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Tea consumption reduces the risk of *de novo* myelodysplastic syndromes

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ABSTRACT

Epidemiologic data suggest that green tea consumption may protect against certain cancers, but no previous study has examined myelodysplastic syndromes (MDS). A hospital-based case-control study was conducted in China in 2012–2013 to investigate the association between tea intake and the risk of *de novo* MDS in adults. The study included 208 cases aged 19–85 years with MDS and 208 controls individually matched to the cases by gender, 5-year age group and residential locality. Odds ratios (ORs) were estimated using conditional logistic regression. Compared with non-tea drinkers, the adjusted ORs (95% confidence intervals) for all MDS combined were 0.39 (0.20–0.74), 0.45 (0.25–0.79), and 0.40 (0.21–0.77) for those who consumed tea >20 years, ≥2 cups daily, and dried tealeaves ≥750 g per annum, respectively. Significant dose-response trends were observed across all the measures. The inverse association existed in both genders, in the refractory anemia with excessive blasts subtype, in cytogenetic 'good' and 'intermediated/poor' prognosis groups, and in the International Prognostic Scoring System lower and higher risk groups, but not in the refractory cytopenia with multilineage dysplasia subtype. The study suggests that regular tea consumption reduces the risk of *de novo* MDS in the Chinese population.

1. Introduction

Myelodysplastic syndromes (MDS) include a complex and heterogeneous group of clonal hematopoietic malignancies, characterized by dysplastic and ineffective hematopoiesis, one or more lineages of peripheral blood cytopenias, and an elevated risk of progression into acute myeloid leukemia [1]. The World Health Organization (WHO) criteria of 2008 classified MDS as the following subtypes: refractory cytopenia with unilineage dysplasia (RCUD); refractory anemia with ring sideroblasts (RARS); refractory cytopenia with multilineage dysplasia (RCMD); refractory anemia with excess of blasts (RAEB); MDS associated with isolated del (5q); and MDS unclassifiable (MDS-U) [2]. Currently, the International Prognostic Scoring System (IPSS) is the standard risk classification system for MDS, which takes the percentage of blasts, karyotype and number of cytopenias into account. Patients can be categorized into four IPSS groups: low, intermediate-1 (INT-1), intermediate-2 (INT-2), or high risk, with median survival times of 5.7, 3.5, 1.2 and 0.4 years, respectively [3].

The average annual age-adjusted incidence per 100,000 was lower in Asia (1.1 in Shanghai, China in 2004–2007 [4], 1.6 for men and 0.8 for women in Japan in 2008 [5]) than that in Western countries (3.3 in the United States in 2001–2003 [6], 3.2 in Australia in 2005–2007 [7]). MDS occurs more frequently in older men with sharp increases at older ages. The male-to-female ratio has been calculated from a meta-analysis as 1.2 [8]. The etiology of *de novo* MDS is still largely unknown, except that benzene and smoking are established risk factors. A large cohort study in China suggested that occupational exposure to benzene increased the risk of acute non-lymphocytic leukemia and related MDS [9]. The elevated risk associated with benzene exposure was found again in a hospital-based case-control study conducted in a Chinese population [10] and in a pooled analysis of three nested case-control studies from Australia, Canada and the United Kingdom [11]. A recent meta-analysis of 14 observational studies has shown that ever exposed to cigarette smoking significantly increased the risk of MDS [12]. Other possible hazards have been proposed that might drive up MDS incidence based on several case-control studies, including solvents [13], agricultural chemicals [13–18], ionizing radiation [19] and hair dye use [20]. Lifestyle factors may have an influence on MDS incidence. For instance, a prospective cohort study in the United States suggested that obesity is a risk factor for MDS [21].

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Moreover, a US hospital-based case-control study found that wine drinking was associated with a lower risk of MDS [15], although a subsequent meta-analysis did not confirm an association between overall alcohol consumption and MDS [22].

Tea is one of the most commonly consumed beverages worldwide. Teas from the plant *Camellia sinensis* can be grouped into green, black and oolong tea, depending on the processing methods. Green tea is dried and roasted immediately to preclude the oxidation, whereas black tea is well fermented and oolong tea is partially fermented [23]. Green tea contains tea polyphenols, known as catechins, up to 30% of its dry weight, compared with only 3–10% of black tea. About 78% of the tea production worldwide is black tea; whereas green tea, consumed primarily in China and Japan, accounts for 20%. Oolong tea constitutes about 2% of tea production [23]. Even though inhibition of tumorigenesis by green tea consumption or green tea extracts has been suspected for certain cancers [24], no previous study has reported on the relationship between tea consumption and MDS risk. This study aimed to investigate the association of tea consumption and the risk of MDS in a Chinese population.

2. Materials and methods

2.1. Study design and participants

A hospital-based case-control study was conducted in Hangzhou, the capital city of Zhejiang Province, China, between September 2012 and December 2013. Adult *de novo* MDS patients were identified from medical records at the Department of Hematology, the First Affiliated Hospital of Zhejiang University. The hospital has the sole MDS center in Zhejiang, attracting MDS patients from the whole province. Eligible male and female patients met the 2008 WHO criteria for diagnosis of MDS, based on morphologic, pathologic and cytogenetic information from clinical records and laboratory data. Patients were excluded if they had any one of these criteria: (1) secondary or therapy-related MDS due to previous chemotherapy or radiotherapy; (2) any other additional malignancy; or (3) less than 18 years old. Furthermore, potential cases were excluded if there was the possibility of peripheral blood cytopenias associated with nutritional deficiencies, inflammation or infection, aplastic anemia, acute myeloid leukemia, myelodysplastic–myeloproliferative neoplasms or myeloproliferative neoplasms [1]. To ascertain cases, all relevant clinical and laboratory reports were reviewed. Five patients refused to participate in the study and six patients could not be contacted. A total of 208 patients aged between 19 and 85 years were included in analysis (response proportion, 95.0%). Among all the cases, the median time interval between date of diagnosis and date of interview was 60 days, and 79.3% were recruited within one year after diagnosis.

During the same period of data collection for cases, each control was selected as the first attendee to match with each case on gender, 5-year age group, and residential locality (urban or rural). Potential controls were excluded if they were not matched to their corresponding cases by predefined matching factors, or if they had a previous diagnosis of MDS or another malignancy. The controls were recruited from the outpatient departments of the participating hospital, with a response proportion of 91.2%. Among the recruited controls, 107 (51.4%) were members of general population seeking an annual routine health examination at the Medical Health Examination Center; 52 (25.0%) were outpatients from the ophthalmologic clinic; and 49 (23.6%) were hospital visitors who visited their family members or friends at the outpatient departments of the hospital. The use of outpatient controls as a valid study base sample for cancer cases identified from medical records has been investigated extensively by our research group [25–27]. We have found that outpatient controls perform similarly to community controls in hospital-based case-control study in the Chinese hospital setting. The study protocol was approved by the Human Research Ethics Committee of The University of Western Australia and the ethics committee of the participating hospital in China.

2.2. Questionnaire and interview

Participants were briefed regarding the general aims of the study, confidentiality and anonymity issues through an initial contact. Written informed consent was obtained prior to interviews. Then a face-to-face interview was administered by the first author and a trained local research assistant using a structured questionnaire that usually took 30–40 min. To minimize information bias, the participants were not informed about the hypotheses of the study. Seven cases (3.4%) were too ill to be interviewed, thus questionnaire information was obtained from their proxies.

Information was sought from the structured questionnaire on: (1) demographic and lifestyle characteristics, including education, cigarette smoking, physical activities; (2) tea consumption; (3) dietary habits and foods consumption assessed by a validated and reliable quantitative food frequency questionnaire [28,29]; (4) reproductive factors and family history of cancer; and (5) chemical exposures and hair dye use, available from the author upon request [15]. Foods consumption and tea consumption were assessed separately. A 'reference' recall period for foods consumption was set as one year prior to diagnosis for cases or 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.

2.3. Tea consumption assessment

Self-reported tea consumption was measured by a comprehensive set of measures adapted from our previous study [30]. Participants were first classified as either 'ever' or 'never' (less than once per month) tea drinkers in their lifetime. Information was then sought from all 'ever' drinkers on their usual consumption patterns, namely types of tea drunk, duration of each type of tea drunk, usual frequency of cups consumed (counting the volume of 375 ml per cup, the typical teacup size used by residents in study area), and amount of dried tealeaves consumed per annum. If tea drinking ceased, the number of years quitting tea drinking was recorded as well. In terms of types, green tea, black tea, oolong tea, and any combined types were considered. Duration of each type of tea drinking was recorded in years. The frequency of tea consumption was classified into nine categories: never or hardly ever, one cup/month, 2–3 cups/month, one cup/week, 2–3 cups/week, 4–6 cups/week, one cup/day, 2–3 cups/day, and $\geq$4 cups/day. The quantity of dried tealeaves consumed per year was measured by the common Chinese measure *liang* (equivalent to 50 g).

2.4. Data coding

Overall tea consumption was derived from the variables for all types of tea consumed. Duration, frequency and quantity of tea consumption were grouped into three categories with non-tea drinkers as the reference group.

Metabolic equivalent task (MET) hours per week during the past year was a measure of physical activities. Body mass index (BMI) was calculated using the Quetelet's index expressed in kg/m^2. A total lifetime consumption of 20 packs of cigarettes or more was defined as cigarette smoking. Ever consumed liquor, beer, wine or any combination was classified as alcohol consumption, with abstainers who never drank alcohol as a reference group. Consumption of coffee and soft drinks more than once per month was classified as coffee and soft drinks consumption, respectively. Total energy intake derived from 107-item foods (including 3 items for tea: green tea, oolong tea, and black tea) was estimated using China Food Composition Tables [31]. Ever used permanent hair dye in a lifetime was defined as hair dye use. Participants self-reporting lifetime exposure to chemicals, either on a job or a hobby, at least eight hours per week for one year or more was defined as ever exposed [15].

Cytogenetic characteristics of cases were grouped as 'good outcomes' (normal;−Y alone; del (5q) alone; del (20q) alone), 'poor outcomes' (complex, *i.e.* more than 3 abnormalities; chromosome 7 anomalies) or 'intermediate outcomes' (other abnormalities) [3]. IPSS low and INT-1 risk groups were combined into 'lower risk'; the IPSS high and INT-2 groups became 'higher risk' [32].

2.5. Statistical analysis

Descriptive analyses were conducted on selected characteristics between cases and controls, and clinical features among cases. Univariate analyses were applied to screen potential confounding factors for subsequent multivariate analyses. Multivariate conditional logistic regression models [33], separate for each measure of tea consumption, were adjusted for education (none, primary, secondary, tertiary), cigarette smoking (no, yes) and alcohol consumption (no, yes). These variables were included in regression models because they were associated with both MDS risk and tea consumption based on univariate analyses [34]. Other factors, such as chemical exposures, physical activity, BMI, and diet (coffee, fruits, soy foods consumption), were not included in the multivariate models, because no material changes in risk estimates were observed.

Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to estimate the associations between tea consumption and MDS risk. To assess potential survival bias, data for 165 incident cases and for all cases were analyzed separately. Subsequently, analyses were performed by stratifying males and females, WHO subtypes of RCMD and RAEB, cytogenetic subgroups and IPSS risk. Each ordinal measure of tea consumption was subjected to a trend test. A two-sided alpha level of <0.05 was considered statistically significance. The data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA) statistical software.

3. Results

Characteristics of cases and controls are shown in Table 1. Cases and controls were comparable on matching factors, BMI, soft drinks consumption, energy intake, hair dye use, and cancer history in first-degree relatives. Compared with controls, cases were less educated, more likely to be physically active and smokers, less likely to be alcohol and coffee drinkers, and more likely to be ever exposed to chemicals over a lifetime. There were 42.8% of cases who were classified as tea drinkers compared with 67.3% of controls. Among tea