Cancer Causes Control (2009) 20:57–65
DOI 10.1007/s10552-008-9217-7

ORIGINAL PAPER

A population-based, case–control study of green tea consumption and leukemia risk in southwestern Taiwan

Yau-Chang Kuo · Chu-Ling Yu · Chen-Yu Liu · Su-Fen Wang · Pi-Chen Pan · Ming-Tsang Wu · Chi-Kung Ho · Yu-Shing Lo · Yi Li · David C. Christiani · the Kaohsiung Leukemia Research Group

Received: 21 March 2008 / Accepted: 5 August 2008 / Published online: 28 August 2008

Abstract
Objective This study investigated the association between green tea consumption and leukemia.
Methods A total of 252 cases (90.3% response) and 637 controls (53.4% response) were enrolled. Controls were matched for cases on age and gender. Information was collected on participants' living habits, including tea consumption. Green tea was used as a standard to estimate the total amount of individual catechin consumption. We stratified individual consumption of catechins into four levels. Conditional logistic regression models were fit to subjects aged 0–15 and 16–29 years to evaluate separate associations between leukemia and catechin consumption.
Results A significant inverse association between green tea consumption and leukemia risk was found in individuals aged 16–29 years, whereas no significant association was found in the younger age groups. For the older group with higher amounts of tea consumption (>550 units of catechins), the adjusted odds ratio (OR) compared with the group without tea consumption was 0.47 [95% confidence interval (CI) = 0.23–0.97]. After we adjusted for smoking status and medical irradiation exposure, the overall OR for all participants was 0.49 (95% CI = 0.27–0.91), indicating an inverse relation between large amounts of catechins and leukemia.
Conclusion Drinking sufficient amounts of tea, especially green tea, which contains more catechins than oolong tea and black tea, may reduce the risk of leukemia.

Y.-C. Kuo · C.-L. Yu · C.-Y. Liu · D. C. Christiani
Environmental and Occupational Medicine and Epidemiology Program, Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA

Y.-C. Kuo
Department of Occupational and Environmental Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

Y.-C. Kuo
Department of Emergency Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

Y.-C. Kuo (✉)
7F, No.13, LN. 8, RongZong Road, Kaohsiung City 813, Taiwan
e-mail: kuo550221@yahoo.com.tw

S.-F. Wang
Department of Geography, National Changhua University of Education, Changhua City, Taiwan

P.-C. Pan
Yuh-Ing Junior College of Health Care & Management, Kaohsiung, Taiwan

M.-T. Wu · C.-K. Ho
School of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan

Y.-S. Lo
Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

Y. Li
Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA

D. C. Christiani
Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

D. C. Christiani
Pulmonary and Critical Care Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

the Kaohsiung Leukemia Research Group
Kaohsiung, Taiwan

Keywords Asia · Catechin · Childhood Leukemia · Epidemiology · Green Tea

Introduction

Inhibition of tumor invasion and angiogenesis are important areas of research in tumor biology. Many clinical researchers have tried to find natural materials to be used as non-toxic chemopreventive agents for decades. Tea is one of the most popularly consumed beverages. Epigallo-catechin-gallate (EGCG), isolated from Japanese green tea (leaves of Camellia sinensis), was found to reduce spontaneous mutations in a mutator strain of Bacillus subtilis [1]. Most experimental studies demonstrating the antimutagenic and anticarcinogenic effects of tea have been conducted with a water extract of green tea or a polyphenolic fraction isolated from green tea [2–4]. Additional research noted that there was a modifying effect of green tea on the clinical characteristics of breast cancer [5]. There have been several recent epidemiologic studies investigating the anticancer effects of EGCG or green tea [6–13]. The protective effects of green tea on gastric cancer, prostate cancer, esophageal squamous cell carcinoma, biliary tract cancers, and epithelial ovarian cancer were found.

According to the statistic report of the National Cancer Institute in USA, acute lymphocytic leukemia (ALL) is the most common childhood cancer (25%). In children, about 98% of leukemias are acute. Multiple risk factors are thought to play a role in hematopoietic malignancies; environmental factors (ionizing radiation, pesticides, benzene), viral infections, diet (vitamin A and D), smoking, and medical radiation have been proposed [14–16]. Although there have been both in vivo and in vitro studies on the antimutagenic effect of green tea, there remains a lack of epidemiologic evidence on the relation between tea consumption and leukemia. We conducted a study of green tea and leukemia risk as part of a multiyear collaborative epidemiologic study to investigate leukemia prevalence among residents in an urban area of southwestern Taiwan.

Materials and methods

The case–control study of leukemia in southwestern Taiwan has been described elsewhere [17]. Recruitment is described below. The questionnaire covered dietary habits of participants, including tea consumption. This database also included complete information on smoking history, family history, history of exposure to medical radiation, history of medication, and environmental exposures. We assessed this information for possible associations between the consumption of green tea and catechins on leukemia.

Study area

Kaohsiung City and its suburbs including four complexes of Tsoying, Tasheh, Jenwu, and Linyuan are in southwestern Taiwan. The area is densely populated and has a mix of industry and agriculture. The study was designed to investigate the possible association between leukemia risk and petrochemical exposures in this region. In the study area, we reported an association between the proximity of lifetime residence to petrochemical plants and leukemia risk [17].

Since pesticide exposure has been suggested to be related to leukemia [18], 12 among the 38 administrative areas in Kaohsiung City were eliminated due to their major occupational activity of agriculture.

Recruitment of subjects

The study protocol was approved by the Institutional Review Boards (IRB) of Harvard School of Public Health and Kaohsiung Medical University. All cases of leukemia were diagnosed during the study period. A portion of cases were enrolled by screening Department of Health cancer registry files in Kaohsiung metropolitan area (International Classification of Diseases, Revision 9, Codes 204-208). Participants recruited between November 1997 and December 2006 were included in the study. All cases were diagnosed during this period. The diagnosis was confirmed by a pathologist at Kaohsiung Medical College Hospital. Some cases were booked from a Rapid Case Ascertainment System set up in the three referral hospitals which included Kaohsiung Medical College Hospital, Kaohsiung Veterans General Hospital, and Kaohsiung Chang-Gung Memorial Hospital. The remaining cases were identified from the records of the mandatory national health insurance system operated by the Department of Health in Kaohsiung, Taiwan. Only cases less than 30 years of age and were living in the Kaohsiung metropolitan area at the time of diagnosis were eligible. Three controls were matched for each case on age and sex. All the controls were randomly selected from the Kaohsiung metropolitan area according to personal identification numbers offered by Household Registration Offices. A total of 279 histologically confirmed incident leukemia cases and 1,194 matched controls were selected initially before any exclusion. Exclusion criteria for selected cases and controls were one of the following: subjects whom could not be contacted (7 cases, 197 controls), subjects who refused to participate (8 cases, 250 controls), missing address information (4 cases, 84 controls), parents were divorced or widowed (3 cases, 15 controls), and missing information of drinking tea (5 cases, 11 controls). In this study, proxy information was offered from the subjects' parents. Once the parents were divorced or widowed, they typically work out of home and would have little time to take care of subjects personally. It was then expected to be difficult for them to offer adequate proxy information of the subjects. Ultimately, 252 cases and 637 controls were enrolled in this study. The participation rates of cases and controls were 90.3 and 53.4%, respectively.

Data collection

A trained interviewer performed an in-person interview on each study subject with a formal questionnaire. Either the mother of the subject or the subject himself/herself answered the questionnaire. The mother of the subject answered a questionnaire if the subject was less than 20 years old, or if the adult subject (more than 20 years old) left home for work or for study. In the latter case, if the mother was not sure about the answer, the interviewer was asked to contact the subject directly to confirm the information. The information was self-reported in 35% of subjects and 65% of subjects' information was obtained from a proxy (the mother of the subject). For food frequency, we used a dietary recall questionnaire. Only those who reported drinking tea more than once a week for at least six months were considered to have the habit of drinking tea. Subjects interviewed had to answer questions including "How many years had the children drunk tea?," "What kinds of tea did they drink?," and "How many cups of tea did they consume per day or per week?." Each cup was defined to be 50 ml of tea. The three major types of tea, oolong, green, and black, were considered. The period of exposure was assessed from birth to the day when leukemia was first diagnosed (for cases) or when the interview was performed (for controls). To prevent misclassification of tea intake for individuals who changed their tea consumption after diagnosis, we collected only cumulative amounts before disease onset. All cases answered the questionnaire soon after the diagnosis of leukemia was confirmed. The range of time from diagnosis to interview for cases was one to five months, and the median of time was three months.

Statistical analysis

Raw data of tea consumption for each subject included total cups of the various types of tea, with a cup defined to be 50 ml in our questionnaire. We calculated an Estimated Total Catechins (ETC) index [19–21], representing the cumulative intake of catechins. The amount of catechins in every cup of green tea was defined to be "one unit." The concentration of catechins in various tea extracts was considered in the following order: green tea (26.7%), oolong tea (23.2%), and black tea (4.3%), which was estimated according to Yen and Chen [22] Since catechins are reportedly distributed among three types of tea (green, oolong, and black tea) in a defined ratio of 1:0.87:0.16, an ETC index could be calculated. After we collected the approximate amount of total catechins consumed by every subject, we used Statistical Product and Service Solutions (SPSS) to create an ordinal scale of 125 levels in order to amplify the possible health effects of catechins.

As the original ETC scale was too fine, in order to get a more sensible estimate of its effect, we categorized ETC into four levels. Individuals were first classified as tea drinkers or non-drinkers, and drinkers were divided into tertiles based upon the distribution of intake among the controls. The resulting new variable was named Estimated Total Catechins Code (ETCC), which reflected the cumulative amounts of tea consumption before interview or disease onset. Specifically, level one of ETCC reflected no tea consumption. Level two, corresponding to ETCs ranging from 1 to 150 units, represented low consumption. ETCs between 151 and 550 units were grouped into level three, considered to be moderate consumption. ETCs more than 550 units (namely a total of 550 cups of green tea) were grouped into level four, meaning high consumption.

The selection of the final regression model was based on Akaike's Information Criterion (AIC), with the outcome being Leukemia case status (case–control). To accommodate the unique design feature of this study, we used the conditional logistic regression to study the association of the ETCC with leukemia, which would reduce the confounding effects of age and gender that the cases and the controls were matched on. Data was analyzed using SPSS, version 11.0, software. Analyses of ETCC association with leukemia risk were performed by conditional logistic regression and were adjusted for environmental factors (ionizing radiation, pesticides, benzene), viral infections, diet (vitamin A and D), exposure to medical radiation (yes/no), subject smoking (ever smoked or not), and parental smoking (either parent smoked or not). Conditional logistic regression was operated in the SPSS system according to the principle suggested by John Hendrickx (University of Texas).

Results

A total of 889 individuals, 252 cases and 637 controls, participated in the study. Leukemia was more common in males than in females, with a ratio of 1.45:1.0. Table 1 summarizes tea consumption among all the participants. Individual ETC consumption ranged from 0 to 32,659 units. The mean value was 945 units and the median value was 253 units. The quartile values were 84 (25%), 253 (50%), and 804 (75%), respectively. There were no significant

Table 1 Characteristics of leukemia cases and controls

Characteristic	Cases	Controls
Age 0–15 years (159 cases and 414 controls)		
Age (years):Median	5.00	4.90
Gender (%):Female/male	40/60	41/59
History of smoking in individuals/family members (%)	58	60
History of medical radiation (%)	22	25
History of tea consumption[a]: *n* (%)		
Green tea only	6 (3.8)	27 (6.5)
Oolong tea only	7 (4.4)	11 (2.7)
Black tea only	20 (12.6)	54 (13.1)
Green tea and Oolong tea	1 (0.6)	3 (0.7)
Green tea and Black tea	8 (5.0)	21 (5.1)
Oolong tea and Black tea	0 (0)	6 (1.4)
Green tea, Oolong tea and Black tea	2 (1.3)	1 (0.2)
Without tea consumption	115 (72.3)	291 (70.3)
Age 16–29 years (93 cases and 223 controls)		
Age (years):Median	21.1	20.7
Gender (%):Female/male	42/58	39/61
History of smoking in individuals/family members (%)	54.8	54.7
History of medical radiation (%)	20	22
History of tea consumption[a]: *n* (%)		
Green tea only	9 (9.7)	24 (10.8)
Oolong tea only	3 (3.2)	11 (4.8)
Black tea only	10 (10.7)	26 (11.7)
Green tea and Oolong tea	1 (1.1)	2 (0.9)
Green tea and Black tea	6 (6.5)	26 (11.7)
Oolong tea and Black tea	0 (0)	2 (0.9)
Green tea, Oolong tea and Black tea	1 (1.1)	9 (4.0)
Without tea consumption	63 (67.7)	123 (55.2)

[a] The population drinking different types of tea may overlap. Percentages are rounded

History of smoking in individuals/family members: Either subjects themselves or subjects' family members who had history of smoking were thought to have history of smoking exposure

associations between either smoking status or medical irradiation and leukemia in our study. The distribution of participants' age strata in cases and controls was not even, and there were two peaks for the age ranges, which were 2–5 and 18–20 years of age, respectively. The participants were stratified by age at the cut point of age 15 years, the mid-point of range of ages. Another reason for us to choose this cut point was that it was located between the above two peaks of the age strata. It prevented the appearance of small sizes of samples in each group (above/below this cut point), which might cause difficulty in analyzing each group. The majority of leukemia cases were acute lymphocytic leukemia (71.8%) in our study. According to the reports from US National Cancer Institute, acute lymphocytic leukemia (ALL) has a peak incidence in ages two to five years, corresponding to one of the peaks observed in our study. Nearly 20% of cases were acute myeloid leukemia. The remaining cases were chronic myeloid leukemia and rare subtypes. Figure 1 shows the tea intake of leukemia cases and controls by age strata. Tea drinking was reported by 167 (29.1%) out of the 573 subjects aged 0–15 years and by 130 (41.1%) of the subjects aged 16–29 years. More catechins were consumed by controls than by leukemia cases for most age groups (Fig. 2). Culturally, young children in Taiwan would be expected to drink tea whereas children in Western countries generally do not drink tea.

We found that the proportion of tea drinking among older and younger participants was different. The proportion of drinking tea for the older (aged 16–29 years) groups was far higher than that for the younger (aged 0–15 years) groups (41.1% versus 29.1%; $p < 0.05$). For the older groups, there was a statistically significant inverse relation between disease status and high consumption of catechins (>550 units of catechins/>a total of 550 cups of green tea). Compared with the group without tea consumption, the adjusted odds ratio in the group with high consumption of tea was 0.47 [$p = 0.04$; 95% confidence interval (CI) = 0.23–0.97]. For the younger groups, no significant association was found. After we adjusted for the smoking status and reported medical irradiation exposure in the conditional logistic regression model, we found a significantly decreased risk of leukemia for subjects drinking

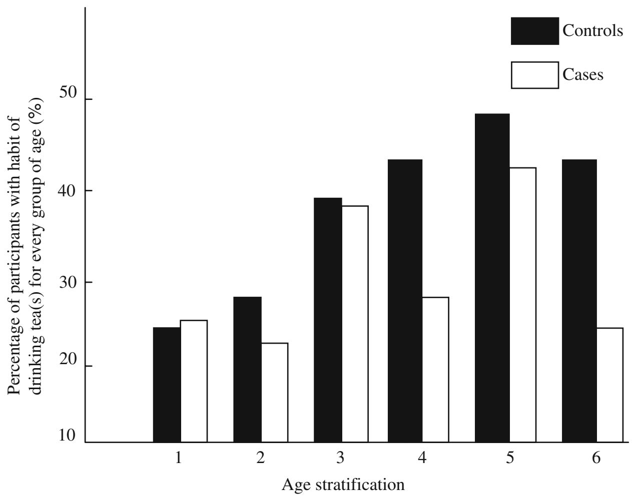

Fig. 1 Different percentages of leukemia cases and controls with habit of drinking tea(s) for every group of age. Age stratifications: 1 = age between 0 and 5 years; 2 = age between 6 and 10 years; 3 = age between 11 and 15 years; 4 = age between 16 and 20 years; 5 = age between 21 and 25 years; 6 = age between 26 and 29 years

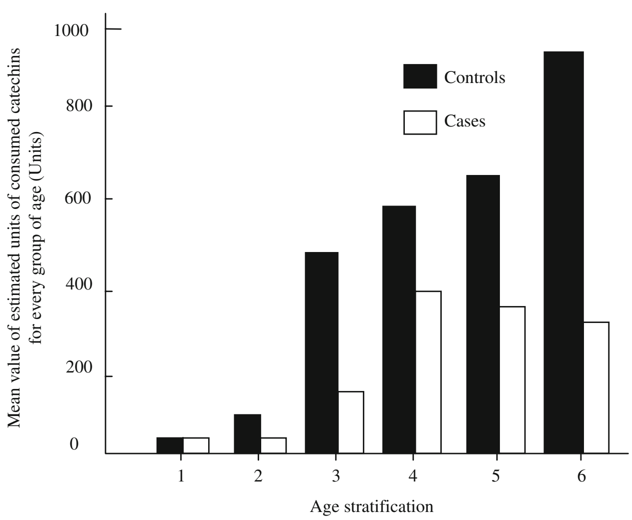

Fig. 2 Mean amount of catechins (expressed in units) consumption in leukemia cases and controls for every group of age. Age stratifications: 1 = age between 0 and 5 years; 2 = age between 6 and 10 years; 3 = age between 11 and 15 years; 4 = age between 16 and 20 years; 5 = age between 21 and 25 years; 6 = age between 26 and 29 years

large amounts of tea. Compared with all the subjects without tea consumption, the overall odds ratio for all age groups with high consumption of tea was 0.49 ($p = 0.02$; 95% CI = 0.27–0.91) (Table 2). We also noted that drinking tea alone (yes/no), without regard to amount, did not affect leukemia incidence.

We used the method of re-scaling of ETC to make the estimate exposure. The primary ETC calculated had a skewed distribution which may result in an interaction between higher and lower ETCC. We did stratified regressions for higher ETCC and lower ETCC, and both two odds ratios compared with the group without ETCC consumption were close to 0.83, ruling out such an interaction.

Discussion

We collected information on these variables and adjusted for them in our analysis. The antimutagenic effect of green tea has been postulated for a long time, but research results remain controversial. Green tea polyphenol, (−)-epigallocatechin-3-gallate, has been shown to inhibit cellular proliferation and induce apoptosis of various cancer cells. Nakazato et al. found that (−)-Epigallocatechin-3-gallate had potential as a novel therapeutic agent for patients with B-cell malignancies including multiple myeloma [23]. TBéliveau et al. found that the inhibitory effect of EGCG might have profound repercussions on tumors that depended on the VEGF-receptor tyrosine kinase for progression. The study of nutraceuticals such as green tea in the prevention and treatment of cancer (both solid and hematologic) has been underexplored [24]. An in vivo study found that green tea extract had both antitumor and chemoprevention effects on low grade lymphoma, which made further clinical trial more feasible [25]. EGC was found to inhibit S phase progression and finally result in leukemia cell death [26].

In a hospital-based case–control study conducted by Li et al., adult acute myeloid leukemia risk was found to be negatively associated with tea intake [27]. Several studies have reported that tea catechins had effects on metabolism and metabolic enzymes affecting growth of cancer cells [19]. Bushman compiled a total of 31 studies and four reviews; the majority of them disclosed an inverse association between tea consumption and cancer of the colon, urinary bladder, stomach, esophagus, lung, and pancreas [28]. Another study held by Geetha et al. noted that a concentrated aqueous extract did have a protective effect against cancer because of its antioxidant nature [20]. The antimutagenic activity of green tea had better activity than ascorbic acid because of the good hydrophilic and lipophilic activity of catechins [28]. Matrix metalloproteinase (MMP)-9 expression affects myeloid cell differentiation and angiogenesis processes related to cancer progression. The tumor-promoting agent PMA could be inhibited by green tea catechins epigallocatechin-gallate, catechin-gallate, and epicatechin-gallate [29]. Additionally, green tea was shown to block certain steps of carcinogenesis [30]. However, epigallocatechin gallate alone becomes toxic to non-cancer cells at about 100 μmol/l [31]. Ng et al. conducted a study to determine a safe dose of green tea extract and concluded that a dose of 1.0 g/m^2 t.i.d. (120 ml of green tea three times daily) could be taken safely for at least six months [32]. In our study, there was only one

Table 2 The association between green tea (catechins) consumption and leukemia in Kaohsiung, southwestern Taiwan

	Individuals: *n* (%)		ETC (units): Median (min, max)		OR (95% CI)[a]	
	Case	Control	Case	Control	Crude	Adjusted[b]
All subjects (252 cases and 637 controls)						
Subjects without tea consumption[c]	178 (70.7)	414 (65.0)	0	0	1	1
Group with low amount of tea consumption	36 (14.3)	77 (12.1)	55.7 (7.68,144)	53.8 (7.7,144.0)	1.19 (0.76,1.89)	1.17 (0.74,1.86)
Group with moderate amount of tea consumption	25 (9.9)	74 (11.6)	273.8 (167.0,537.6)	286.8 (161.3,538.6)	0.62 (0.35,1.09)	0.64 (0.36,1.12)
Group with high amount of tea consumption	13 (5.1)	72 (11.3)	1510.3 (612.5,6048)	1585.9 (556.8,32659.2)	0.49 (0.27,0.91)[a]	0.49 (0.27,0.91)[a]
Age 0–15 years (159 cases and 414 controls)						
Subjects without tea consumption[c]	115 (72.4)	291 (70.3)	0	0	1	1
Group with low amount of tea consumption	27 (17.0)	62 (15.0)	53.8 (7.7,138.2)	50.9 (7.7,144.0)	1.15 (0.68,1.95)	1.14 (0.67,1.93)
Group with moderate amount of tea consumption	12 (7.5)	43 (10.4)	268.8 (167.0,501.1)	268.8 (161.3,538.6)	0.65 (0.32,1.35)	0.69 (0.33,1.44)
Group with high amount of tea consumption	5 (3.1)	18 (4.3)	1559.0 (779.5,3118.1)	1507.2 (556.8,32659.2)	0.54 (0.17,1.73)	0.56 (0.17,1.79)
Age 16–29 years (93 cases and 223 controls)						
Subjects without tea consumption[c]	63 (67.7)	123 (55.2)	0	0	1	1
Group with low amount of tea consumption	9 (9.7)	15 (6.7)	61.4 (15.4,144)	76.8 (30.7,144)	1.34 (0.54,3.36)	1.34 (0.53,3.42)
Group with moderate amount of tea consumption	13 (14.0)	31 (13.9)	353.3 (192,537.6)	384 (161.3,537.6)	0.54 (0.22,1.33)	0.54 (0.22,1.35)
Group with high amount of tea consumption[a]	8 (8.6)	54 (24.2)	1461.6 (612.5,6048)	1585.9 (576,17539.2)	0.48 (0.24,0.98)[a]	0.47 (0.23,0.97)[a]

[a] Groups with statistical significance

[b] Adjusted factors included: Environmental factors (ionizing radiation, pesticides, benzene), viral infections, diet (vitamin A and D), history of exposure to smoking, and medical radiation

[c] Reference category: ORs and CIs used the group without tea consumption as the reference group

The stratification of ETC and corresponding ETCC:ETC (0 unit) = ETCC (no tea consumption); ETC (1–150 units) = ETCC (lower consumption level); ETC (151–550 units) = ETCC (moderate consumption level); ETC (551 and upper units) = ETCC (higher consumption level) control who drank a daily amount (1,500 ml) exceeding this suggested dose.

We acknowledge several limitations to a case–control study such as ours. In order to minimize selection bias, eligible cases were newly diagnosed during the study period. Matched controls were randomly sampled from population registry. In our study, the participation rates of cases and controls were 90.3 and 53.4%, respectively. In order to realize if the low response rate affected the study results, we had to find the distribution of tea exposure on cases and controls not enrolled in the study. Since a lower proportion of drinking tea on non-enrolled cases was found (non-enrolled cases vs. non-enrolled controls; 66.7 vs. 75%), overestimation of an inverse association caused by a low response rate would be unlikely. There could be recall bias from questionnaire-based epidemiologic surveys, particularly in a case–control design because cases might recall exposure more thoroughly than controls [33]. In our study, however, more controls reported drinking tea than cases (35.0 vs. 29.3%), and therefore such a recall bias was not likely to occur. All questionnaires were completed in a conscientious manner by a well-trained interviewer. For younger children, parents answered dietary habits. For adolescents, the information was obtained from them unless they were not at home and could not be contacted by other methods. In that situation, parents answered the questions. Double checking of information was done on recontact when either parents or children were not sure of their (children's) dietary habits. We did not compare proxy information with the actual cases' information because the proxy information was only offered when the subjects were expected too young to answer the question correctly or when the subjects work far from homes with difficulty to answer reviewer's questions in person. Neither cases nor controls were aware of study interest in green tea consumption. So, it is unlikely that participants provided biased information on green tea. We recognized that other diets, such as chocolate, apples, and berries, also contained substantial catechins. Although we collected the information of the frequency of intake of fruits in the questionnaire, it was not detailed enough to know what kinds of fruits they ate. The intake of chocolate, apples, and berries was not mentioned in our questionnaire. It may cause limitations and underestimate the amounts of catechins consumption.

Infants were certainly thought to be less likely to consume tea of their own accord. In Taiwan, culturally, many adults drink tea in their daily life. We knew some parents rarely pour traditional Chinese tea for both infants and themselves. That was why we decided to include infants in the cumulative exposure.

We also noted few cases and controls drank moderate amount of tea, particularly high amount of tea. Although the sample size was moderate, the statistical power was enough to detect a difference in tea consumption.

The ages of disease onset are generally different in the four subtypes of leukemia: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). As expected, we found that older age groups consumed more catechins. Hence, age was considered as an important confounding factor and was matched initially. Although green tea was the major focus of this study design, we also considered consumption of other teas. Drinking different kinds of tea could cause an interaction with green tea. Hence, we took the total catechins into account, not only the catechins in green tea, recognizing that content of catechins in green tea was richer than those contained in other teas. The possibility of dietary modifying effects caused by the postdiagnostic symptoms should also be considered. To prevent misclassification of tea intake for individuals who changed their tea consumption after diagnosis, we collected only cumulative amounts before disease onset. We recognize that adjustment for total energy or body weight would be helpful to address the change of habits of drinking tea caused by the disease status. We failed to do that because the information was not collected in this study.

In Table 1, we used the age 15 years as a cut point to describe our findings. Since ALL has a peak incidence at ages two to five years according to the US NCI data,, we tried to use five years as a new cut point and did further analysis for groups between six and 15 years. We studied the difference on leukemia risk in groups reporting different habits of tea consumption ($p > 0.05$). Compared with subjects without consumption of tea, those subjects with low, moderate, and high amounts of tea consumption had an odds ratio of 0.85, 1.58, and 1.46, respectively. However, none of them were statistically significant, possibly due to the small number of tea consumers within this age group.

The study was designed to test whether the total catechins human consumed have a health effect on childhood leukemia. All three types of Chinese tea commonly consumed by people in Taiwan were investigated. Most people drinking tea consumed more than one type of tea. Subjects who drank only one type of tea were rare in our database, so analyses by types of tea were not included initially. Fortunately, we knew the distribution of catechins among those three types of tea. When we found the catechins' effect on children leukemia, we extrapolated the association between the amounts of specific type of tea consumption and leukemia risk.

According to an investigation at the Analysis and Inspection Center of Da Yeh University in Taiwan, it was found that Taiwan Green Tea had higher quality in terms of total catechins, EGCG, and EGCG of total catechins than

Japan Green Tea. From the result of their analysis, Taiwan Green Tea showed a total of 4.32 gm of EGCG per hundred grams of green tea leaf, a total of 9.33 gm of total catechins per hundred grams of green tea leaf, and a total of 46.2% of EGCG contents of total catechins. There were other minor components of catechins such as (−) Epigallocatechin (3.36 gm/100 gm of green tea leaf), (+) Catechin (0.07 gm/100 gm of green tea leaf), (−) Epicatechin (0.33 gm/100 gm of green tea leaf), and (−) Epicatechin gallate (0.27 gm/100 gm of green tea leaf). Green tea is a better source of catechins when compared with oolong or black tea. Most previous research focused on the possible mechanisms of green tea's anticarcinogenic effects, but epidemiologic evidence for an association between green tea (catechins) and leukemia risk reduction is lacking [34]. Our study offers some evidence from a population-based case–control study. Since our participants consisted of young people aged 0–29 years, it is uncertain whether the same protection occurs in older people. Furthermore, it is not clear whether consumption of greater amounts of green tea, in the range noted by Ng et al. [32] is associated with even greater reductions in leukemia risks. Further research is warranted to evaluate if there are age differences in the benefits associated with green tea consumption and to assess the amounts of green tea consumption needed for inducing a protective effect.

As stated in the first sentence in the Abstract and the Introduction, the chemopreventive effects of green tea on several malignancies have been reported in the literature. Assessing dose-response relationship is a common practice in causal inference according to the Hill's criteria of causation, and therefore subset analyses are common. The positive effect was also observed in the "moderate" group, although not statistically significant, and the dose-response pattern was similar to that observed in the younger group. We would agree that our study results should be replicated in independent studies.

Acknowledgments The authors gratefully acknowledge Chien-Chin Chou for questionnaire data verification, Janna Frelich for data management, and Thomas J., Yuhao Chen, and Lia Shimada for technical assistance. The study was funded by National Institutes of Health (ES09723, ES00002). The members of the Kaohsiung Leukemia Research Group were as follows: Kaohsiung Medical University Chung-Ho Memorial Hospital—Tai-Tsung Chang, Sheng-Fung Lin, Shyh-Shin Chiou, Ren-Chin Jang, Hui-Hua Hsiao, Ta-Chih Liu, and Pei-Chin Lin; Kaohsiung Chang Gung Memorial Hospital—Chih-Cheng Hsiao, Jiunn-Ming Sheen, Ching-Yuan Kuo, Ming-Chung Wang, Cheng-Hua Huang, and Chung-Bin Huang; and Kaohsiung Veterans General Hospital—Shyh-Jer Lin, Yu-Ming Sun, Kai-Sheng Hsieh, and Yu-Hsiang Chang; and Shaw Chwan Memorial Hospital—Yuk-Cheung Wong; and E-Da Hospital—Hung-Bo Wu.

Funding National Institutes of Health (ES09723, ES00002).

Conflict of interest None declared.

References

1. Kada T, Kaneko K, Matsuzaki S, Matsuzaki T, Hara Y (1985) Detection and chemical identification of natural bio-antimutagens. A case of the green tea factor. Mutat Res 150(1–2):127–132. doi:10.1016/0027-5107(85)90109-5
2. Mukhtar H, Ahmad N (1999) Green tea in chemoprevention of cancer. Toxicol Sci 52(2 Suppl):111–117. doi:10.1093/toxsci/52.2.111
3. Spinella F, Rosano L, Di Castro V et al (2006) Green tea polyphenol epigallocatechin-3-gallate inhibits the endothelin axis and downstream signaling pathways in ovarian carcinoma. Mol Cancer Ther 5(6):1483–1492. doi:10.1158/1535-7163.MCT-06-0053
4. Zhang Q, Tang X, Lu Q, Zhang Z, Rao J, Le AD (2006) Green tea extract and (−)-epigallocatechin-3-gallate inhibit hypoxia- and serum-induced HIF-1alpha protein accumulation and VEGF expression in human cervical carcinoma and hepatoma cells. Mol Cancer Ther 5(5):1227–1238. doi:10.1158/1535-7163.MCT-05-0490
5. Mukhtar H (1994) Cancer chemoprevention by green tea components. Adv Exp Med Biol 354:123–134
6. Tsugane S, Sasazuki S (2007) Diet and the risk of gastric cancer: review of epidemiological evidence. Gastric Cancer 10(2):75–83. doi:10.1007/s10120-007-0420-0
7. Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB (2007) Diet and breast cancer: a review of the prospective observational studies. Cancer 109(12):2712–2749. doi:10.1002/cncr.22654
8. Jian L, Lee AH, Binns CW (2007) Tea and lycopene protect against prostate cancer. Asia Pac J Clin Nutr 16(1):453–457
9. Wang JM, Xu B, Rao JY, Shen HB, Xue HC, Jiang QW (2007) Diet habits, alcohol drinking, tobacco smoking, green tea drinking, and the risk of esophageal squamous cell carcinoma in the Chinese population. Eur J Gastroenterol Hepatol 19(2):171–176. doi:10.1097/MEG.0b013e32800ff77a
10. Kuriyama S, Shimazu T, Ohmori K et al (2006) Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 296(10):1255–1265. doi:10.1001/jama.296.10.1255
11. Sun CL, Yuan JM, Koh WP, Yu MC (2006) Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies. Carcinogenesis 27(7):1301–1309. doi:10.1093/carcin/bgl024
12. Zhang XH, Andreotti G, Gao YT et al (2006) Tea drinking and the risk of biliary tract cancers and biliary stones: a population-based case–control study in Shanghai, China. Int J Cancer 118(12):3089–3094. doi:10.1002/ijc.21748
13. Larsson SC, Wolk A (2005) Tea consumption and ovarian cancer risk in a population-based cohort. Arch Intern Med 165(22):2683–2686. doi:10.1001/archinte.165.22.2683
14. Linet MS (1996) Leukemias. In: Harras A (ed) Cancer rates and risks, 4th edn. National Cancer Institute, Bethesda, MD
15. Linet MS, Cartwright RA (1996) The leukemias. Oxford University Press, New York, NY
16. Miller R et al (1996) Childhood. In: Harras A (ed) Cancer rates and risks, 4th edn. National Cancer Institute, Bethesda, MD
17. Yu CL, Wang SF, Pan PC et al (2006) Residential exposure to petrochemicals and the risk of leukemia: using geographic information system tools to estimate individual-level residential exposure. Am J Epidemiol 164(3):200–207. doi:10.1093/aje/kwj182
18. Zahm SH, Ward M (1998) Pesticides and childhood cancer. Environ Health Perspect 106(3):893–908. doi:10.2307/3434207
19. Dreosti IE (1996) Bioactive ingredients: antioxidants and polyphenols in tea. Nutr Rev 54:S51–S58

20. Geetha T, Garg A, Chopra K, Pal Kaur I (2004) Delineation of antimutagenic activity of catechin, epicatechin and green tea extract. Mutat Res 556:65–74. doi:10.1016/j.mrfmmm.2004.07.003
21. Weisburger JH, Hara Y, Dolan L, Luo FO, Pittman B, Zang E (1996) Tea polyphenols as inhibitors of mutagenicity of major classes of carcinogens. Mutat Res 371:57–63. doi:10.1016/S0165-1218(96)90094-4
22. Yen GC, Chen HY (1996) Relationship between antimutagenic activity and major components of various teas. Mutagenesis 11:37–41. doi:10.1093/mutage/11.1.37
23. Nakazato T, Ito K, Ikeda Y, Kizaki M (2005) Green tea component, catechin, induces apoptosis of human malignant B cells via production of reactive oxygen species. Clin Cancer Res 11:6040–6049. doi:10.1158/1078-0432.CCR-04-2273
24. Béliveau R, Gingras D (2004) Green tea: prevention and treatment of cancer by nutraceuticals. Lancet 364(9439):1021–1022. doi:10.1016/S0140-6736(04)17076-1
25. Hamblin T (2006) Natural products and the treatment of leukemia. Leuk Res 30:649–650. doi:10.1016/j.leukres.2005.10.023
26. Smith DM, Dou OP (2001) Green tea polyphenol epigallocatechin inhibits DNA replication and consequently induces leukemia cell apoptosis. Int J Mol Med 7(6):645–652
27. Li YL, Moysich KB, Baer MR et al (2006) Intakes of selected food groups and beverages and adult acute myeloid leukemia. Leuk Res 30(12):1507–1515. doi:10.1016/j.leukres.2006.03.017
28. Bushman JL (1998) Green tea and cancer in humans: a review of the literature. Nutr Cancer 31:151–159
29. Annabi B, Currie JC, Moghrabi A, Beliveau R (2006) Inhibition of HuR and MMP-9 expression in macrophage-differentiated HL-60 myeloid leukemia cells by green tea polyphenol EGCg. Leuk Res 31(9):1277–1284
30. Komori A, Yatsunami J, Okabe S et al (1993) Anticarcinogenic activity of green tea polyphenols. Jpn J Clin Oncolo 23:186–190
31. Morre DJ, Bridge A, Wu L-Y, Morre DM (2000) Epigallocatechin gallate inhibits preferentiallythe NADH oxidase and growth of transformed cells in culture. Biochem Pharmacol 60:937–946. doi:10.1016/S0006-2952(00)00426-3
32. Ng KK, Miller VA, Grant SC et al. (1999) Phase I and clinical pharmacologic study of green tea extract (GTE) in patients with advanced solid tumors (ASCO). Am Soc Clinical Oncology Meeting abstract #853
33. Rothman KJ, Green IS (1998) Modern epidemiology. Lippincott-Raven, Philadelphia, PA
34. Kuroda Y, Hara Y (1999) Antimutagenic and anticarcinogenic activity of tea polyphenols. Mutat Res 436(1):69–97. doi:10.1016/S1383-5742(98)00019-2