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Alcohol Consumption Has a Protective Effect against Hematological Malignancies: a Population-Based Study in Sweden Including 420,489 Individuals with Alcohol Use Disorders[1,2,3,4,5]

Jianguang Ji*, Jan Sundquist*,† and Kristina Sundquist*,†

*Center for Primary Health Care Research, Lund University/Region Skåne, Malmö, Sweden; †Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA

Abstract

BACKGROUND: It has been suggested that alcohol consumption is associated with increased risk of a few solid cancers, although studies that examined the association with hematological malignancies have shown inconsistent results. In this study, we examined the risk of hematological malignancies among individuals who had alcohol use disorders (AUDs) in Sweden. *METHODS:* Individuals with AUDs were identified from the nationwide Swedish Hospital Discharge Register and Outpatient Register, the Crime Register, and the Prescription Drug Register, and they were linked to the Swedish Cancer Registry to calculate standardized incidence ratios (SIRs) of hematological malignancies, using those Swedes without AUDs as a reference. In addition, we used a quasi-experimental sibling design to investigate the odds ratios among sibling pairs who were discordant with AUDs. *RESULTS:* A total of 420,489 individuals were identified with AUDs. After more than 15 million person-years of follow-up, a total of 1755 individuals developed hematological malignancies demonstrating a low risk, i.e., SIR = 0.60 (95% confidence interval = 0.57-0.63). People with AUDs had low risks for developing specific types of malignancies. The lowest risk (0.51) was for leukemia, followed by myeloma (0.52), non-Hodgkin lymphoma (0.65), and Hodgkin disease (0.71). The risk was lower among AUDs identified at an older age. The low risks of hematological malignancies were also noted using sibling analysis. *CONCLUSIONS:* Our data suggest that alcohol consumption has a protective effect against hematological malignancies. However, further studies are needed to identity the underlying mechanisms of the protective effect of alcohol consumption against hematological malignancies.

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Address all correspondence to: Jianguang Ji, Center for Primary Health Care Research, Clinical Research Center, Floor 11, Building 28, Jan Waldenströms gata 35, Skåne University Hospital, 205 02 Malmö, Sweden. E-mail: Jianguang.ji@med.lu.se

[1] J.J., K.S., and J.S. were responsible for the study concept and design. J.S. and K.S. obtained funding and acquired the data. J.J. analyzed and interpreted the data, did the statistical analysis, and drafted the manuscript. All authors revised it for important intellectual content. J.S. is the guarantor.

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[3] Ethical approval: This study was approved by the Regional Ethical Review Board of Lund University in Sweden.

[4] Supplementary information is available at Leukemia's website.

[5] This article refers to supplementary material, which is designated by Table W1 and is available online at www.neoplasia.com.

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Introduction

Alcohol use disorders (AUDs), including alcohol abuse and/or dependence, is a substantial worldwide health problem and a major contributor to the global burden of diseases [1,2]. In Sweden, AUDs affect around 18% of men and 5% of women [3,4]. Many diseases, including depressive episodes, severe anxiety, insomnia, suicide, abuse of other drugs, hypertension, heart disease, stroke, liver cirrhosis, fatal accident, and some types of solid cancers, are potentially related to excessive alcohol use [1,2]. According to the report from the International Agency for Research on Cancer [5,6], a few cancer sites, including the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast, are believed to be causally related to alcohol consumption. Acetaldehyde derived from the metabolism of ethanol in alcohol contributes to the development of malignant esophageal cancers [5,6], but the mechanism of carcinogenesis to the other cancers is not clear.

Hematological malignancies include a heterogeneous group of malignancies, and their etiology is not fully understood. Studies that examine the associations of alcoholic beverage consumption with the risk for these hematological malignancies are limited compared to studies on the associations with solid cancers [7]. Interestingly, several previous studies found a negative association of alcohol consumption with non-Hodgkin lymphoma [8–12]. However, inconsistent data are reported in many other studies [13–15]. Possible reasons for the observed inconsistencies are different study designs, small numbers of cases, and bias due to reporting of alcohol consumption. Studies examining the associations with Hodgkin lymphoma, myeloma, and leukemia are also limited [7]. In this study, we used the national Swedish Registries including data from a total population to examine the risk of hematological malignancies (Hodgkin and non-Hodgkin lymphomas, myeloma, and leukemia) among a total of 420,489 individuals with AUDs, compared to those without AUDs. In addition, we used the quasi-experimental sibling design, which was believed to provide stronger causal evidence by controlling for unmeasured confounding factors (unmeasured genetic and environmental factors) [16], to confirm our observation by studying the effect of different AUD exposures among siblings on hematological malignancies.

Methods

This study was approved by the Ethics Committee at Lund University (Malmö, Sweden), 2013. Patients diagnosed with AUDs were identified using data from the following: 1) the Swedish Hospital Discharge Register and Outpatient Register for 1987 to 2010 (international classification of diseases-9: 291A-291F, 291W, 291X, 303, and 305A; and ICD-10: F10), 2) the Crime Register for 1973 to 2010 (to identify individuals who committed alcohol-related crimes), and 3) the Prescription Drug Register for 2005 to 2010 (to identify individuals prescribed with disulfiram, naltrexone, or acamprosate, which are usually used to treat AUDs) [17].

The Swedish Hospital Discharge Register contains hospital discharge records for all Swedish residents. Data were initially collected in the 1960s by 26 regional health authorities and were compiled by the National Board of Health and Welfare. From 1987 forward, the register included nationwide data. The National Board of Health and Welfare estimates that it contains information on 99% of all public hospitalizations. Because Sweden has very few providers of private inpatient care, this registry covers the majority of hospital admissions. Each year, 1.5 million records are added to the Hospital Discharge Register. The results of a recent external review suggest that the overall accuracy of diagnoses in this register is about 85% to 95% [18]. The information for each hospitalization comprises dates of admission and discharge, hospital and clinic codes, and up to eight discharge diagnosis codes, the first of which defines the principal cause of hospitalization. Patients were identified as AUDs if any of the eight discharge codes contained the ICD codes listed above. The Swedish Outpatient Register was created in 2001 by the National Board of Health and Welfare. Although data on outpatient care from public hospitals are almost 100% complete, the register contains no data from small private outpatient clinics, meaning that its overall national coverage is around 80%.

The Swedish Crime Register contains complete nationwide data on all convictions, including those for alcohol abuse, from 1973 to 2010. Individuals with alcohol-associated drunk driving were identified as AUDs. The Swedish Prescribed Drug Register has 100% coverage. Information on prescriptions and expenditures for prescribed drugs in the entire Swedish population covers the period July 2005 to December 2010. From the above-listed Swedish Registers, we identified 420,489 unique individuals with a phenotype of AUDs between 1973 and 2010 (lifetime prevalence in Sweden ~ 3.8%). We did a sensitivity analysis to examine the risks of cancers in the esophagus and upper aerodigestive tract (including oral, larynx, and pharynx), which are known to be associated with alcohol consumption, among individuals with AUDs to see whether AUDs identified in this study can represent the general population with excess alcohol consumption (Table W1).

We further linked these individuals with AUDs to the Swedish Cancer Registry to identify all incident cases of hematological malignancies during the study period. Hematological malignancies examined in this study include non-Hodgkin lymphoma (international classification of diseases-7 codes 200, 202, and 2041), Hodgkin disease (201), myeloma (203), and leukemia (204-209, except 2041). We also examined the risks of a few subtype lymphomas. Only those subtypes that were significantly associated with AUDs were presented (diffuse, follicular non-Hodgkin lymphoma and mixed cellularity and nodular sclerosis classic Hodgkin lymphoma). The Swedish Cancer Registry was founded in 1958 by the National Board of Health and Welfare. Since the mid-80s, there are six regional registries associated with the oncological centers in each medical region of Sweden where the registration, coding, major check-up, and correction work are performed with a close to 100% coverage in the whole Sweden. In Sweden, it is compulsory for clinicians and pathologists/cytologists to report all newly diagnosed cancers to the Cancer Registry [19]. Additional linkages were made to the Swedish National Population and Housing Census [20] to obtain information on individual-level characteristics, such as year of birth, sex, place of living, and country of birth, to the Cause of Death Register to identify date of death, and to the Emigration Registry to identify date of emigration. All linkages were performed using individual national identification numbers, which were replaced with serial numbers to preserve anonymity.

Among individuals with AUDs including a total of 420,489, we calculated person-years at risk for the hematological malignancies from the latter from the date of birth, immigration, or 1 January 1961 (when the Death of Cause Registry was started in Sweden) to the earliest of the date of diagnosis of cancer, death, emigration, or the end of the study period (31 December 2010). Standardized incidence ratios (SIRs) were calculated as the ratio of the observed to expected number of cases [21,22]. The expected number of cases was