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Original Article

Family History and Prior Allergies of Cancers and the Risk of Adult Leukemia in Shandong Province, China

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Abstract

Background: A case-control study was carried out to investigate the roles of prior allergies and family history of cancers and their interaction in the etiology of adult leukemia.

Methods: Prior allergies status and family history of cancers in first-degree relatives were compared between 131 incident leukemia cases and 206 hospital-based controls. Odds ratios (OR) were estimated using an unconditional regression model taking into account potential confounding factors.

Results: Significant association between adult leukemia and prior allergies and family history of cancer (OR=2.09, 95% CI: 1.22-3.58 for prior allergies; and OR=2.35, 95% CI: 1.09-5.03 for family history of cancer, OR=15.88, 95% CI: 1.77-142.55 for both the two factors (+), respectively) was found after adjusting for potential confounding factors.

Conclusion: Prior allergies and family history of cancers may be risk factors for adult leukemia; their interaction was likely to be synergistic rather than additive for the risk of leukemia.

Keywords: Leukemia, Prior allergies, Family history of cancers, Case-control study, China

Introduction

Leukemia is a group of malignancies that originate from hematopoietic or lymphocytic stem cell clones, characterized by abnormal differentiation or proliferation of functionally incompetent neoplastic cells.

Leukemia is a common hematologic malignancy worldwide, with approximately 300,000 new cases (2.8% of all cancer cases) and 220,000 deaths annually (1). Many of the deaths occur in developing countries, where complex treatment regimens may not be available for all eligible patients. Leukemia is heterogeneous, and the risk factors, as well as the prognosis, may differ from adults and children (2). In adults, benzene (3, 4) and ionizing radiation (5, 6) are well-documented causal agents for some types of leukemia. Other reported risk factors include pesticides (7), cigarette smoking (8), family history of cancers (9), and electromagnetic fields (10). Prior allergy status has also been examined by many studies, although, there has not been a conclusion whether it is related to elevated risk of leukemia or not; for example, in some studies (11), it was found to be related to the increased risk; however, some others discovered a protective effect (12). It is important to investigate the influence of past allergy status and family history of cancers on the occurrence of leukemia, and also their interaction.

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According to the three cancer mortality surveys conducted in China in 1973-75, 1990-92 and 2004-05, respectively, the mortality rates of leukemia in China were 2.54, 3.64, 3.84 per 100,000 person-years, and listed among the ten leading causes of cancer death (13). However, fewer etiologic studies of leukemia have previously been conducted in this region or elsewhere in China (14-16).

The study described here was a hospital-based case-control study implemented to examine the relationship between the prior allergies and family history of cancers and risk of adult leukemia in Shandong Province, China (Fig. 1), with the main aim to explore the etiology of the disease in Chinese population.

Materials and Methods

Data collection

This case-control study was conducted at Qilu Hospital, the largest hospital in Shandong Province, China, during the period from April 2009 to June 2010. Eligible cases were leukemia patients aged 18 years and above, with histologically confirmed leukemia diagnosed within the 6 months before the current study. The study was restricted to patients who resided in Shandong Province. Controls were selected from patients who were admitted to the same hospital during the same period with cases other than any type of cancers or any diagnosed diseases associated with hematological system. Controls were frequency-matched with cases according to sex and age distribution. If the first control selected was ineligible or refused to be interviewed, a second control was then chosen using the same method. The study was restricted to patients who resided in Shandong Province. Approval to conduct this study was granted by the Medical Ethics Committee of Shandong University. Informed consent was obtained before each interview.

Face-to-face interviews were conducted in-hospital by trained interviewers using a structured questionnaire. Interviews were administered directly to the cases and controls, rather than to the next of kin unless the subjects were too ill to be interviewed. In addition to detailed information collected on medically related items, information was also collected for demographic factors, tobacco smoking, drinking, family history of cancers, occupational exposures, house decoration, prior allergies and prior disease, etc. In this study, “occupational exposure” was defined as ever being exposed to benzene, toluene, other organic solvents, pesticides, X-ray, or other radioactive materials; “house decoration” was defined as whether there was any decoration in their home or office before the diagnosis of the current disease. And “prior disease” was defined as whether the participants had any disease diagnosed by a doctor.

For the history of allergies, the subjects were asked whether they had any allergy condition diagnosed by doctors prior to the leukemia diagnosis (for cases) or prior to the interview (for controls). Five allergic conditions, asthma, hives, hay fever, food or drug allergies, and eczema, were defined as allergies.

Cases and controls (or their proxies) were asked to report history leukemia and any other type of tumors in their first-degree relatives, including their parents, children and siblings. Only the cancers diagnosed by a doctor were considered.

While interviewers could not be blinded to the case/control status, they were unaware of the main study hypothesis and were trained to administer strictly the structured questionnaires in an equal manner to cases and controls.

Statistical analysis

All data were double keyed into a database using Excel software. χ^2 tests or t tests were used to test differences of socio-demographic factors between the cases and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for the two factors using unconditional logistic regression analysis with age, sex, income, education, smoking, drinking, prior

disease, occupational exposure and house decoration included in the model as adjustment variables.

To clarify the interaction between prior allergies and family history of cancers for the risk of leukemia, these two factors were classified into four categories by whether specific types of experience existed or not: prior allergies (-) and family cancer history (-); prior allergies (+) and family cancer history (-); and prior allergies (-) and family cancer history (+); and prior allergies (+) and family cancer history (+). RRs and 95% CIs were calculated using both prior allergies (-) and family cancer history (-) as the reference.

All data management and statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, a total of 131 leukemia cases and 206 controls were enrolled in this study, including 88 with acute myeloid leukemia (AML), 21 with acute lymphoblastic leukemia (ALL), 12 with chronic myelogenous leukemia (CML), and two with unclassified acute leukemia. All identified eligible cases participated in the study with a participation rate of 100%. Originally, there were 210 eligible controls, four refused due to the time conflict, which gave us a 98.10% response rate, and final 206 controls.

The distribution of socio-demographic factors and other factors among the cases and controls was shown in Table 1. More cases than controls had occupational exposure before they were being interviewed (13.7% versus 3.4%; *P*=0.001). There were no significant differences between cases and controls in mean age, sex, education level, income level, smoking status, drinking status, prior disease condition and house decoration (Table 1). Generally, cases were slightly younger than controls (42.9 VS 46.7), but not statistical significant (*P*=0.06). Slightly more cases were males and had lower education level and lower income level than controls.

The crude and adjusted ORs and 95% CIs for prior allergies and family history of cancers were illustrated in Table 2. Leukemia cases reported significantly more prior allergies than controls (RR=1.78, *P*=0.03), the significant associations of adult leukemia with prior allergies persisted after various potential confounding factors were adjusted (OR=2.09, *P*=0.01).

Family history of cancers at any site, as self reported by the subjects (or proxies), appeared to double the risk of adult leukemia in the current study. A significantly greater proportion of cases had family history of cancers than controls (OR=2.47, *P*=0.01); Likewise, controlling for the possible confounding factors did not materially affect the estimates (OR=2.35, *P*=0.03) as shown in Table 2.

Table 3 shows the interaction between prior allergies and family history for leukemia. Out of the total 41 cases with allergies, 7 (17.07%) were classified as with family cancer history (+) and 34 (82.93%) were family cancer history (-). Of 42 controls with allergies, only 1 (2.38%) had family cancer history. The most striking finding was the high OR (15.88) in those with prior allergies (+) and family cancer history (+), whereas the ORs were 1.95 for those with allergies (+) and family cancer history (-); and 1.92 for persons with allergies (-) and family cancer history (+) after control for potential confounding factors, respectively. Therefore, it was suggested that the interaction between prior allergies and family cancer history for the risk of leukemia was likely to be synergistic rather than additive.

Table 1: Comparison of major risk factors between cases and controls

Factor	Case (n=131) n (%)	Control (n=206) n (%)	*P* value
Age (yr)	42.9	46.7	0.06
Sex			0.62
Male	64(48.9)	95(46.1)	
Female	67(51.1)	111(53.9)	
Education (yr)			0.5
< 6	29(22.1)	41(19.9)	
6-11	72(550)	106(51.5)	
>11	30(22.9)	59(28.6)	
Income			0. 18
Low	54(41.2)	73(35.4)	
Median	39(29.8)	53(25.8)	
High	38(29.0)	80(38.8)	
Tobacco smoking			0.72
Never	95(72.5)	153(74.3)	
Ever	36(27.5)	53(25.7)	
Drinking			0.16
Never	84(64.1)	147(71.4)	
Ever	47(35.9)	59(48.6)	
Prior disease			0.54
No	82(62.6)	122(59.2)	
Yes	49(37.4)	84(40.8)	
Occupational exposure			0.001
No	113(86.3)	199(96.6)	
Yes	18(13.7)	7(3.4)	
House decoration			0.8
No	68(51.9)	104(50.5)	
Yes	63(48.1)	102(49.5)	

Table 2: Crude and adjusted ORs for risk factors related to adult leukemia

Factor	Case (n=131)	Control (n=206)	OR (95% CI) Crude OR (CI)	*P*	Adjusted OR (CI)*	*P*
Prior allergies				0.03		0.01
No	90(68.7)	164(79.6)	1		1	
Yes	41(31.3)	42(20.4)	1.78(1.08-2.94)		2.09(1.22-3.58)	
Family history of cancers				0.01		0.03
No	111(84.7)	192(93.2)	1		1	
Yes	20(15.3)	14(6.8)	2.47(1.20-5.09)		2.35(1.09-5.03)	

* Adjusted for age, sex, education level, income, tobacco smoking, drinking, prior disease, occupational exposure and house decoration.

Table 3: ORs for interaction of prior allergies and family cancer history for risk of leukemia

Factors	Case 131(39%)	Control 206(61%)	OR (95% CI) Crude OR (CI)	*P*	Adjusted OR (CI)*	*P*
Allergies (-) and family cancer history (-)	77	151	1	-	1	-
Allergies (+) and family cancer history (-)	34	41	1.63(0.96-2.77)	0.17	1.95(0.10-3.42)	0.31
Allergies (-) and family cancer history (+)	13	13	1.96(0.87- 4.44)	0.5	1.92(0.81- 4.57)	0.39
Allergies (+) and family cancer history (+)	7	1	13.72(1.66-113.47)	0.04	15.88(1.77-142.55)	0.04

Adjusted for age, sex, education level, income, tobacco smoking, drinking, prior disease, occupational exposure and house decoration

Fig.1: Location of the study area in China

Discussion

To our knowledge, this is the first attempt to explore the relationship between prior allergies and family history of cancers related to adult leukemia in Shandong Province, China. In this hospital-based case-control study, we found an elevated risk of adult leukemia in those with prior allergic disorders or family history of cancers in this population.

There are two contradictory hypotheses about the relationship between allergic disorders and cancer occurrence; especially leukemia. The immune surveillance hypothesis suggests that allergic disorders are protective against occurrence of cancers because an enhanced immune system can detect and destroy malignant mutant cells. However, it has also been suggested that immune-

stimulating conditions (including infectious diseases, allergic conditions, and other immune-related diseases) increase cancer risks through a mechanism of chronic stimulation of cells that results in the occurrence of random mutations in actively dividing stem cells (12). Both the two hypotheses have been supported by some epidemiologic studies (12, 17-19).

The complexity and heterogeneity of the relationship between various allergic disorders and cancers and the underlying mechanism need to be further examined in future studies. There has been no epidemiology study to explore this relationship in Chinese population in Shandong Province. In an effort to improve our understanding on this issue, we present here the epidemiologic evidence on the association between prior allergies and adult leukemia, using the data obtained from a hospital-based case-control study. Our findings are in line with the hypothesis that an allergic diathesis is accompanied by an abnormal immune system rather than a hypercompetent one (20). It is also possible that the prior allergies might be protective in children and young age population, but if in adults, it might become a risk factor, as protective effects were more often reported in children leukemia (17, 21-25).

Previous leukemia studies in US, UK and other countries have reported inconsistent associations with familial history of cancers. Two population-based case-control studies in America found increased risk of leukemia for sibling breast cancer, but the results were not statistically significant (26, 27). In UK, one hospital-based case-control study of adult acute leukemia did not find an association for family history of breast cancer. Significant increased risk of leukemia was reported in other studies in different countries (9, 28, 29); our study detected a positive association between history of cancers of first degree relatives and the risk of adult leukemia. Family history of cancers may serve as a marker for shared genetic and environmental risk factors for adult leukemia (9).

No study has documented the interaction of allergies and family cancer history for the risk of leukemia. The current analysis found that these two factors might have a synergistic effect on the risk of leukemia; it was believed that this result could be a chance finding entirely, despite a small number of the subjects in the double (+) subgroup. The direction and strength of the association persisted when various confounding factors were included in the analysis. This finding highlights that future studies on risk factors for adult leukemia should take into account the interaction of prior allergies and family cancer history.

Our study has some limitations. As in most hospital-based study, selection bias might be a concern. In the current, the subjects were recruited from only one hospital, which was one concern, however, it is very unlikely that there are some significant differences between our subjects and patients who went to seek health care in other hospitals in respect to the prior allergies and family history of cancers; and the high participation rates of cases and controls and the similar demographical characteristics between cases and controls enabled us to believe that selection bias might not very serious. Recall bias should not distort our results to a great extent. We tried to minimize this bias by introducing the study to both the cases and controls as a general health study. Further more most participates did not know the linkage between the factors and the disease, it was unlikely that cases recalled better or over-reported than controls. Inaccurately recall was possible, and should be non-differential, thus could cause dilution of the association. And this study was limited by small numbers of subjects, which did not allow us to do the subgroup analysis for specific cancer type and allergy type.

In short, the present study found increased risk of adult leukemia among individuals with allergies and those with family cancer histories. The finding implied that hypersensitivity may play a role in the genesis of the adult leukemia, and supported that family history of cancers could be a risk factor for adult leukemia, as well, indicated that some tumor-related genes might play a role in development of cancers. Prior allergies and family history of cancers might have a

synergistic effect in risk of adult leukemia. However, due to the limitations outlined, further work is necessary to ascertain the relationships.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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