and HNC diagnosis,

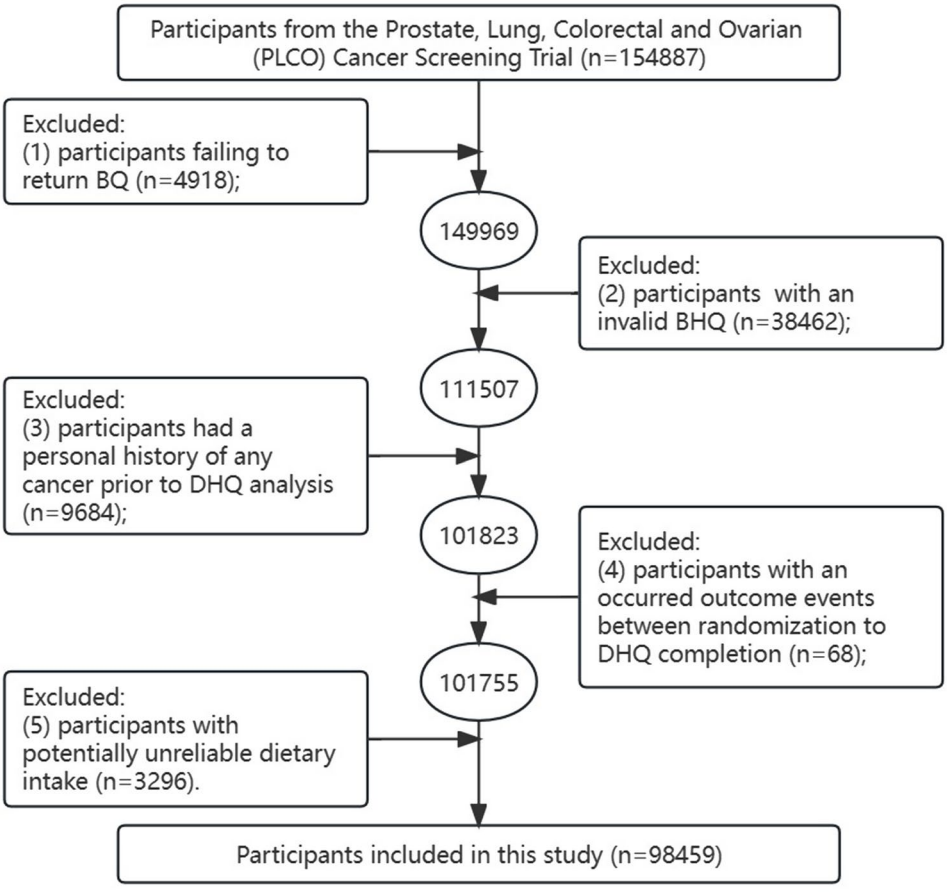

Fig. 1 The flow chart of identifying eligible participants. PLCO, Prostate, Lung, Colorectal, and Ovarian; BQ, baseline questionnaire; DHQ, diet history questionnaire

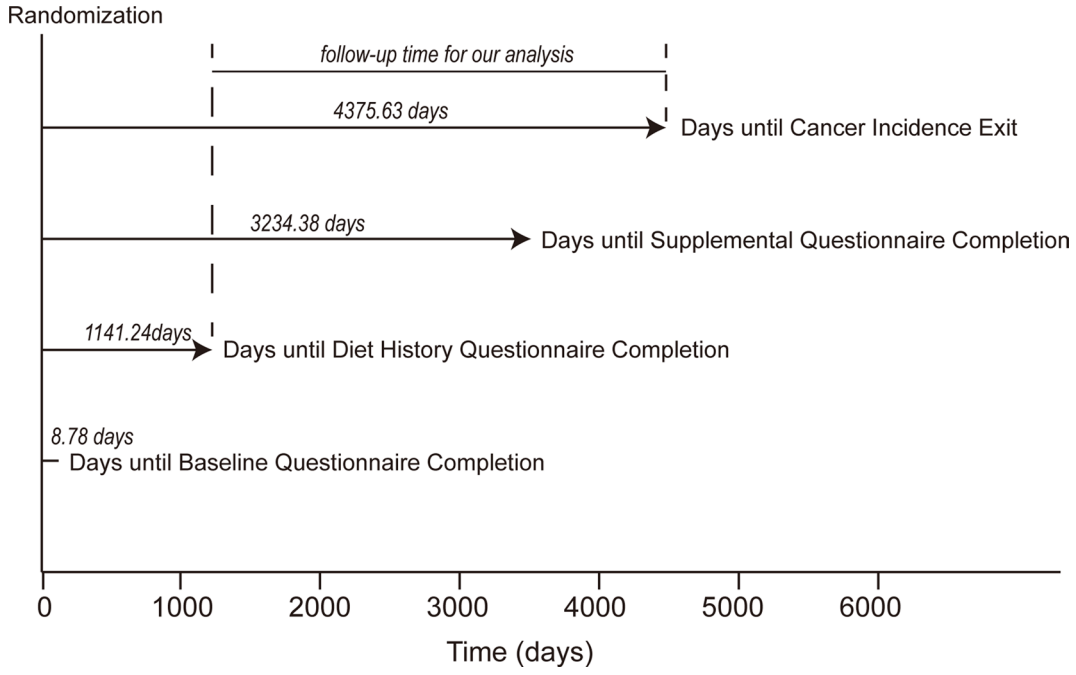

Fig. 2 The timeline and follow-up scheme of our study

death, loss to follow-up, or end of follow-up on December 31, 2009, whichever came first (Fig. 2)

Characteristics of the study population

Baseline characteristics of the 98,459 study participants across quartiles of LFD score are presented in table 1. Quartile 1 (n=26,715) had scores of 0–10. Quartile 2 (n=26,151) had scores of 11–15. Quartile 3 (n=24,764) had scores of 16–20. Quartile 4 (n=20,829) had scores of 21–30. The mean (standard deviation) LFD score was 15.00 (6.27), with higher scores indicating greater adherence to the LFD dietary pattern. Compared to participants in the lowest LFD quartile, those in the highest quartile were more likely to be older (66.19±5.79 vs. 65.52±5.73), female (64.60% vs. 44.71%), other race/ethnicity (4.89% vs. 2.84%), college-educated (41.47% vs. 32.85%), control group (50.74% vs. 47.91%), physically active (140.27±114.12 vs109.42±102.98), no drinker (33.66% vs. 22.55%), never smokers (56.87% vs. 40.13%), with a lower BMI (26.57±4.74 vs. 27.58±4.86), lower energy intake from diet (1502.45±529.56 vs. 1936.85±722.85) and no family history of HNC (96.49% vs. 95.53%) (all P<0.001). Intakes of saturated fatty acids (12.15±5.31 vs. 27.39±12.51), mono-unsaturated fatty acids (14.47±6.21 vs. 32.39±13.82), and poly-unsaturated fatty acids (9.41±4.04 vs. 18.94±8.32) were lower among participants in the highest versus lowest LFD quartile (all P<0.001). In terms of energy sources, percent of energy from fat (23.59±3.97 vs. 39.44±6.15) were lower, while percent of energy from carbohydrates (61.10±5.89 vs. 43.36±6.86), and percent of energy from protein (16.98±2.39 vs. 14.34±2.72) were higher among participants in the highest versus lowest LFD quartile (all P<0.001). Intakes of saturated fatty acids (12.15±5.31 vs. 27.39±12.51), mono-unsaturated fatty acids (14.47±6.21 vs. 32.39±13.82), and poly-unsaturated fatty acids (9.41±4.04 vs. 18.94±8.32) were lower among participants in the highest versus lowest LFD quartile (all P<0.001). Intakes of vegetables (4.24±2.58 vs. 3.72±2.01), fruits (3.62±2.19 vs. 1.89±1.35), dairy foods (1.69±1.25 vs. 1.21±0.97), fish and other seafood (0.51±0.60 vs. 0.43±0.44), eggs (0.83±4.52 vs. 0.20±2.07), total dietary fiber from diet (20.28±8.94 vs. 16.41±7.24) were higher, while intakes of grain (4.50±2.21 vs. 4.70±2.32), discretionary fat (27.88±12.03 vs. 69.02±28.65), red processed meat (6.33±8.30 vs. 17.74±18.66), cakes, cookies, pies, and pastries (17.81±18.34 vs. 32.40±33.78), sugars and sweets (19.89±18.35 vs. 28.51±27.41), total lean meat (5.90±3.35 vs. 8.17±4.60), added sugars (10.52±6.41 vs. 12.98±8.59), alcohol (0.25±0.47 vs. 1.06±2.11), and cholesterol from diet (139.49±72.63 vs. 269.60±152.36) were lower among participants in the highest versus lowest LFD quartile (all P<0.001) (table 1)

Association between LFD score and risk of HNC

Over a mean (standard deviation) follow-up time of 8.84 (1.94) years, representing 869,807.9 person-years, 268 incident HNC cases were ascertained, including 161 cases of oral cavity and pharynx cancer, and 96 cases of larynx cancer. In the unadjusted Cox model, participants in the highest versus lowest quartile of LFD score had

Table 1 Baseline characteristics of study population according to quartiles of LFD scores

Characteristics	Overall	Quartiles of LFD score				$P_{overall}$
		Quartile 1(≤ 10)	Quartile 2(11–15)	Quartile 3(16–20)	Quartile 4(≥ 21)	
Number of participants	**98,459**	**26,715**	**26,151**	**24,764**	**20,829**	< 0.001
LFD score	15.00 ± 6.27	7.33 ± 2.40	12.98 ± 1.42	18.03 ± 1.43	23.75 ± 2.36	< 0.001
Age	65.52 ± 5.73	65.08 ± 5.63	65.24 ± 5.67	65.73 ± 5.77	66.19 ± 5.79	< 0.001
Sex						< 0.001
Male	47,218 (47.96%)	14,771 (55.29%)	13,807 (52.80%)	11,267 (45.50%)	7373 (35.40%)	
Female	51,241 (52.04%)	11,944 (44.71%)	12,344 (47.20%)	13,497 (54.50%)	13,456 (64.60%)	
Race						< 0.001
Non-Hispanic White	89,811 (91.22%)	24,667 (92.33%)	24,024 (91.87%)	22,058 (89.07%)	19,062 (91.52%)	
Non-Hispanic Black	3121 (3.17%)	864 (3.23%)	779 (2.98%)	973 (3.93%)	505 (2.42%)	
Hispanic	1410 (1.43%)	425 (1.59%)	395 (1.51%)	346 (1.40%)	244 (1.17%)	
Other race/ethnicity[2]	4117 (4.18%)	759 (2.84%)	953 (3.64%)	1387 (5.60%)	1018 (4.89%)	
Education level						< 0.001
College below	62,599 (63.58%)	17,938 (67.15%)	16,900 (64.62%)	15,571 (62.88%)	12,190 (58.52%)	
College graduate	17,353 (17.62%)	4486 (16.79%)	4585 (17.53%)	4334 (17.50%)	3948 (18.95%)	
Postgraduate	18,507 (18.80%)	4291 (16.06%)	4666 (17.84%)	4859 (19.62%)	4691 (22.52%)	
BMI (kg/m^2)	27.20 ± 4.79	27.58 ± 4.86	27.47 ± 4.75	27.04 ± 4.72	26.57 ± 4.74	< 0.001
Physical activity (min/week)[3]	123.36 ± 108.74	109.42 ± 102.98	119.70 ± 106.86	128.05 ± 109.89	140.27 ± 114.12	< 0.001
Alcohol intake						< 0.001
No	26,681 (27.10%)	6023 (22.55%)	6388 (24.43%)	7259 (29.31%)	7011 (33.66%)	
Yes	71,778 (72.90%)	20,692 (77.45%)	19,763 (75.57%)	17,505 (70.69%)	13,818 (66.34%)	
Family history of HNC						< 0.001
No	94,516 (96.00%)	25,521 (95.53%)	25,120 (96.06%)	23,777 (96.01%)	20,098 (96.49%)	
Yes	1402 (1.42%)	421 (1.58%)	350 (1.34%)	346 (1.40%)	285 (1.37%)	
Possibly	2541 (2.58%)	773 (2.89%)	681 (2.60%)	641 (2.59%)	446 (2.14%)	
History of diabetes						0.126
No	91,990 (93.43%)	25,028 (93.69%)	24,365 (93.17%)	23,139 (93.44%)	19,458 (93.42%)	
Yes	6469 (6.57%)	1687 (6.31%)	1786 (6.83%)	1625 (6.56%)	1371 (6.58%)	
Trial group						< 0.001
Intervention group	50,151 (50.94%)	13,917 (52.09%)	13,442 (51.40%)	12,531 (50.60%)	10,261 (49.26%)	
Control group	48,308 (49.06%)	12,798 (47.91%)	12,709 (48.60%)	12,233 (49.40%)	10,568 (50.74%)	
Energy intake from diet(kcal/day)	1728.71 ± 658.04	1936.85 ± 722.85	1785.82 ± 657.33	1634.18 ± 603.05	1502.45 ± 529.56	< 0.001
Smoker						< 0.001
Never	47,233 (47.97%)	10,720 (40.13%)	11,892 (45.47%)	12,775 (51.59%)	11,846 (56.87%)	
Current or former	51,226 (52.03%)	15,995 (59.87%)	14,259 (54.53%)	11,989 (48.41%)	8983 (43.13%)	
Aspirin						0.050
No	52,242 (53.06%)	14,308 (53.56%)	13,781 (52.70%)	13,220 (53.38%)	10,933 (52.49%)	
Yes	46,217 (46.94%)	12,407 (46.44%)	12,370 (47.30%)	11,544 (46.62%)	9896 (47.51%)	
History of hypertension						0.760
No	66,641 (67.68%)	18,150 (67.94%)	17,666 (67.55%)	16,731 (67.56%)	14,094 (67.67%)	
Yes	31,818 (32.32%)	8565 (32.06%)	8485 (32.45%)	8033 (32.44%)	6735 (32.33%)	
LFD score components						
Percent of energy from carbohydrates	51.99 ± 9.36	43.36 ± 6.86	49.37 ± 6.04	56.41 ± 7.29	61.10 ± 5.89	< 0.001
Percent of energy from fat	31.78 ± 7.52	39.44 ± 6.15	33.61 ± 4.13	28.47 ± 4.27	23.59 ± 3.97	< 0.001
Percent of energy from protein	15.44 ± 2.93	14.34 ± 2.72	15.48 ± 2.89	15.28 ± 3.02	16.98 ± 2.39	< 0.001
Fatty acid series						
Saturated fatty acids (g/day)	19.80 ± 10.83	27.39 ± 12.51	21.48 ± 9.43	16.28 ± 7.29	12.15 ± 5.31	< 0.001
Mono-unsaturated fatty acids (g/day)	23.48 ± 12.25	32.39 ± 13.82	25.37 ± 10.43	19.45 ± 8.30	14.47 ± 6.21	< 0.001
Poly-unsaturated fatty acids (g/day)	14.05 ± 7.15	18.94 ± 8.32	14.79 ± 6.12	11.90 ± 5.13	9.41 ± 4.04	< 0.001
Other components						
Grain – Pyramid servings/Day	4.67 ± 2.27	4.70 ± 2.32	4.79 ± 2.24	4.66 ± 2.28	4.50 ± 2.21	< 0.001
Vegetables – Pyramid servings/Day	3.90 ± 2.24	3.72 ± 2.01	3.84 ± 2.11	3.87 ± 2.30	4.24 ± 2.58	< 0.001
Fruit - Pyramid servings/Day	2.74 ± 1.99	1.89 ± 1.35	2.47 ± 1.63	3.22 ± 2.29	3.62 ± 2.19	< 0.001

Table 1 (continued)

Characteristics	Overall	Quartiles of LFD score				$P_{overall}$
		Quartile 1(≤ 10)	Quartile 2(11–15)	Quartile 3(16–20)	Quartile 4(≥ 21)	
Discretionary fat (g/day)	48.22 ± 25.73	69.02 ± 28.65	51.86 ± 20.62	39.05 ± 16.23	27.88 ± 12.03	< 0.001
Dairy - Pyramid servings/Day	1.37 ± 1.11	1.21 ± 0.97	1.34 ± 1.07	1.33 ± 1.09	1.69 ± 1.25	< 0.001
Fish and other seafood (oz./day)	0.46 ± 0.51	0.43 ± 0.44	0.47 ± 0.50	0.44 ± 0.50	0.51 ± 0.60	< 0.001
Red processed meat, (g/day)	12.26 ± 14.62	17.74 ± 18.66	13.93 ± 14.57	9.58 ± 10.97	6.33 ± 8.30	< 0.001
Eggs (g/day)	0.42 ± 3.12	0.20 ± 2.07	0.31 ± 2.70	0.43 ± 3.00	0.83 ± 4.52	< 0.001
Cakes, cookies, pies, and pastries (g/day)	26.25 ± 27.81	32.40 ± 33.78	28.84 ± 28.58	23.97 ± 24.21	17.81 ± 18.34	< 0.001
Sugars and sweets (g/day)	25.18 ± 24.22	28.51 ± 27.41	26.51 ± 24.95	24.63 ± 23.32	19.89 ± 18.35	< 0.001
Total lean meat	7.20 ± 4.30	8.17 ± 4.60	7.94 ± 4.62	6.48 ± 3.90	5.90 ± 3.35	< 0.001
Added sugars (tsp/day)	12.43 ± 8.77	12.98 ± 8.59	12.77 ± 8.67	13.08 ± 10.40	10.52 ± 6.41	< 0.001
Alcohol (drinks/day)	0.65 ± 1.41	1.06 ± 2.11	0.74 ± 1.36	0.45 ± 0.80	0.25 ± 0.47	< 0.001
Total dietary fiber from diet (g/day)	18.03 ± 8.07	16.41 ± 7.24	17.49 ± 7.55	18.44 ± 8.21	20.28 ± 8.94	< 0.001
Cholesterol from diet (mg/day)	207.53 ± 127.19	269.60 ± 152.36	228.66 ± 122.19	175.48 ± 97.62	139.49 ± 72.63	< 0.001

[2] "Other race/ethnicity" refers to Asian, Pacific Islander, or American Indian

[3] Total time of moderate-to-vigorous physical activity per week

Table 2 Association of LFD scores with the risk of HNC and its subtypes

	No. of	No. of		Hazard ratio (95% confidence interval)		
Quartiles of LFD score	**Participants**	**Cases**	**Person-years**	**Unadjusted**	**Model 1[a]**	**Model 2[b]**
HNC	98,459	268				
Quartile 1 (≤ 10)	26,715	101	232483.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2 (11–15)	26,151	69	229877.9	0.69 (0.51, 0.94)	0.71 (0.52, 0.96)	0.75 (0.56, 1.03)
Quartile 3 (16–20)	24,764	65	220840.0	0.68 (0.50, 0.92)	0.75 (0.55, 1.03)	0.85 (0.62, 1.16)
Quartile 4 (≥ 21)	20,829	33	188678.3	0.40 (0.27, 0.59)	0.51 (0.34, 0.75)	0.60 (0.40, 0.90)
P for trend				**< 0.001**	**0.001**	**0.026**
Oral Cavity and Pharynx cancer	98,352	161				
Quartile 1 (≤ 10)	26,669	55	232261.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2 (11–15)	26,127	45	229760.9	0.83 (0.56, 1.22)	0.84 (0.57, 1.24)	0.88 (0.59, 1.31)
Quartile 3 (16–20)	24,736	37	220692.6	0.71 (0.47, 1.07)	0.75 (0.49, 1.14)	0.82 (0.54, 1.25)
Quartile 4 (≥ 21)	20,820	24	188639.7	0.53 (0.33, 0.86)	0.62 (0.38, 1.00)	0.70 (0.43, 1.15)
P for trend				**0.007**	**0.039**	**0.147**
Larynx cancer	98,287	96				
Quartile 1 (≤ 10)	26,660	46	232228.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quartile 2 (11–15)	26,100	18	229634.0	0.40 (0.23, 0.68)	0.41 (0.24, 0.71)	0.45 (0.26, 0.78)
Quartile 3 (16–20)	24,722	23	220613.7	0.53 (0.32, 0.87)	0.62 (0.38, 1.03)	0.75 (0.45, 1.24)
Quartile 4 (≥ 21)	20,805	9	188546.9	0.24 (0.12, 0.49)	0.35 (0.17, 0.73)	0.46 (0.22, 0.96)
P for trend				**< 0.001**	**0.003**	**0.039**

a: Adjusted for age (years), sex (male, female) and race (white, non-white)

b: Adjusted for model 1 plus educational level (college below, college graduate, postgraduate), trial group (intervention, control), energy intake from diet (kcal/day), BMI (kg/m2), family history of HNC (no, yes, possibly), smoker (never, current or former), alcohol intake (no, yes), aspirin use (no, yes), history of hypertension (no, yes), history of diabetes (no, yes), and physical activity (min/week)

a 60% lower hazard of HNC ($HR_{Q4\ vs.\ Q1}$ = 0.40, 95% CI: 0.27–0.59; P_{trend} < 0.001). In multivariate Cox proportional hazards models adjusting for age, sex, race, education, trial group, energy intake from diet, family history, smoking, alcohol intake, aspirin use, physical activity, BMI, and diabetes, participants in the highest versus lowest quartile of LFD score had a 40% lower hazard of HNC ($HR_{Q4\ vs.\ Q1}$ = 0.60, 95% CI: 0.40–0.90; P_{trend} = 0.026). Furthermore, a similar inverse relationship was observed between the LFD score and the risk of HNC subtype (for larynx cancer, $HR_{Q4\ vs.\ Q1}$: 0.46; 95% CI: 0.22–0.96; P_{trend}= 0.039) (table 2). We employed RCS model to illustrate the fluctuations in the incidence of HNC, oral and pharynx cancer, as well as larynx cancer across the entire range of LFD score. As depicted in Fig. 3, as LFD score increased, there was a corresponding decrease in the risk of these cancers, displaying a linear dose-response relationship (all *P* for nonlinearity > 0.05)

- In addition, we also added the results for models with the LFD score run as a continuous variable. In the unadjusted Cox model, LFD score was

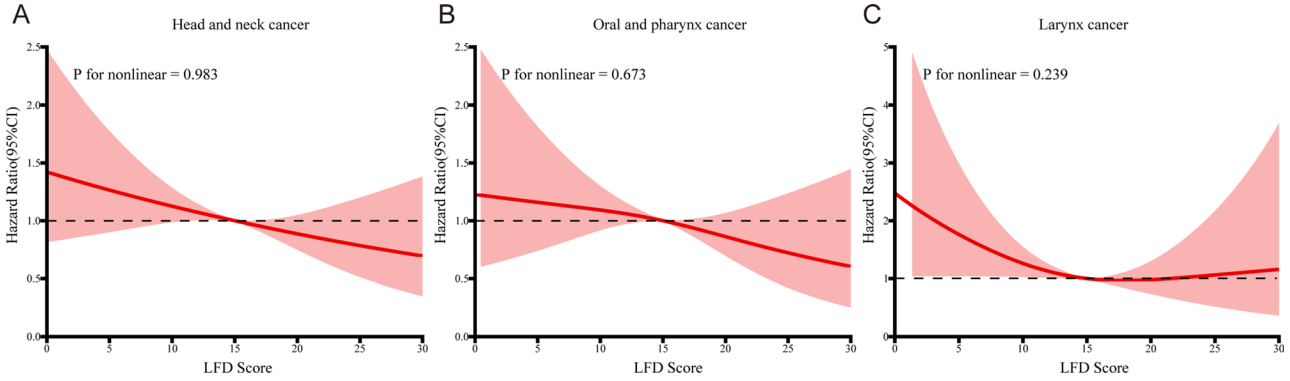

Fig. 3 Dose–response analyses on the association of LFD scores with the risk of HNC (**A**), oral and pharynx cancer (**B**), and larynx cancer (**C**). HRs were adjusted for age(years), sex (male, female) and race (non-Hispanic White, non-Hispanic Black, Hispanic, and other race/ethnicity), educational level (college below, college graduate, postgraduate), BMI (kg/m2), family history of HNC (no, yes, possibly), smoker (never, current or former), drinker (no, yes), aspirin use (no, yes), history of hypertension (no, yes), history of diabetes (no, yes), and physical activity (min/week)

associated with clinically significant HNC (HR = 0.96, 95% CI: 0.94–0.97; $P < 0.001$). In multivariate Cox proportional hazards models adjusting for age, sex, race, education, trial group, energy intake from diet, family history, smoking, alcohol intake, aspirin use, history of hypertension, physical activity, BMI, and diabetes, LFD score was still associated with clinically significant HNC (HR = 0.98, 95% CI: 0.96-1.00; $P = 0.028$) (Supplementary Table 3). Association of intake of PUFA, MUFA, or SFA with the risk of HNC was also analyzed, indicating non-significant result (Supplementary Table 4).

Subgroup and sensitivity analyses

In subgroup analyses, the inverse association between LFD score and HNC risk did not differ significantly by age, sex, trial group, energy intake from diet, BMI, smoking status, alcohol intake, or history of hypertension or diabetes (all P for interaction > 0.05) (table 3). Subgroup analyses demonstrated that the inverse association was stronger among participants with no aspirin use ($P_{interaction}$ <0.001). In sensitivity analyses, results remained unchanged restricted to participants excluding those with a history of diabetes or family history of HNC at baseline (P_{trend} <0.05). The associations remained similar when we further excluded cases observed within the first 2 years or 4 years of follow-up although the p-value did not reach statistical significance (table 4). This suggests that the inverse association between LFD score and HNC risk is well robust. Non-significant results are associated with a smaller number of cases remaining after exclusion

Discussion

In this large prospective cohort study, we found that adherence to an LFD pattern was significantly associated with a reduced risk of HNC. Restricted cubic spline analysis showed linear dose-response relationships between LFD score and risks of total HNC as well as its subtypes. A series of sensitivity analyses yielded consistent results without significant changes after multiple adjustments

Over the past few decades, substantial epidemiologic evidence has accumulated to suggest that adherence to an LFD pattern may help prevent obesity, type 2 diabetes, cardiovascular disease, and certain types of cancer [30]. Early ecological studies revealed associations between national fat consumption and mortality rates from these diseases [31, 32]. This stimulated extensive research on the health effects of reducing dietary fat intake. Several landmark randomized controlled trials including the women's Health Initiative did not find protective effects of LFD on cancer or cardiovascular outcomes [33, 34]. However, most of these trials had poor long-term compliance, limiting their ability to truly test LFD. The role of dietary fat intake in cancer development has been investigated, but findings on LFD and cancer risk have been inconsistent. Some results showing no association between greater adherence to an LFD pattern and risk of cancer align with the totality of evidence from both observational studies and clinical trials. For example, pooled analyses of prospective cohort studies have found no significant associations between lower fat intake and risk of prostate cancers [35]. Randomized trials including the women's Health Initiative also demonstrated no effects of an LFD intervention on incidence of breast and colorectal cancers over 7–8 years of follow-up [33, 34]. The LFD patterns emphasized in previous studies focused on reducing dietary fat and increasing intakes of fruits, vegetables, and grains. Recent studies have also reported different conclusions. LFD may reduce the risk

Table 3 Subgroup analyses on the association of LFD scores with the risk of HNC

	No. of		Hazard Ratio (95% Confidence Interval) by LFD Scores					
Subgroup variable	**Cases**	**Person-years**	**Quartile 1 (≤ 10)**	**Quartile 2 (11–15)**	**Quartile 3 (16–20)**	**Quartile 4 (≥ 21)**	P_{trend}	$P_{interaction}$
Age (years)								0.227
≤ 65	121	455497.19	1.00 (reference)	0.533 (0.331, 0.858)	0.796 (0.498, 1.272)	0.588 (0.313, 1.103)	0.105	
> 65	147	416382.43	1.00 (reference)	1.031 (0.679, 1.563)	0.969 (0.621, 1.512)	0.688 (0.398, 1.191)	0.242	
Sex								0.467
Male	213	413369.39	1.00 (reference)	0.689 (0.487, 0.974)	0.869 (0.608, 1.241)	0.638 (0.395, 1.030)	0.103	
Female	55	458510.2	1.00 (reference)	1.224 (0.601, 2.490)	0.945 (0.445, 2.004)	0.678 (0.294, 1.563)	0.296	
Trial group								0.696
Intervention	133	427859.26	1.00 (reference)	0.875 (0.568, 1.349)	0.889 (0.561, 1.408)	0.596 (0.330, 1.076)	0.130	
Control	135	444020.36	1.00 (reference)	0.672 (0.431, 1.048)	0.852 (0.543, 1.337)	0.662 (0.374, 1.173)	0.201	
Energy intake from diet								0.705
<=median	96	436424.28	1.00 (reference)	0.856 (0.491, 1.492)	0.810 (0.466, 1.409)	0.675 (0.370, 1.231)	0.227	
> median	172	435455.3	1.00 (reference)	0.734 (0.506, 1.065)	0.943 (0.637, 1.394)	0.566 (0.311, 1.030)	0.144	
BMI (kg/m2)								0.480
≤ 30	215	678412.9	1.00 (reference)	0.784 (0.556, 1.104)	0.816 (0.566, 1.177)	0.688 (0.441, 1.073)	0.123	
> 30	53	193466.71	1.00 (reference)	0.704 (0.349, 1.420)	1.108 (0.563, 2.180)	0.424 (0.141, 1.276)	0.344	
Alcohol intake								0.871
No	60	234366.13	1.00 (reference)	0.717 (0.350, 1.469)	0.923 (0.467, 1.823)	0.742 (0.345, 1.599)	0.595	
Yes	208	637513.5	1.00 (reference)	0.784 (0.557, 1.104)	0.858 (0.595, 1.237)	0.576 (0.351, 0.947)	0.049	
Family history of HNC								0.175
No	251	837764.70	1.00 (reference)	0.771 (0.566, 1.05)	0.847 (0.616, 1.165)	0.573 (0.379, 0.867)	0.043	
Yes/possibly	17	34114.92	1.00 (reference)	0 (0, Inf)	0.546 (0.051, 5.892)	2.902 (0.331, 25.428)	0.991	
Smoker								0.607
Never	62	424544.34	1.00 (reference)	1.037 (0.531, 2.022)	0.847 (0.418, 1.714)	0.672 (0.304, 1.489)	0.278	
Current or former	206	447335.28	1.00 (reference)	0.709 (0.499, 1.008)	0.904 (0.629, 1.299)	0.630 (0.387, 1.027)	0.120	
Aspirin use								< 0.001
No	123	466406.80	1.00 (reference)	0.406 (0.244, 0.675)	0.915 (0.595, 1.406)	0.292 (0.130, 0.652)	0.017	
Yes	145	405472.82	1.00 (reference)	1.257 (0.828, 1.909)	0.862 (0.530, 1.403)	0.991 (0.591, 1.660)	0.630	
History of hypertension								0.130
No	183	594960.31	1.00 (reference)	0.740 (0.506, 1.083)	1.068 (0.734, 1.553)	0.601 (0.354, 1.020)	0.266	
Yes	85	276919.32	1.00 (reference)	0.827 (0.488, 1.402)	0.516 (0.272, 0.980)	0.660 (0.342, 1.276)	0.075	
History of diabetes								0.997
No	252	818456.1	1.00 (reference)	0.774 (0.564, 1.064)	0.875 (0.628, 1.219)	0.641 (0.420, 0.980)	0.070	
Yes	16	53423.56	1.00 (reference)	0.648 (0.180, 2.327)	0.767 (0.207, 2.836)	0.475 (0.090, 2.514)	0.424	
Physical activity								0.099
<=median	159	440583.91	1.00 (reference)	1.059 (0.723, 1.551)	1.000 (0.650, 1.538)	0.739 (0.417, 1.312)	0.436	
> median	109	431295.72	1.00 (reference)	0.437 (0.256, 0.747)	0.692 (0.427, 1.119)	0.479 (0.266, 0.863)	0.033	

HRs were adjusted for age (years), sex (male, female) and race (white, non-white), educational level (college below, college graduate, postgraduate), trial group (intervention, control), energy intake from diet (kcal/day), BMI (kg/m2), smoker (never, current or former), alcohol intake (no, yes), family history of HNC (no, yes/possibly), aspirin use (no, yes), history of hypertension (no, yes), history of diabetes (no, yes), and physical activity (min/week)

of colorectal cancer [36]. LFD scores were negatively associated with risks of liver and lung cancer [27, 37]. No studies have yet examined the association between LFD and HNC risk. Established high-risk factors for HNC include alcohol drinking and cigarette smoking. Some studies have also examined associations between dietary patterns and HNC risk. Mediterranean dietary patterns may reduce the incidence of HNC in US populations [4, 38]. Moderate egg intake (<4 eggs per week) and daily vitamin intake help lower HNC risk [4]. Consumption of healthful diets rich in fruits and vegetables correlates with reduced HNC risk [39]. The dietary pattern scores constructed in this study considered the energy proportion of three macronutrients and the low-fat contribution, overcoming the limitations of traditional methods for evaluating LFD patterns. Our results demonstrate that after adjusting for potential confounders, LFD score was inversely associated with HNC risk in a nonlinear

Table 4 Sensitivity analyses on the association of LFD scores with the risk of HNC

Categories	No. of Participants	No. of Cases	Hazard Ratio (95% Confidence Interval) by LFD Scores [a]				P_{trend}
			Quartile 1 (≤ 10)	Quartile 2 (11–15)	Quartile 3 (16–20)	Quartile 4 (≥ 21)	
Repeated analysis in participants with non-missing data	71,492	169	1.00 (reference)	0.80 (0.54, 1.18)	0.94 (0.63, 1.41)	0.74 (0.46, 1.21)	**0.355**
Excluded participants with family history of HNC [b]	96,516	251	1.00 (reference)	0.77 (0.56, 1.06)	0.85 (0.61, 1.18)	0.59 (0.39, 0.90)	**0.025**
Excluded participants with a history of diabetes [c]	91,990	252	1.00 (reference)	0.76 (0.56, 1.04)	0.85 (0.61, 1.17)	0.61 (0.41, 0.93)	**0.036**
Excluded cases observed within the first 2 years of follow-up	98,407	216	1.00 (reference)	0.80 (0.57, 1.13)	0.91 (0.64, 1.30)	0.71 (0.46, 1.10)	**0.189**
Excluded cases observed within the first 4 years of follow-up	98,341	150	1.00 (reference)	0.80 (0.52, 1.19)	0.93 (0.61, 1.42)	0.64 (0.37, 1.11)	**0.201**

a: HRs were adjusted for age (years), sex (male, female) and race (white, non-white), educational level (college below, college graduate, postgraduate), trial group (intervention, control), energy intake from diet (kcal/day), BMI (kg/m2), family history of HNC (no, yes, possibly), smoker (never, current or former), alcohol intake (no, yes), aspirin use (no, yes), history of hypertension (no, yes), history of diabetes (no, yes), physical activity (min/week)

b: Hazard ratio was not adjusted for family history of HNC

c: Hazard ratio was not adjusted for history of diabetes

dose-response manner. To our knowledge, this is the first prospective study with up to 98,456 participants demonstrating an inverse association between LFD patterns and HNC risk

Several potential mechanisms may be involved in the association between LFD scores and risk of HNC. LFD patterns may inhibit carcinogenesis in the head and neck region by regulating hormone levels, improving insulin sensitivity, controlling body weight, reducing intake of detrimental fats, and increasing intake of beneficial foods. Fat intake is associated with changes in hormone levels. High-fat diets may increase levels of estrogen and testosterone, and higher endogenous estrogen is linked to increased risk of HNC [40]. LFD may exert anticancer effects by decreasing hormone levels. High-fat diets can lead to insulin resistance, while activation of insulin and IGF-1 signaling pathways is implicated in cancer development [41]. LFD may suppress tumor development by improving insulin sensitivity and lowering IGF-1 levels. Excess fat intake is associated with obesity, which is a risk factor for HNC [42]. LFD patterns can control body weight and thus lower cancer risk. Different types of fats have varying mechanisms of action. Saturated fats provoke inflammatory responses while trans fats cause oxidative stress [43]. LFD can restrict intake of these detrimental fats. LFDs are rich in beneficial components like dietary fiber and antioxidant nutrients which may have anticancer effects [44].

Strengths of the present analysis include the prospective design, large sample size, long follow-up duration, ability to control for smoking and alcohol as major risk factors, and assessment of overall dietary patterns rather than individual nutrients or foods. Most importantly, this is the first study to demonstrate that adherence to an LFD pattern is associated with reduced risks of total HNC as well as its subtypes, suggesting a potential preventive effect against HNC

This study also has some limitations. First, although we considered a comprehensive range of confounding factors, and sensitivity analysis also showed that the results are stable, residual confounding factors cannot be completely ruled out. Moreover, due to the unavailability of data, we were unable to conduct analyses for certain confounding factors such as HPV infection. There is currently little evidence on whether the association between diet and HNC risk changes in people with different HPV infection status. One study showed that fruit consumption was associated with a reduced HNSCC risk among HPV-16-seronegative individuals but an increased HNSCC risk among the HPV-16-seropositive individuals [45]. The mechanism is currently unclear. It is also possible that the LFD score is associated with HNC risk differently in people with different HPV status, which needs to be explored in more clinical studies in the future. Second, as with other nutritional epidemiology studies, measurement error in dietary assessment remains a concern despite the survey questionnaires used in the cohort being validated and showing good validity. Third, we were unable to evaluate the impact of potential dietary changes over time since only baseline diet information was comprehensive in the PLCO trial, and subsequent supplementary diet questionnaires had missing diet data. Forth, in our study, over 90% of participants were non-hispanic White; over 60% had educational degree of some college or less; and around half were aspirin users or ever smokers. Therefore, our results may not be applicable to other populations. Finally, participants in this study were U.S. adults aged 55 to 74, so the results need to be applied with caution to other populations

Conclusion

In summary, we established an association between higher LFD score and reduced risk of HNC and larynx cancer. Thus, our findings support potential benefits of adhering to LFD dietary patterns as a HNC and larynx cancer prevention strategy

Abbreviations

NCI	National cancer institute
PLCO	Prostate lung colorectal and ovarian
BQ	Baseline questionnaire
CIs	Confidence intervals
DHQ	Dietary history questionnaire
SQX	Supplemental questionnaire
HRs	Hazard ratios
LFD	Low-fat diet
BMI	Body mass index
HNC	Head and neck cancer

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-024-01026-z.

Supplementary Material 2: Supplementary table 1. Criteria for determining the LFD scores.Supplementary table 2. Distribution of variables with missing data before and after imputation.

Supplementary Material 2: Supplementary table 4. Association of intake of PUFA, MUFA, or SFA with the risk of HNC.

Supplementary Material 3: Supplementary table 3. Association of LFD scores with the risk of HNC.

Acknowledgements

We sincerely appreciate the PLCO study group and PLCO participants. This research has been conducted using the PLCO resource (https://cdas.cancer.gov/plco/) under application number PLCO-1335.

Author contributions

R.W. and L.X. designed the research and applied for the original data, R.W., H.L. and Q.C. performed data collection, statistical analysis, and drafted the original manuscript. Y.Y., and L.X. assisted in statistical methodology. L.X. and Q.C. revised the manuscript.

Funding information

This work was supported by National Natural Science Foundation of China (Grant Nos. 81860526). This research was funded by China Postdoctoral Science Foundation funded project (Grant Nos. 2021M703683).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

The study is in line with the Helsinki Declaration. The PLCO Cancer Screening Trial design was approved by the Institutional Review Board of the NCI and each of the screening centers. Participants provided written informed consent prior to participation in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 March 2024 / Accepted: 9 October 2024

Published online: 17 October 2024

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
2. Hashim D, Genden E, Posner M, Hashibe M, Boffetta P. Head and neck cancer prevention: from primary prevention to impact of clinicians on reducing burden. Ann Oncol. 2019;30:744–56.
3. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Alles B, Mejean C, Deschasaux M, Fassier P, Latino-Martel P, Beslay M, Hercberg S, Lavalette C, Monteiro CA, Julia C, Touvier M. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort. BMJ. 2018;360:k322.
4. Saka-Herran C, Pereira-Riveros T, Jane-Salas E, Lopez-Lopez J. Association between the Mediterranean Diet and Vitamin C and the Risk of Head and Neck Cancer, Nutrients, 15 (2023).
5. Giraldi L, Panic N, Cadoni G, Boccia S, Leoncini E. Association between Mediterranean diet and head and neck cancer: results of a large case-control study in Italy. Eur J Cancer Prev. 2017;26:418–23.
6. Kawakita D, Lee YA, Turati F, Parpinel M, Decarli A, Serraino D, Matsuo K, Olshan AF, Zevallos JP, Winn DM, Moysich K, Zhang ZF, Morgenstern H, Levi F, Kelsey K, McClean M, Bosetti C, Garavello W, Schantz S, Yu GP, Boffetta P, Chuang SC, Hashibe M, Ferraroni M, La Vecchia C, Edefonti V. Dietary fiber intake and head and neck cancer risk: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. Int J Cancer. 2017;141:1811–21.
7. Li WQ, Park Y, Wu JW, Goldstein AM, Taylor PR, Hollenbeck AR, Freedman ND, Abnet CC. Index-based dietary patterns and risk of head and neck cancer in a large prospective study. Am J Clin Nutr. 2014;99:559–66.
8. Bradshaw PT, Siega-Riz AM, Campbell M, Weissler MC, Funkhouser WK, Olshan AF. Associations between dietary patterns and head and neck cancer: the Carolina head and neck cancer epidemiology study. Am J Epidemiol. 2012;175:1225–33.
9. Edefonti V, Bravi F, La Vecchia C, Randi G, Ferraroni M, Garavello W, Franceschi S, Talamini R, Boffetta P, Decarli A. Nutrient-based dietary patterns and the risk of oral and pharyngeal cancer. Oral Oncol. 2010;46:343–8.
10. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13:3–9.
11. Mentella MC, Scaldaferri F, Ricci C, Gasbarrini A, Miggiano GAD. Cancer and Mediterranean Diet: A Review, Nutrients, 11 (2019).
12. Filomeno M, Bosetti C, Garavello W, Levi F, Galeone C, Negri E, La Vecchia C. The role of a Mediterranean diet on the risk of oral and pharyngeal cancer. Br J Cancer. 2014;111:981–6.
13. Fakhri S, Moradi SZ, Farzaei MH, Bishayee A. Modulation of dysregulated cancer metabolism by plant secondary metabolites: a mechanistic review. Semin Cancer Biol. 2022;80:276–305.
14. Dauer P, Lengyel E. New roles for Glycogen in Tumor Progression. Trends Cancer. 2019;5:396–9.
15. Halczy-Kowalik L, Drozd A, Stachowska E, Drozd R, Zabski T, Domagala W. Fatty acids distribution and content in oral squamous cell carcinoma tissue and its adjacent microenvironment. PLoS ONE. 2019;14:e0218246.
16. Krontiras H, Roye GD, Beenken SE, Myers RB, Mayo MS, Peters GE, Grizzle WE. Fatty acid synthase expression is increased in neoplastic lesions of the oral tongue. Head Neck. 1999;21:325–9.
17. Uma RS, Naresh KN, D'Cruz AK, Mulherkar R, Borges AM. Metastasis of squamous cell carcinoma of the oral tongue is associated with down-regulation of epidermal fatty acid binding protein (E-FABP). Oral Oncol. 2007;43:27–32.
18. De Vito R, Lee YCA, Parpinel M, Serraino D, Olshan AF, Zevallos JP, Levi F, Zhang ZF, Morgenstern H, Garavello W, Kelsey K, McClean M, Schantz S, Yu GP, Boffetta P, Chuang SC, Hashibe M, La Vecchia C, Parmigiani G, Edefonti V. Shared and Study-specific dietary patterns and Head and Neck Cancer Risk in an International Consortium. Epidemiology. 2019;30:93–102.
19. Edefonti V, Hashibe M, Ambrogi F, Parpinel M, Bravi F, Talamini R, Levi F, Yu G, Morgenstern H, Kelsey K, McClean M, Schantz S, Zhang Z, Chuang S, Boffetta P, La Vecchia C, Decarli A. Nutrient-based dietary patterns and the risk of head and neck cancer: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium. Ann Oncol. 2012;23:1869–80.

20. Brennan SF, Cantwell MM, Cardwell CR, Velentzis LS, Woodside JV. Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr. 2010;91:1294–302.
21. Yang WS, Zeng XF, Liu ZN, Zhao QH, Tan YT, Gao J, Li HL, Xiang YB. Diet and liver cancer risk: a narrative review of epidemiological evidence. Br J Nutr. 2020;124:330–40.
22. Zhu CS, Pinsky PF, Kramer BS, Prorok PC, Purdue MP, Berg CD, Gohagan JK. The prostate, lung, colorectal, and ovarian cancer screening trial and its associated research resource. J Natl Cancer Inst. 2013;105:1684–93.
23. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, McIntosh A, Rosenfeld S. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the eating at America's table study. Am J Epidemiol. 2001;154:1089–99.
24. Thompson FE, Kipnis V, Midthune D, Freedman LS, Carroll RJ, Subar AF, Brown CC, Butcher MS, Mouw T, Leitzmann M, Schatzkin A. Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. Public Health Nutr. 2008;11:183–95.
25. Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JE, Willett W, Rexrode KM, Rimm EB, Hu FB. Healthful and unhealthful plant-based diets and the risk of Coronary Heart Disease in U.S. adults. J Am Coll Cardiol. 2017;70:411–22.
26. Shan Z, Guo Y, Hu FB, Liu L, Qi Q. Association of Low-Carbohydrate and Low-Fat Diets with Mortality among US adults. JAMA Intern Med. 2020;180:513–23.
27. Peng L, Xiang L, Xu Z, Gu H, Zhu Z, Tang Y, Jiang Y, He H, Wang Y, Zhao X. Association between low-fat diet and liver cancer risk in 98,455 participants: results from a prospective study. Front Nutr. 2022;9:1013643.
28. Csizmadi I, Boucher BA, Lo Siou G, Massarelli I, Rondeau I, Garriguet D, Koushik A, Elenko J, Subar AF. Using national dietary intake data to evaluate and adapt the US Diet History Questionnaire: the stepwise tailoring of an FFQ for Canadian use. Public Health Nutr. 2016;19:3247–55.
29. Dziak JJ, Coffman DL, Lanza ST, Li R, Jermiin LS. Sensitivity and specificity of information criteria. Brief Bioinform. 2020;21:553–65.
30. Smith JD, Hou T, Ludwig DS, Rimm EB, Willett W, Hu FB, Mozaffarian D. Changes in intake of protein foods, carbohydrate amount and quality, and long-term weight change: results from 3 prospective cohorts. Am J Clin Nutr. 2015;101:1216–24.
31. Kinlen LJ. Fat and cancer aetiology. Prog Lipid Res. 1986;25:527–31.
32. Armstrong BK, Mann JI, Adelstein AM, Eskin F. Commodity consumption and ischemic heart disease mortality, with special reference to dietary practices. J Chronic Dis. 1975;28:455–69.
33. Beresford SA, Johnson KC, Ritenbaugh C, Lasser NL, Snetselaar LG, Black HR, Anderson GL, Assaf AR, Bassford T, Bowen D, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Harrigan RC, Hays J, Heber D, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Kotchen JM, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lewis CE, Manson JE, Margolis KL, Mossavar-Rahmani Y, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Stefanick ML, Van Horn L, Vitolins MZ, Wactawski-Wende J, Wallace RB, Whitlock E. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial, JAMA, 295 (2006) 643–54.
34. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, Margolis KL, Limacher MC, Manson JE, Parker LM, Paskett E, Phillips L, Robbins J, Rossouw JE, Sarto GE, Shikany JM, Stefanick ML, Thomson CA, Van Horn L, Vitolins MZ, Wactawski-Wende J, Wallace RB, Wassertheil-Smoller S, Whitlock E, Yano K, Adams-Campbell L, Anderson GL, Assaf AR, Beresford SA, Black HR, Brunner RL, Brzyski RG, Ford L, Gass M, Hays J, Heber D, Heiss G, Hendrix SL, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Kotchen JM, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Henderson MM. Low-fat dietary pattern and risk of invasive breast cancer. Volume JAMA. the Women's Health Initiative Randomized Controlled Dietary Modification Trial; 2006. pp. 629–42.
35. Kohler LN, Garcia DO, Harris RB, Oren E, Roe DJ, Jacobs ET. Adherence to Diet and Physical Activity Cancer Prevention guidelines and Cancer outcomes: a systematic review. Cancer Epidemiol Biomarkers Prev. 2016;25:1018–28.
36. Sneyd MJ, Cox B. Do low-fat foods alter risk of colorectal cancer from processed meat? Public Health. 2020;183:138–45.
37. Zhu Z, Peng L, Zhou H, Gu H, Tang Y, Zhou Z, Xiang L, Wang Y. Low-fat dairy consumption and the risk of lung cancer: a large prospective cohort study. Cancer Med. 2023;12:16558–69.
38. Saraiya V, Bradshaw P, Meyer K, Gammon M, Slade G, Brennan P, Abedi-Ardekani B, Olshan A. The association between diet quality and cancer incidence of the head and neck. Cancer Causes Control. 2020;31:193–202.
39. Galvao OP, De Podesta SV, Peres LB, Salaroli M, Cattafesta JRV, De Podesta SLV, von Zeidler JC, de Oliveira LP, Kowalski MK, Ikeda P, Brennan MP, Curado. Consumption of minimally processed foods as protective factors in the genesis of squamous cell carcinoma of the head and neck in Brazil. PLoS ONE. 2019;14:e0220067.
40. Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and head and neck cancer risk in a large United States prospective cohort study. Int J Cancer. 2008;122:2330–6.
41. Zheng Y, Wu C, Yang J, Zhao Y, Jia H, Xue M, Xu D, Yang F, Fu D, Wang C, Hu B, Zhang Z, Li T, Yan S, Wang X, Nelson PJ, Bruns C, Qin L, Dong Q. Insulin-like growth factor 1-induced enolase 2 deacetylation by HDAC3 promotes metastasis of pancreatic cancer. Signal Transduct Target Ther. 2020;5:53.
42. Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lissowska J, Zaridze D, Winn DM, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Schwartz SM, Rudnai P, Eluf-Neto J, Muscat J, Morgenstern H, Menezes A, Matos E, Bucur A, Levi F, Lazarus P, La Vecchia C, Koifman S, Kelsey K, Herrero R, Hayes RB, Franceschi S, Wunsch-Filho V, Fernandez L, Fabianova E, Daudt AW, Dal Maso L, Curado MP, Chen C, Castellsague X, Benhamou S, Boffetta P, Brennan P, Hashibe M. Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. Int J Epidemiol. 2010;39:1091–102.
43. Nowak J, Weylandt KH, Habbel P, Wang J, Dignass A, Glickman JN, Kang JX. Colitis-associated colon tumorigenesis is suppressed in transgenic mice rich in endogenous n-3 fatty acids. Carcinogenesis. 2007;28:1991–5.
44. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. Gastroenterology. 2015;148:1244–e12601216.
45. Meyer MS, Applebaum KM, Furniss CS, Peters ES, Luckett BG, Smith JF, Bryan J, McClean MD, Marsit C, Kelsey KT. Human papillomavirus-16 modifies the association between fruit consumption and head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev. 2008;17:3419–26.

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