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ORIGINAL PAPER

Diet and risk of adult leukemia: a multicenter case–control study in China

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Abstract
Purpose Epidemiologic studies on diet and leukemia risk have shown inconsistent results. This study examined the associations between dietary factors and the risk of adult leukemia in Chinese populations.
Methods A multicenter case–control study was conducted in southeast and northeast China between 2008 and 2013. It included 442 incident cases with hematologically confirmed leukemia and 442 controls, individually match to cases by gender, birth quinquennium, and study site. Information on diet was sought from face-to-face interviews using a validated and reliable 103-item food frequency questionnaire. Odds ratios (ORs) and confidence intervals (CIs) were estimated by conditional logistic regression.
Results Vegetables intake was associated with decreased risk of adult leukemia, with a significant dose–response relationship and adjusted OR of 0.30 (95 % CI 0.18–0.50) for the highest versus the lowest quartiles intake. Compared with non-consumers, the adjusted OR was 0.51 (95 % CI 0.29–0.93) for those who consumed milk at the highest tertile. Intakes of fruits, red meat, poultry, and fish were not associated with the risk. Dietary nutrients, including dietary fiber, carotenoids, vitamins B_1, B_2, and C, niacin, and folate, were significantly associated with reduced risks. Elevated risk was related to dietary intake animal fat and dietary habits with frequent intakes of fat, deep-fried, and smoked foods (p for trend <0.05).
Conclusions Our findings suggest that diets rich in vegetables and adequate amount of milk reduce the risk of adult leukemia, whereas diets preferring fat, deep-fried, and smoked foods increase the risk in Chinese populations.

Keywords Diet · Foods · Nutrients · Adult leukemia · Case–control

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Introduction

Leukemias are a group of diverse malignancies arising from hematopoietic stem cells. In the USA, 48,610 leukemia cases were newly diagnosed in 2013, with an estimated 23,720 deaths [1]. The age-standardized incidence rate of leukemia per 100,000 person-years in China is 4.3, which is about one half of the rates typically found in countries such as Australia, the USA, and Canada, being 9.4, 8.6, and 9.5, respectively [2]. Few established risk factors, such as smoking [3] and benzene exposure [4], account for only small proportions of myeloid leukemia incidence [5]. The etiology of leukemia in adults has not well understood.

To date, previous epidemiological studies, mostly from North America and Europe, have produced inconsistent results on the relationship between diet and adult leukemia risk [6–18]. Western-style diet is regarded as high in animal products such as red meat and poor in vegetables; yet traditional diets among Asian populations as well as Mediterranean diets consist largely of foods of plant origin [19]. Given the fact of lack of studies in Chinese

populations, whose diets are different from Western populations, this study aimed to investigate the association between dietary factors and the risk of adult leukemia in Chinese populations.

Materials and methods

Study design and subjects

A case–control study was conducted in three participating hospitals in southeast and northeast China between 2008 and 2013, namely the First and the Second Affiliated Hospitals of Zhejiang University in Hangzhou, Zhejiang Province, and the First Affiliated Hospital of China Medical University in Shenyang, Liaoning Province. These hospitals were the major public and teaching hospitals in the provinces. At participating hospitals, interviewers were trained by a chief investigator to identify and interview eligible subjects using the same questionnaire.

Eligibility criteria for cases were incident patients with a first-time hematologically confirmed diagnosis of leukemia [20], aged 15 years or over, residing in the respective provinces for at least 1 year, and presenting as an inpatient to the participating hospitals. An eligible leukemia incidence date, which was defined as the date of specimen collection leading to the first confirmed diagnosis, occurred from 1 July 2009 to 30 June 2011 for cases recruited at the First Hospital of China Medical University in Shenyang; from 1 July 2008 to 30 June 2012 at the Second Affiliated Hospital of Zhejiang University; and from 1 July 2011 to 30 June 2012 at the First Affiliated Hospital of Zhejiang University. Cases with other malignancies were excluded. Of the 452 eligible patients, ten refused to participate, resulting in a final number of 442 cases (response proportion 97.8 %). All cases were interviewed within 1 year of initial diagnosis and mostly (86.7 %) within 3 months.

Eligible outpatient controls were free of malignancies at the time of recruitment and were approached at the Medical Examination Center of the outpatient department at the same hospitals as their cases. Large panels of controls had been selected and interviewed for our series of case–control studies of colorectal cancer, breast cancer, and leukemia. Post hoc matching was then conducted with each control for this study selected as the first attendee to individually match with each case by gender, birth quinquennium, and study site. The date of recruitment of a control never exceeded that for the matching case by more than 1 year. The use of outpatient controls as a valid study base sample for inpatient cancer cases in our studies has been investigated extensively by our research group. Consistent with expectations based on an understanding of the dynamics of the Chinese health system, we have found that outpatient controls in our research perform similar to community controls [21–23]. The project protocol was approved by the Human Research Ethics Committee of The University of Western Australia and the ethics committees of the participating hospitals in China.

Food frequency questionnaire

A structured questionnaire was used to collect information on demographic characteristics, height and weight, detailed lifestyle, family history of malignancy, and food consumption assessed by a quantitative food frequency questionnaire (FFQ). The FFQ originated from a dietary questionnaire for cancerous research in Shanghai, China [24], with additional questions adapted from the diet questionnaire for the Hawaii and Los Angeles Cohort Study [25, 26], and the Australian Health Survey 1995 [27]. The FFQ has been validated and its reliability has been assessed in previous studies [28–30]. The FFQ was checked for internal reliability using the Cronbach's alpha coefficient calculated across preliminary test, test, and retest values with Cronbach's alpha being 0.81, 0.72, and 0.78, respectively [29, 31]. These high Cronbach's alpha scores suggested that the FFQ was a consistent and reliable instrument for measuring food consumption overall. The quantitative FFQ included 103 foods commonly consumed in both southeast and northeast China.

Dietary information was sought on the usual frequency and amount of food intakes, as well as dietary habits, and vitamins or mineral supplements taken. The frequency of food consumption was classified into nine categories: never or hardly ever, once a month, 2–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2 times a day, and $\geq$3 times a day. The amount of each food item consumed per meal was estimated using the common Chinese measure *liang* (equivalent to 50 g).

Face-to-face interviews

Face-to-face interviews were conducted after obtaining each subject's informed consent. The interviews usually took 30–40 min. To increase the accuracy of amount of food estimation, standard-sized containers were displayed to subjects during the interview. For seasonal vegetables and fruits, only the frequencies consumed during the available period were sought. Then, average daily intake in grams was estimated by calculating the percentage of months that the food was available on the market over a 1-year period. Food consumption reflected the 1-year period before the diagnosis for cases and before interview for controls. If there were any recent changes in dietary habits, only information on the habits before the change was used in data analysis.

Statistical analysis

Food groups, including vegetables, fruits, red meat, poultry, fish, and milk, were investigated. The composition of food groups is given in Table 1. The calculation of nutrients and energy intake was adjusted for edible portions of foods, seasonal factors, and market availability [29]. Nutrients and energy intake derived from 103 foods were estimated using the China Food Composition Tables [32]. Figures for folate were derived from previous edition of China Food Composition [33, 34]. For those nutrients containing α-carotene, β-carotene, β-cryptoxanthin, lutein and zeaxanthin, and lycopene, and not available from the China Food Composition Tables, figures were substituted from the nutrients database of the US Department of Agriculture [35]. As few subjects reported regularly taking vitamins or mineral supplements, we only analyzed nutrients derived from foods. Dietary nutrients were adjusted for energy intake (kilocalorie/day) with the density method [36].

The quantities of daily intake of food groups and nutrients density were split into quartiles based on the distribution among the controls, except that tertiles consumption of milk was used, with non-consumers as reference group. Average daily intake of food groups, demographic, lifestyle characteristics, and other potential confounding factors were compared between cases and controls using univariate conditional logistic regression. Adjusted odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were used to estimate the association of adult leukemia risk with dietary factors.

Food groups, dietary nutrients, and dietary habits were assessed separately. All multivariate conditional logistic regression models were adjusted for resident locality (urban, rural), education (none, primary, secondary, tertiary), body mass index (kg/m^2, continuous), cigarette smoking (no, yes), alcohol consumption (no, yes), tea consumption (no, yes), and energy intake (kilocalorie/day, continuous). These variables were included in the models because they were both associated with diet and associated with leukemia risk based on either the univariate analyses or previous studies [37–39]. Moreover, multivariate analyses on six food groups were further mutually adjusted for each other. For example, when analyzing vegetables, intakes of fruits, red meat, poultry, fish, and milk were included in the model along with aforementioned adjustments, and vice versa for other food groups. Multivariate analyses on dietary habits were also further simultaneously adjusted for each other. We present the risk estimates for food groups and dietary habits from both models in tables but describe estimates from only the mutually adjusted model in the text. We conducted tests for trend by the method of likelihood ratio test. Tests for trend for food groups were performed using the original values in the continuous format. We found no material change in p values for trend by using the median values of the food group categories and modeling the variable as a continuous variable. Tests for trend for quartile intakes of dietary nutrients and for dietary habits were conducted by modeling the categorical variable as a continuous variable. The associations of intakes of food groups and dietary nutrients with the risks of AML were provided in subgroup analyses. For continuous variables of food groups, risk estimates were further provided for per 50 g/day increase of intake. A two-sided alpha level of <0.05 was considered as statistical significance. All statistical analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Leukemia subtype information was available in 363 (82.1 %) of the 442 cases. Among these patients, 243 (66.9 %) had AML, 62 (17.1 %) had ALL, 38 (10.5 %) had CML, and 20 (5.5 %) had CLL. Table 2 shows selected characteristics of leukemia cases and control subjects.

Table 1 Composition of food groups

Food groups	No. of item	Composition
Vegetables	29	Greens, spinach, cabbage, Chinese cabbage, cauliflower, celery, bean sprouts, eggplant, (white) radish root, pea pods, green peas, green beans/green broad beans, potato, white gourd, cucumber, carrot, fresh mushrooms, sweet green/red peppers, tomato, wax gourd, dishcloth/sponge gourd, garlic, garlic stalks, Chinese chives, onion, spring onion, ginger, green/red fresh chili, sweet corn
Fruits	11	Apple, pear, orange/tangerine, banana, grape, watermelon, peaches, plums/apricot, dates, pineapple, strawberries
Red meat	7	Pork chops/spareribs, pig feet, fresh pork (lean), fresh pork (fat and lean), pork liver, organ meats, beef, and mutton
Poultry	2	Chicken, duck
Fish	3	Salt water fish (e.g., hairtail, yellow croaker), fresh water fish (e.g., silver carp, golden carp), eel
Milk	1	Fresh milk

Table 2 Demographic, lifestyle, and dietary factors among cases and controls

Characteristics	Cases ($n = 442$)	Controls ($n = 442$)	p value
Age at interview (years)	45.3 ± 14.5	45.4 ± 14.4	–
<30	70 (15.8)	70 (15.8)	
30–39	85 (19.2)	85 (19.2)	
40–49	113 (25.6)	113 (25.6)	
50–59	93 (21)	93 (21)	
60–69	63 (14.3)	63 (14.3)	
>69	18 (4.1)	18 (4.1)	
Male	256 (57.9)	256 (57.9)	–
Resident locality			0.001
Urban	351 (79.4)	375 (84.8)	
Rural	91 (20.6)	67 (15.2)	
Education			<0.001
None	15 (3.4)	13 (2.9)	
Primary	60 (13.6)	48 (10.9)	
Secondary	286 (64.7)	199 (45.0)	
Tertiary	81 (18.3)	182 (41.2)	
Cigarette smoking	162 (36.7)	130 (29.4)	0.01
Alcohol consumption	256 (57.9)	231 (52.3)	0.07
Tea consumption	222 (50.2)	276 (62.4)	<0.001
Body mass index (kg/m^2)			0.27
<25	367 (83.0)	355 (80.3)	
≥25	75 (17.0)	87 (19.7)	
Physical activity (weekly MET-hour)	85.2 ± 89.8	82.1 ± 80.1	0.55
Dietary intake (g/day)			
Vegetables	227.1 ± 158.5	262.1 ± 122.4	<0.001
Fruits	114.1 ± 126.0	142.9 ± 136.5	<0.001
Red meat	100.5 ± 87.9	96.7 ± 64.1	0.41
Poultry	20.6 ± 24.3	24.3 ± 26.0	0.02
Fish	32.3 ± 36.4	40.4 ± 38.8	<0.001
Milk	33.3 ± 70.1	64.7 ± 86.3	<0.001
Energy intake (kilocalorie/day)	2740.6 ± 1219.9	2429.9 ± 687.7	0.01
Any cancer in first-degree relatives	46 (10.4)	44 (10.0)	0.82

Values expressed as mean ± SD or number (percent)

p value was from univariate conditional logistic regression

Compared with controls, cases were more likely to live in a rural area, to be less educated, and to smoke. They consumed less tea, vegetables, fruits, poultry, fish, and milk, but had higher total energy intake. There was no meaningful difference between cases and controls in body mass index, physical activity, alcohol drinking, red meat intake, and cancer history in first-degree relatives.

Table 3 reports the adjusted ORs for adult leukemia risk in quartiles of daily intake of food groups. Compared with the lowest consumption, the adjusted OR (95 % CI) was 0.30 (0.18–0.50) for the highest intake of vegetables. Compared with non-consumers, the adjusted OR (95 % CI) was 0.51 (0.29–0.93) for those who consumed milk at the highest tertile. We observed inverse trends with increasing intakes of vegetables (p value for trend <0.001) and milk (p value for trend = 0.07). There was no notable association with leukemia risk in relation to consumption of fruits, red meat, poultry, and fish.

When the associations for vegetables and milk were analyzed in AML, similar inverse trend was observed for vegetables intake, but not for milk. The adjusted ORs (95 % CIs) from the mutually adjusted model were 0.35 (0.14–0.85) for the highest versus the lowest intake of vegetables (p value for trend = 0.002) and 0.86 (0.34–2.17) for the highest milk intake versus non-consumers (p value for trend = 0.53) (Table 3). The small number of cases hampered the further investigation of associations in subtypes of ALL, CML and CLL.

Table 3 Associations between intake of selected food groups and adult leukemia risk

Food groups (g/day)	All leukemias			AML		
	Cases/controls	OR (95 % CI)[a]	OR (95 % CI)[b]	Cases/controls	OR (95 % CI)[a]	OR (95 % CI)[b]
Vegetables						
<181.5	194/110	1.0 (ref)	1.0 (ref)	112/58	1.0 (ref)	1.0 (ref)
181.5–239.7	96/111	0.57 (0.38–0.86)	0.56 (0.37–0.86)	48/65	0.38 (0.20–0.72)	0.38 (0.19–0.75)
239.8–310.3	77/111	0.32 (0.21–0.51)	0.34 (0.22–0.54)	39/64	0.19 (0.09–0.37)	0.19 (0.09–0.40)
>310.3	75/110	0.26 (0.16–0.43)	0.30 (0.18–0.50)	44/56	0.20 (0.09–0.44)	0.35 (0.14–0.85)
P-trend[c]		<0.001	<0.001		<0.001	0.002
Per 50 g/day		0.84 (0.78–0.90)	0.85 (0.79–0.92)		0.79 (0.70–0.88)	0.83 (0.73–0.93)
Fruits						
<44.7	155/110	1.0 (ref)	1.0 (ref)	99/62	1.0 (ref)	1.0 (ref)
44.7–96.6	114/111	0.91 (0.60–1.37)	1.09 (0.71–1.67)	64/68	0.65 (0.35–1.19)	0.74 (0.39–1.42)
96.7–198.2	101/111	0.67 (0.42–1.07)	0.97 (0.58–1.63)	51/54	0.44 (0.21–0.90)	0.62 (0.28–1.36)
>198.2	72/110	0.43 (0.26–0.71)	0.65 (0.38–1.11)	29/59	0.13 (0.06–0.32)	0.18 (0.07–0.45)
P-trend[c]		0.006	0.28		<0.001	0.002
Per 50 g/day		0.91 (0.85–0.98)	0.96 (0.89–1.04)		0.78 (0.69–0.89)	0.81 (0.71–0.94)
Red meat						
<47.3	128/110	1.0 (ref)	1.0 (ref)	67/61	1.0 (ref)	1.0 (ref)
47.3–82.6	81/111	0.61 (0.38–0.97)	0.70 (0.43–1.14)	48/64	0.76 (0.39–1.48)	1.03 (0.49–2.18)
82.7–137.2	130/111	0.99 (0.62–1.57)	1.05 (0.64–1.72)	72/62	1.17 (0.56–2.41)	1.67 (0.71–3.93)
>137.2	103/110	0.65 (0.38–1.12)	0.85 (0.47–1.52)	56/56	0.54 (0.24–1.22)	0.75 (0.29–1.90)
P-trend[c]		0.85	0.47		0.48	0.95
Per 50 g/day		0.99 (0.87–1.12)	1.06 (0.91–1.22)		0.93 (0.77–1.13)	0.99 (0.77–1.28)
Poultry						
<8.2	152/148	1.0 (ref)	1.0 (ref)	83/76	1.0 (ref)	1.0 (ref)
8.2–15.1	64/73	0.94 (0.58–1.53)	1.05 (0.63–1.77)	33/35	0.75 (0.35–1.60)	1.06 (0.45–2.48)
15.2–35.6	160/106	1.47 (0.95–2.28)	1.72 (1.08–2.72)	92/60	1.14 (0.59–2.17)	1.58 (0.76–3.31)
>35.6	66/115	0.57 (0.34–0.95)	0.65 (0.36–1.16)	35/72	0.22 (0.09–0.52)	0.31 (0.11–0.88)
P-trend[c]		0.08	0.27		0.02	0.26
Per 50 g/day		0.72 (0.50–1.05)	0.79 (0.52–1.20)		0.48 (0.26–0.89)	0.65 (0.31–1.39)
Fish						
<11.5	136/104	1.0 (ref)	1.0 (ref)	67/49	1.0 (ref)	1.0 (ref)
11.5–28.4	138/128	0.82 (0.54–1.25)	0.92 (0.59–1.44)	76/67	0.87 (0.45–1.66)	1.07 (0.53–2.19)
28.5–58.3	97/100	0.65 (0.39–1.10)	0.76 (0.44–1.34)	60/57	0.60 (0.27–1.35)	0.65 (0.26–1.66)
>58.3	71/110	0.48 (0.28–0.83)	0.64 (0.35–1.16)	40/70	0.33 (0.14–0.73)	0.50 (0.19–1.31)
P-trend[c]		0.01	0.17		<0.001	0.05
Per 50 g/day		0.75 (0.59–0.95)	0.84 (0.66–1.08)		0.53 (0.36–0.77)	0.68 (0.45–1.02)
Milk						
Non-consumers	273/194	1.0 (ref)	1.0 (ref)	152/100	1.0 (ref)	1.0 (ref)
>0–71.1	105/104	0.81 (0.53–1.23)	0.89 (0.58–1.39)	63/60	0.86 (0.47–1.59)	1.31 (0.65–2.65)
71.2–178.1	33/64	0.49 (0.29–0.84)	0.61 (0.34–1.08)	14/40	0.40 (0.17–0.92)	0.61 (0.23–1.61)
>178.1	31/80	0.39 (0.22–0.69)	0.51 (0.29–0.93)	14/43	0.43 (0.19–1.00)	0.86 (0.34–2.17)
P-trend[c]		0.002	0.07		0.03	0.53
Per 50 g/day		0.84 (0.76–0.94)	0.90 (0.80–1.01)		0.83 (0.70–0.98)	0.94 (0.78–1.13)

[a] Estimates from separate conditional logistic regression models adjusted for resident locality (urban, rural), education (none, primary, secondary, tertiary), body mass index (kg/m^2, continuous), cigarette smoking (no, yes), alcohol consumption (no, yes), tea consumption (no, yes), and energy intake (kcal/day, continuous)

[b] Further mutually adjusted other food groups (g/day, continuous) listed above for each other

[c] Tests for trend across continuous variables

Table 4 shows the numerical summaries of selected nutrients derived from 103 foods and the adjusted ORs for leukemia risk. Significant inverse associations were observed for dietary fiber (OR 0.26, for the highest versus the lowest quartiles of intake) and α-carotene (OR 0.25), β-carotene (OR 0.43), β-cryptoxanthin (OR 0.56), lycopene (OR 0.49), vitamin B_1 (OR 0.46), vitamin B_2 (OR 0.62), vitamin C (OR 0.46), niacin (OR 0.43), and folate (OR 0.43); yet an increased risk was seen for animal fat intake (OR 1.95).

For the analyses of AML and their controls (Table 5), we also found significant decreased risks for dietary fiber (OR 0.12, the highest compared with the lowest quartiles), α-carotene (OR 0.24), β-carotene (OR 0.33), β-cryptoxanthin (OR 0.22), lycopene (OR 0.18), vitamin B_1 (OR 0.32), vitamin B_2 (OR 0.52), vitamin C (OR 0.38), and folate (OR 0.28).

Table 6 presents the associations between dietary habits and adult leukemia risk. Significant elevated risk was observed for frequent intakes of fat (OR 2.66, 95 % CI 1.54–4.59), deep-fried food (OR 3.58, 95 % CI 1.70–7.52), and smoked food (OR 6.48, 95 % CI 1.49–28.20).

Discussion

This multicenter case–control study in Chinese populations found a significant inverse relationship between vegetables and milk intake and adult leukemia risk. Dietary nutrients, including dietary fiber, carotenoids, vitamins B_1, B_2, and C, niacin, and folate, were also inversely related to the risk. Conversely, dietary intake animal fat and dietary habits favoring fat, deep-fried, and smoked foods increased the risk.

Few studies have considered the association between vegetable consumption and adult leukemia risk [6, 8, 10–16]. In the present study, we found a reduced risk of adult leukemia with vegetables consumption, where the inverse association at least existed in the most common subtype of AML. Our results relating higher vegetables intake to

Table 4 Associations between intake of selected dietary nutrients and adult leukemia risk

Dietary nutrients per 1,000 kcal[a]	Median (IQR)[b]		ORs (95 % CIs)[c] for quartiles of intake			*P-trend*[d]
	Cases	Controls	II	III	IV	
Total fat (g)	27.9 (23.0–33.6)	26.5 (22.8–30.7)	1.07 (0.69–1.65)	1.08 (0.69–1.68)	1.79 (1.17–2.73)	0.01
Plant fat	15.8 (11.9–22)	15.4 (12.4–19.7)	0.69 (0.44–1.09)	0.80 (0.52–1.24)	1.23 (0.77–1.96)	0.33
Animal fat	10.9 (7.1–14.9)	10.4 (6.4–13.7)	1.37 (0.88–2.14)	1.50 (0.94–2.39)	1.95 (1.19–3.19)	0.01
Dietary fiber (g)	3.8 (2.9–5.7)	4.3 (3.4–6.1)	0.33 (0.20–0.54)	0.30 (0.17–0.50)	0.26 (0.14–0.46)	<0.001
Cholesterol (mg)	155.0 (93.9–221.2)	169.5 (110.1–233.8)	1.06 (0.69–1.63)	0.93 (0.58–1.49)	0.98 (0.57–1.68)	0.82
Fat-soluble vitamins						
α-Carotene (μg)	51.0 (27.6–80.7)	74.0 (49.7–142.7)	0.47 (0.31–0.70)	0.37 (0.24–0.57)	0.25 (0.16–0.41)	<0.001
β-Carotene (μg)	737.8 (509.3–1087.6)	914.4 (670.9–1216.4)	0.59 (0.39–0.88)	0.31 (0.19–0.51)	0.43 (0.27–0.69)	<0.001
β-Cryptoxanthin (μg)	36.2 (22.5–72.9)	46.1 (31.5–80.4)	0.46 (0.30–0.72)	0.54 (0.35–0.83)	0.56 (0.36–0.87)	0.01
Lutein and zeaxanthin (μg)	355.7 (245.6–639.4)	404.2 (312.8–555.6)	0.38 (0.24–0.60)	0.27 (0.17–0.44)	0.78 (0.49–1.24)	0.07
Lycopene (μg)	232.2 (108.2–565.4)	332.5 (193.8–634.0)	0.50 (0.33–0.76)	0.39 (0.25–0.61)	0.49 (0.31–0.77)	<0.001
Vitamin A (μg)	161.2 (120.8–217.2)	181.2 (136.2–231.2)	0.84 (0.56–1.25)	0.70 (0.45–1.08)	0.89 (0.59–1.36)	0.43
Vitamin E (mg)	11.0 (8.4–14.7)	10.8 (8.8–14.1)	0.78 (0.49–1.23)	0.97 (0.63–1.50)	1.17 (0.73–1.88)	0.39
Water-soluble vitamins						
Vitamin B_1 (mg)	0.5 (0.4–0.5)	0.5 (0.4–0.6)	0.43 (0.28–0.66)	0.49 (0.30–0.79)	0.46 (0.29–0.73)	0.003
Vitamin B_2 (mg)	0.4 (0.3–0.4)	0.4 (0.3–0.5)	0.80 (0.55–1.16)	0.71 (0.47–1.07)	0.62 (0.40–0.96)	0.02
Vitamin C (mg)	20.9 (14.5–28.9)	22.8 (17.7–32.4)	0.59 (0.39–0.90)	0.78 (0.52–1.18)	0.46 (0.29–0.73)	0.01
Niacin (mg)	7.2 (6.1–8.4)	7.8 (6.7–9.4)	0.71 (0.46–1.08)	0.56 (0.36–0.88)	0.43 (0.26–0.70)	<0.001
Folate (μg)	112.4 (95.9–128.8)	118.9 (105.2–138.3)	0.68 (0.45–1.03)	0.76 (0.50–1.17)	0.43 (0.27–0.68)	0.001

[a] Nutrient density energy adjusted

[b] Median, interquartile range (IQR) of daily intake among cases and controls

[c] Estimates from separate conditional logistic regression models included terms for resident locality (urban, rural), education (none, primary, secondary, tertiary), body mass index (kg/m^2, continuous), cigarette smoking (no, yes), alcohol consumption (no, yes), tea consumption (no, yes), and energy intake (kcal/day, continuous), using the lowest quartile as the referent category

[d] Tests for trend across quartiles

Table 5 Associations between intake of selected dietary nutrients and adult AML risk

Dietary nutrients per 1,000 kcal[a]	Median (IQR)[b]		ORs (95 % CIs)[c] for quartiles of intake			*P-trend*[d]
	Cases	Controls	II	III	IV	
Total fat (g)	29.3 (24.0–33.8)	26.4 (22.9–31.0)	0.99 (0.53–1.88)	0.92 (0.48–1.74)	1.60 (0.85–3.01)	0.16
Plant fat	16.0 (11.9–22.7)	15.3 (11.8–19.1)	1.04 (0.53–2.04)	0.68 (0.32–1.43)	1.55 (0.76–3.18)	0.25
Animal fat	11.2 (7.1–15.4)	10.7 (7.0–14.1)	1.50 (0.77–2.89)	1.25 (0.61–2.56)	2.02 (1.00–4.07)	0.07
Dietary fiber (g)	3.5 (2.8–5.2)	4.2 (3.3–5.8)	0.24 (0.11–0.51)	0.17 (0.07–0.37)	0.12 (0.05–0.29)	<0.001
Cholesterol (mg)	151.1 (93.7–223.5)	178.7 (128.0–240.6)	0.70 (0.38–1.28)	0.77 (0.39–1.51)	0.70 (0.32–1.51)	0.35
Fat-soluble vitamins						
α-Carotene (μg)	49.8 (26.6–80.1)	77.0 (48.8–142.5)	0.45 (0.25–0.82)	0.32 (0.16–0.63)	0.24 (0.12–0.50)	<0.001
β-Carotene (μg)	693.7 (509.3–1046.6)	925.2 (708.9–1207.2)	0.30 (0.16–0.58)	0.15 (0.07–0.34)	0.33 (0.16–0.66)	<0.001
β-Cryptoxanthin (μg)	33.1 (20.7–66.3)	46.2 (31.3–93.3)	0.33 (0.17–0.64)	0.47 (0.25–0.90)	0.22 (0.10–0.47)	<0.001
Lutein and zeaxanthin (μg)	323.1 (246–498.3)	396.7 (313.1–538.2)	0.39 (0.21–0.74)	0.24 (0.12–0.49)	0.63 (0.33–1.21)	0.02
Lycopene (μg)	197.9 (95.2–412.6)	360.1 (196.8–611.1)	0.37 (0.19–0.71)	0.18 (0.09–0.38)	0.18 (0.08–0.40)	<0.001
Vitamin A (μg)	160.8 (116.3–212.7)	191.4 (146.8–242.6)	0.76 (0.43–1.35)	0.38 (0.19–0.74)	0.70 (0.37–1.31)	0.05
Vitamin E (mg)	11.4 (8.5–15.1)	10.9 (8.8–14.0)	0.64 (0.32–1.28)	0.57 (0.27–1.19)	0.88 (0.43–1.80)	0.89
Water-soluble vitamins						
Vitamin B_1 (mg)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.62 (0.32–1.18)	0.65 (0.32–1.32)	0.32 (0.16–0.67)	0.004
Vitamin B_2 (mg)	0.4 (0.3–0.4)	0.4 (0.3–0.5)	0.72 (0.41–1.25)	0.74 (0.42–1.30)	0.52 (0.27–0.99)	0.05
Vitamin C (mg)	19.9 (14.7–27.5)	23.6 (18.1–33.6)	0.55 (0.31–0.99)	0.38 (0.20–0.72)	0.38 (0.20–0.75)	0.001
Niacin (mg)	7.4 (6.2–8.5)	8.1 (6.9–9.9)	1.14 (0.62–2.10)	0.48 (0.24–0.99)	0.52 (0.25–1.07)	0.02
Folate (μg)	114.6 (94.0–129.9)	122.5 (107.7–141.4)	0.62 (0.33–1.16)	0.70 (0.37–1.31)	0.28 (0.14–0.58)	0.002

[a] Nutrient density energy adjusted

[b] Median, interquartile range (IQR) among AML and their controls

[c] Estimates from separate conditional logistic regression models included terms for resident locality (urban, rural), education (none, primary, secondary, tertiary), body mass index (kg/m^2, continuous), cigarette smoking (no, yes), alcohol consumption (no, yes), tea consumption (no, yes), and energy intake (kcal/day, continuous), using the lowest quartile as the referent category

[d] Tests for trend across quartiles

lower risk of AML were consistent with case–control studies in Poland [6] and USA [12], and a cohort study conducted in American women aged 55–69 years [13]. Moreover, we found that a series of nutrients, predominantly from vegetables, were associated with lower risks of leukemia. Vegetables contain antioxidant vitamins and other natural phytonutrients, which might potentially possess antileukemia properties. For instance, dietary flavonoids inhibited proteasome activity and induced apoptosis in human leukemia T cells in vitro [40]. Dietary carotenoids, especially phytomixture lycopene, inhibited the growth and differentiation of human promyelocytic leukemia cells [41].

In addition, of the animal source foods, milk consumption was associated with a reduced risk of leukemia in this study. This finding was contradictory to the results of case–control studies in Poland [6] and Uruguay [10]. Regarding these contradictory findings, we have noticed the differences in measuring milk intake in different studies. For instance, one study only reported frequency of milk consumption [6], and another analysis restricted to whole milk consumption [10]. The variation of milk consumption pattern in different study populations should also be acknowledged, as evidenced by the facts that less one half of subjects reported milk drinking and the amounts of milk consumed were much less than those reported in Western populations [6, 16]. Finally, a case–control study reported a decreased risk of AML in female Americans [11]; however, the current study did not find a significant inverse association with the AML subtype. The association found in Chinese populations should be cautiously interpreted.

On the other hand, the study found no associations with leukemia for food groups of fruits, red meat, poultry, and fish. There was little evidence that fruits intake was associated with the incidence of leukemia, which has been demonstrated in previous studies [8, 12–16]. Likewise, in agreement of our findings, previous studies found no significant association with poultry intake [9, 12, 16, 17]. Inconsistent results for red meat and fish intake on leukemia risk have been reported previously. The increased risk of leukemia due to red meat intake has been observed in case–control studies [10, 12]; however, the association has

Table 6 Associations between dietary habits and adult leukemia risk

Dietary habits	Cases/controls	OR (95 % CI)[a]	OR (95 % CI)[b]
Meat eaten			
Normal/under done	385/398	1.0 (ref)	1.0 (ref)
Well done (not burnt)	54/43	1.26 (0.73–2.17)	1.09 (0.60–1.98)
Missing	3/1		
Saltiness			
Low salty	52/69	1.0 (ref)	1.0 (ref)
Somewhat	256/273	1.50 (0.92–2.42)	1.34 (0.78–2.30)
Very salty	134/100	1.61 (0.95–2.72)	1.30 (0.72–2.36)
P-trend[c]		0.11	0.47
Fat			
Never/seldom	93/145	1.0 (ref)	1.0 (ref)
Sometimes	153/187	1.76 (1.15–2.68)	1.63 (1.04–2.55)
Frequently	195/109	3.47 (2.11–5.70)	2.66 (1.54–4.59)
P-trend[c]		<0.001	<0.001
Missing	1/1		
Deep-fried food			
Never/seldom	240/312	1.0 (ref)	1.0 (ref)
Sometimes	138/113	2.18 (1.42–3.35)	1.67 (0.99–2.80)
Frequently	64/17	4.72 (2.42–9.21)	3.58 (1.70–7.52)
P-trend[c]		<0.001	<0.001
Cured food			
Never/seldom	144/206	1.0 (ref)	1.0 (ref)
Sometimes	181/154	1.50 (1.05–2.15)	1.01 (0.66–1.53)
Frequently	117/82	1.51 (1.01–2.26)	1.11 (0.70–1.78)
P-trend[c]		0.03	0.68
Smoked food			
Never/seldom	290/370	1.0 (ref)	1.0 (ref)
Sometimes	139/68	3.08 (1.96–4.84)	2.19 (1.28–3.75)
Frequently	13/4	7.21 (1.94–26.84)	6.48 (1.49–28.20)
P-trend[c]		<0.001	<0.001
Grilled food			
Never/seldom	284/300	1.0 (ref)	1.0 (ref)
Sometimes	136/120	1.82 (1.21–2.75)	1.50 (0.92–2.46)
Frequently	22/22	1.00 (0.48–2.08)	0.48 (0.21–1.10)
P-trend[c]		0.09	0.72

[a] Estimates from separate conditional logistic regression models adjusted terms for resident locality (urban, rural), education (none, primary, secondary, tertiary), body mass index (kg/m^2, continuous), cigarette smoking (no, yes), alcohol consumption (no, yes), tea consumption (no, yes), and energy intake (kilocalorie/day, continuous)

[b] Further mutually adjusted variables listed above

[c] Tests for trend across ordinal variables

not been confirmed in cohort studies [13, 16, 18]. A beneficial effect of fish or seafood consumption has been suggested in two case–control studies [7, 12], again not in prospective studies [13, 16, 17]. Generally, previous cohort studies have recommended that intakes of vegetables, fruits, milk and dairy products, red meat, poultry, fish, and other seafood were unlikely to be linked to the development of leukemias [16, 17] and leukemia subtypes of AML, CML, and CLL [13–16]. These inconsistent findings of epidemiologic investigations might be attributed to variations in study design, study populations, statistical power, subtypes of leukemia investigated, adjustment for potential confounders, and the instruments used in the measurement of diet. Other explanations might

partly be that, in general, increasing intake of total vegetables may not have an observable impact on leukemia incidence in relatively well-nourished and affluent Western populations [42], or partly be that insufficient range of variation in diet within study population, who share a common culture or geographic location, may not permit meaningful comparisons [36].

To the best of our knowledge, this is the first study investigated the association between dietary habits and leukemia risk in adults. Positive associations were observed with frequent intakes of fat, deep-fried, and smoked foods. Individuals preferring fat, particularly animal fat, had an elevated risk of leukemia. The unfavorable role of deep-fried foods is accompanied with fat consumption, because excess fat is usually used in the process of deep frying. Furthermore, deep-fried foods through high-heat cooking potentially contain mutagens and carcinogens [43]. The present study found that intake of smoked animal foods was linked with an elevated risk of adult leukemia. Smoked meat products, usually made by smoking over a wood fire after salting the meat for several days, contain *N*-nitroso precursors. Ingestion of smoked food can result in the endogenous formation of carcinogenic *N*-nitroso compounds [44].

Some limitations and issues should be considered in regard to our study. First, the case–control design may have introduced selection bias. The leukemia cases were identified from medical records in the participating hospitals. To ascertain cases completely, inpatient medical records at each participating hospital were reviewed daily, and all patients eligible as cases because they were diagnosed with leukemia during the defined incidence period were invited to participate in the study (response proportion 97.8 %). We adopted hospital outpatient controls in this study, whose responses might have been relatively health conscious. However, our research team conducted a validation study to compare differences in distributions of key exposures between outpatient controls in the Chinese hospital setting and alternative community controls. We found that there was no significant difference between the two control groups in the vast majority of demographic characteristics, lifestyle factors, and diet measured [21–23].

Second, to assess the association between diet and cancer risks in case–control studies is challenging. As the cases have been diagnosed with cancer, their report of usual dietary practices might be affected by their cancer diagnosis or related treatment. While effort was taken to reduce the possibility of information bias due to a change in diet in cases or controls during the previous year, it would not have been possible to overcome potential bias from a longer-term change caused by developing symptoms of a very gradual disease onset. However, most cases (84.0 %) in this study were diagnosed with acute leukemia, all were recruited newly diagnosed, and most cases (86.7 %) were interviewed within 3 months after diagnosis. Their memory was still 'fresh' to recall their dietary information. It appears less likely that symptoms and treatment of leukemia materially affected the interview responses among cases. Furthermore, any associations between foods and leukemia risk were inconclusive and not revealed during the study period; thus, any information bias from that source was probably minor. If misclassification of exposure occurred, such errors would attenuate the strength of any true association and could not account for the inverse associations reported here. A feature of the study was that food consumption was sought from a validated and reproducible, 103-item FFQ administered by face-to-face interviews, whereas diet information was obtained from subjects using self-administered questionnaires in other studies [6, 8, 11–14, 16] or from use of FFQs with fewer food items [6, 8, 10, 11], or did not report whether the FFQs were validated [6, 10, 11]. Despite adjustment for a variety of important potential confounders, not every conceivable potential confounder was measured, e.g., occupational chemical agents, radiation, and virus infection. It is not obvious, however, that these unmeasured potential confounders would have associations with dietary habits sufficiently strong to explain our results. Adjusting for pack-years of smoking compared with adjusting for smoking status as 'yes/no' in the models made little difference to the risk estimates (data not shown).

In summary, this study found significant inverse risks of adult leukemia in Chinese populations for intakes of vegetables, milk, and various dietary nutrients mainly from vegetables. Excess risks were associated with preferring fat, deep-fried, and smoked foods. Further studies to examine the role of diet on the etiology of leukemia are needed.

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Conflict of interest The authors declare that they have no conflict of interest.

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