Plasma Cysteinylglycine Levels and Breast Cancer Risk in Women

Jennifer Lin,[1] JoAnn E. Manson,[1,2,4] Jacob Selhub,[5] Julie E. Buring,[1,3,4] and Shumin M. Zhang[1,4]

[1]Division of Preventive Medicine, [2]Channing Laboratory, Department of Medicine, and [3]Department of Ambulatory Care and Prevention, Brigham and Women's Hospital and Harvard Medical School; [4]Department of Epidemiology, Harvard School of Public Health; and [5]Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts

Abstract

Cysteinylglycine, a prooxidant generated during the catabolism of glutathione, has been suggested to induce oxidative stress and lipid peroxidation, leading to the development of human cancers. Observational data relating cysteinylglycine status to breast cancer risk are lacking. We prospectively evaluated plasma cysteinylglycine levels and invasive breast cancer risk among 812 case-control pairs nested in the Women's Health Study, a completed randomized trial evaluating low-dose aspirin and vitamin E in middle-aged and older women. We additionally evaluated the effect modification by risk factors for oxidative stress, such as vitamin E assignment, alcohol consumption, obesity, and postmenopausal hormone use. Logistic regression controlling for matching factors, as well as other risk factors for breast cancer, was used to estimate relative risks (RR) and 95% confidence intervals (95% CI). All statistical tests were two sided. We observed no overall association between plasma cysteinylglycine and invasive breast cancer risk. However, higher cysteinylglycine levels were marginally associated with an increased risk of breast cancer in the high oxidative stress groups. Women in the highest quintile group of cysteinylglycine relative to the lowest group had multivariate RRs (95% CIs) of 1.64 (1.01–2.66; P_{trend} = 0.04) in the vitamin E placebo group, 2.51 (1.01–6.24; P_{trend} = 0.07) in the high alcohol intake group (≥9 g/day), and 1.66 (0.97–2.84; P_{trend} = 0.03) in the overweight and obese group. Our findings suggest that women who are susceptible to experiencing oxidative stress may be at a greater risk for developing breast cancer. [Cancer Res 2007;67(23):11123–7]

Introduction

Oxidative stress, known to play a role in the promotion and progression of human cancers, including breast cancer (1–3), is a disturbance in the balance between reactive oxygen species production and antioxidant defenses, favoring the overproduction of reactive oxygen species (4). Cysteinylglycine, a sulfhydryldipeptide, is generated from the extracellular glutathione, a nonprotein thiol, through the catalytic activity of γ-glutamyltransferase (5). Cysteinylglycine is a highly reactive metabolite which has been suggested to cause the reduction of ferric iron Fe^{3+} to ferrous iron Fe^{2+}, resulting in an iron redox cycling process liable to the production of reactive oxygen species and stimulation of oxidative reactions (6). The prooxidant, cysteinylglycine, has been shown to cause lipid peroxidation in human plasma LDL lipoproteins (7), as well as oxidative damage on DNA bases (8).

A small case-control study reported a significantly positive association between serum cysteinylglycine levels and risk for ischemic heart disease (9). However, there are no data evaluating cysteinylglycine status in relation to risk for developing breast cancer. We prospectively evaluated the association between plasma levels of cysteinylglycine and invasive breast cancer risk in a case-control study nested in a large female cohort.

Materials and Methods

Participants in this study were drawn from the Women's Health Study, a completed randomized trial evaluating low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease among 39,876 women who were 45 years or older and free of cancer and cardiovascular disease at the time of enrollment beginning in 1992 (10, 11). Upon enrollment into the study, participants completed a baseline questionnaire about their medical history and life-style factors. Participants also filled out a 131-item food frequency questionnaire, which has been validated in a large female cohort (12). After an average of 10 years of treatment, the Women's Health Study trial observed no overall benefit of 600 IU of vitamin E or aspirin at a dose of 100 mg given every other day in the prevention of breast cancer development; the observed relative risks (RR) were 1.00 [95% confidence intervals (95% CI), 0.90–1.12] for randomized vitamin E treatment and 0.98 (95% CI, 0.89–1.08) for randomized aspirin treatment (10, 11).

Blood samples were collected from 28,345 women (71% among the total) at baseline. Baseline characteristics of women who gave blood samples were largely similar to those who did not (13). Briefly, both groups were not different in mean age in years (54.7 and 54.4), proportions of women with body mass index (BMI) of ≥25kg/m^2 (48.4% versus 51.1%), alcohol intake (1.1 versus 0.9 g/day), physical activity (median expenditure per week, 599 versus526 kcal/week), and current use of multivitamin supplements (29.4% versus 28.6%).

In the present study, we included 812 cases who had a confirmed diagnosis of invasive breast cancer incidence during an average of 10 years of follow-up between 1992 and 2004. Each breast cancer case was individually matched to one control with no diagnosis of cancer on age (up to 5 years of difference), ethnicity, menopausal status (premenopausal, postmenopausal, or uncertain/unknown), fasting status (≥8 h or fewer), month and year of blood return (4-month interval), postmenopausal hormone use (never, past, or current), and trial randomization date (12-month difference). Plasma cysteinylglycine levels were determined using high-performance liquid chromatography with fluorescence detection (14). Blood samples were handled identically and together in the same batch. The mean coefficient of variation for quality control samples (78 repeated samples) was 14.7%.

We first $\log_e$-transformed plasma cysteinylglycine and then categorized plasma cysteinylglycine into quintiles on the basis of the distribution in the controls. Differences between case-control pairs in mean levels of plasma nutrients and other continuous covariates were tested using a paired t test. The McNemar test was used to compare the difference between case-control pairs in proportions of covariates as categorical variables. We used conditional logistic regression to estimate RRs and 95% CIs for invasive breast cancer with adjustment for age and randomized treatment assignment, matching factors, and, additionally, potential risk factors for breast cancer assessed at baseline.

Requests for reprints: Jennifer Lin, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue East, Boston, MA 02215. Phone: 617-278-0894; Fax: 617-232-3541; E-mail: jhlin@rics.bwh.harvard.edu.

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