

A Study of the Health Effects of Alcohol Consumption in Individuals with Genetic Polymorphisms of Aldehyde Dehydrogenase (ALDH2*2) and Predisposition to Alcohol Related End-Organ Damage

Mari Ikeguchi

A. Introduction

a. Rationale

In recent years numerous studies regarding alcohol consumption have evaluated the potential health benefits of wine with respect to cardiovascular disease. Several studies have shown that moderate alcohol consumption may be associated with a reduction in myocardial infarction, mortality, and favorable alterations to lipoprotein profiles such as elevations in HDL and lowering of LDL. Based on the outcomes of these studies many have been touting the health benefits of moderate (2 drinks/day) alcohol consumption and have adopted the habit of drinking a glass of wine per day. Given the potential for dependency, alcohol induced illness, and the associated morbidity, and mortality it inflicts, population wide recommendations regarding alcohol have not yet been advocated and are justifiably complex.

Differences in alcohol sensitivity and metabolism have been studied and permissive amounts of daily alcohol are felt to be influenced by factors such as age, gender, body mass index, and ethnicity. Epidemiological studies of alcohol use, alcoholism, and alcohol sensitivity in certain ethnic groups have attributed these differences to the kinetics of differing alcohol metabolizing enzymes. Alcohol dehydrogenase and aldehyde dehydrogenase are the principal enzymes in the liver responsible for ethanol metabolism in humans. Both of these enzymes exhibit genetic/ethnic variation felt to arise from different genetic polymorphisms which exist in these genes. The class I alcohol dehydrogenase (ADH) isoenzymes are encoded by ADH I, ADH2, ADH3. Among Caucasian populations variant alleles at the ADH3 locus are found in up to 40-50% of subjects studied. Depending on the presence or absence of such polymorphisms it is felt that there may be associations with various alcohol associated diseases such as alcoholism, end-organ damage, or conversely, with a substantial reduction in the incidence of myocardial infarction. Similarly, polymorphisms have been found in Aldehyde dehydrogenase. Aldehyde dehydrogenase (ALDH2* 1) catalyzes the second step of ethanol metabolism by converting the acetaldehyde produced by alcohol dehydrogenase into acetate. The presence of a point mutation in Aldehyde dehydrogenase (ALDH2*2) results in a less active form of this enzyme, leading to excess levels of acetaldehyde. This mutation has been found more commonly in various East Asian populations and is present in approximately 50% of subjects from Chinese, Korean, and Japanese descent. ALDH2*2 has been associated with increased levels of acetaldehyde following low to moderate alcohol ingestion which in turn has been related to alcohol induced facial flushing reactions. Other symptoms include tachycardia, nausea, hypotension, and headache. A lower incidence of alcoholism has been associated with individuals possessing this gene and it has been strongly suggested to be a negative risk factor for the development of alcohol dependency. Still other studies have suggested that a local carcinogenic effect from elevated levels of acetaldehyde may predispose ALDH2*2 subjects to aerodigestive cancers and end-organ damage.

Currently, light to modest consumption of alcohol is viewed as neither a primary prevention nor as an unhealthy behavior. However, the derivation of most studies on ethanol consumption leading to this view have not taken into account the genetic and ethnic differences that exist with respect to polymorphisms of these alcohol metabolizing genes, specifically ALDH2*2. This study would suggest that the generalizability of these observed findings must be addressed in the context of inherent differences in alcohol metabolism brought about by these genetic polymorphisms. In subjects with

polymorphisms of ALDH2 alcohol consumption in even low to moderate quantities which are not currently viewed as unhealthy behavior, may indeed have adverse health effects especially with respect to aerodigestive cancers. This study will attempt to identify the degree to which ALDH2*2 confers increased susceptibility to these cancers and at what level of alcohol consumption.

b. Hypotheses

Subjects with polymorphisms of Aldehyde Dehydrogenase will be more susceptible to the deleterious effects of alcohol (i.e. cancer, cirrhosis) and at lower levels of consumption.

B. Methods

a. Study Design and Statistical Analysis

This will be a case-control study based on a cohort of men from the Honolulu Heart Study. The Honolulu Heart Program originated as a prospective study of coronary heart disease and stroke among a cohort of 8006 men of Japanese ancestry residing on the Hawaiian island of Oahu in 1965. Information collected from the baseline examination of these men between 1965 and 1968 consisted of various parameters including demographic, medical history, and socio-cultural factors including blood pressure, cigarette smoking, dietary habits, and alcohol consumption. A blood sample was obtained from subjects for laboratory testing. Follow up studies between 1971-1974 again obtained similar detailed clinical information.

For this study the medical records of all men with documented gastrointestinal cancers, and or alcoholic cirrhosis will be retrospectively obtained. Of those eligible cases, classification of alcohol consumption patterns will be determined as will liver function profiles. Alcohol intake has been defined in the Honolulu Heart Program as light, moderate, and heavy based on subjects who reported consuming from 1-14ml, 15-39ml, and >40ml of alcohol per day. Genotyping of ADH2, ADH3, and ALDH2 alleles will then be determined by polymerase chain reaction and restriction fragment length polymorphism. Patients with documented cases of digestive tract cancers will be compared with respect to genotype and allele frequency of ALDH2 to establish if this genetic polymorphism confers greater susceptibility to the development of alcohol related end-organ damage as compared with subjects who do not possess this allele. Controls will be selected from the same population from which patients were derived. They will be selected randomly and matched to patient age, sex, alcohol consumption pattern, smoking history, comorbid illness, and genotype of ALDH2 and will be free of the diagnosis of cancer or cirrhosis at the time of subsequent evaluation. Subjects with a prior history of malignancy will be excluded as will patients with any history of underlying hepatitis, and/or liver disease. ANOVA and X2 test for trends will be used to determine differences in selected continuous and categorical variables in alcohol comparison groups stratified according to age. A proportional-hazards multivariable regression approach should be used to examine the association of alcohol consumption with pooled cancer events while controlling for differences in potentially confounding factors. Sample size will be determined as follows: Where p_1 = (incidence of aerodigestive cancer in abstainers with ALDH2) is assumed to be: 24% and p_2 = (incidence of aerodigestive cancer in alcohol consumers with ALDH2) to be: 35% = 287 subjects in Group 1. This assumes an alpha of 0.05 and power of 0.80.

C. Study Procedures

There are no experimental procedures.

D. Study Drugs

There are no investigational drugs.

E. Medical Devices

There are no investigational medical devices.

F. Study Questionnaire

Will be based on the Honolulu Heart Study baseline and follow-up questionnaires.

G. Study Subjects

Will be based on those patients defined in the Honolulu Heart Study. Patients will be excluded if the cause of death is unknown, does not meet criteria applied for purposes of the study, have underlying documented liver disease, or whose alcohol intake patterns have not remained stable so as to minimize misclassification of alcohol consumption.

H. Recruitment of Subjects

Will be based on the Honolulu Heart Study cohort.

I. Confidentiality of Study Data

Confidentiality will be maintained by means of unique code numbers which will be generated for all study subjects.

J. Potential Conflict of Interest

Neither the investigator nor the University will benefit financially or otherwise from the investigation.

K. Location of the Study

The study will be conducted at Columbia Presbyterian Medical Center in conjunction with the Honolulu Heart Program Pacific Rim Investigators Kuakini Medical Center in Honolulu, Hawaii.

L. Potential Risks

This is a retrospective data analysis and will pose no potential risks to study subjects.

M. Potential Benefits

Potential Benefits of the study include a broader understanding of how genetic variation plays a role in the metabolism of ethanol and how that will impact public health recommendations of alcohol consumption with regard to mortality.

N. Alternative Therapies

There are no alternative therapies.

O. Compensation of Subjects

No compensation will be provided.

P. Costs to Subjects

Subjects will incur no additional costs.

Q. Minors as Research Subjects

There will be no minors as research subjects.

R. Radiation or Radioactive Substances

There is no exposure to radiation or radioactive substances.

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