

V. 研究成果の論文要旨

RESEARCH ARTICLE

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Higher serum uric acid level is inversely associated with renal function assessed by cystatin C in a Japanese general population without chronic kidney disease: the KOBE study

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Abstract

Background: Although several epidemiological studies have suggested that high serum uric acid (SUA) levels are related to a decline in kidney function, only a few studies have investigated using cystatin C to calculate estimated glomerular filtration rate (eGFR). We aimed to clarify the relationship between SUA levels and kidney function assessed by cystatin C in a Japanese general community population without chronic kidney disease (CKD).

Methods: We conducted a community-based cross-sectional study that included 1086 healthy participants, aged 40–74 years, without CKD and not undergoing treatment of hyperuricemia, who had participated in the baseline survey of the Kobe Orthopedic and Biomedical Epidemiological (KOBE) study. The preconditions for participation in this study were no past histories of cardiovascular disease or cancer, and not undergoing treatment for diabetes, hypertension, or dyslipidemia. We classified the participants into quartiles stratified by sex according to their SUA level and then examined the relationship with eGFR. The odds ratios for having a low eGFR, defined as the lowest quartile of eGFR (i.e., ≤ 78.4 mL/min/1.73m²) was estimated according to SUA quartiles (men, Q1 ≤ 5.0 , Q2 5.1–5.9, Q3 6.0–6.6, and Q4 ≥ 6.7 ; women, Q1 ≤ 3.8 , Q2 3.9–4.3, Q3 4.4–4.9, and Q4 ≥ 5.0 mg/dL) after adjustment for age, body mass index, systolic blood pressure, HbA1c, high and low density lipoprotein cholesterol, and smoking and drinking habits. The adjusted mean of each quartile was also calculated.

Results: Multivariable-adjusted means of eGFR showed a graded decrease in higher SUA quartiles (men, Q1 90.5, Q2 88.0, Q3 83.5, and Q4 82.0; women, Q1 95.7, Q2 91.3, Q3 89.2, and Q4 86.7). In addition, the multivariable-adjusted odds ratios for having a lower eGFR (95% confidence interval) for each SUA quartile compared with Q1 was Q2 2.29 (0.98, 5.35), Q3 4.94 (2.04, 11.97), and Q4 8.01 (3.20, 20.04) for men, and was Q2 2.20 (1.12, 4.32), Q3 2.68 (1.39, 5.20), and Q4 4.96 (2.62, 9.41) for women.

Conclusions: There was a graded inverse relationship between mild elevations in SUA levels and eGFR assessed by cystatin C in an apparently healthy Japanese population without CKD. This association was similar in both men and women.

Keywords: Chronic kidney disease, Serum uric acid, Cystatin C, A community-based study

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Article

Being Conscious of Water Intake Positively Associated with Sufficient Non-Alcohol Drink Intake Regardless of Seasons and Reasons in Healthy Japanese; the KOBE Study: A Cross Sectional Study

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Received: 24 September 2019; Accepted: 19 October 2019; Published: 28 October 2019



Abstract: The present study sought to clarify if being conscious of water intake (CWI) is associated with sufficient non-alcohol drink (NAD) intake. We used data of healthy participants without diabetes, aged 40–74 years, in the Kobe Orthopedic and Biomedical Epidemiologic (KOBE) study. The association between being CWI and NAD intake was evaluated by multivariate linear regression analyses after adjusting for age, sex, surveyed months (seasons), alcohol drinking, health-awareness life habits, socioeconomic factors, serum osmolarity, estimated daily salt intake, and reasons for NAD intake. Among 988 (698 women and 290 men) participants eligible for the present analyses, 644 participants (65.2%) were CWI and 344 participants (34.8%) were not CWI (non-CWI). The most popular reason for being CWI was to avoid heat stroke in summer and to prevent ischemic cerebral stroke in winter. The CWI group took more NAD, especially decaffeinated beverages, than the non-CWI group (1846.7 ± 675.1 mL/day vs. 1478.0 ± 636.3 mL/day, $p < 0.001$). There was a significant association between being CWI and NAD intake in multivariate linear regression analyses ever after adjusting for the relevant variables ($\beta = 318.1$, $p < 0.001$). These findings demonstrated CWI, regardless of the reasons and the seasons, was associated with high NAD intake in Japanese healthy population.

Keywords: water intake conscious; non-alcohol drink; seasons; daily salt intake; serum osmolarity; cross-sectional study

1. Introduction

In contrast to most developed countries, the event risks of cerebrovascular diseases are high and it remains one of top-ranked causes of death and disability in Japan [1,2]. Recent studies demonstrated

Daily Habit of Water Intake in Patients with Cerebral Infarction before its Onset; Comparison with a Healthy Population: A Cross-Sectional Study

Nishikawa T, Miyamatsu N, Higashiyama A, Hojo M, Nishida Y, Fukuda S, Hirata T, Ichiura K, Kubota Y, Kubo S, Ueba T, Kadota A, Sugiyama D, Okamura T. Daily Habit of Water Intake in Patients with Cerebral Infarction before its Onset; Comparison with a Healthy Population: A Cross-sectional Study.

Cerebrovascular Dis. 2019; 47: 143-150.

Abstract

Background: While water intake is frequently recommended to prevent cerebral infarction (CI), only few studies have been published on this topic. Objectives: This study retrospectively estimated the daily non-alcohol drink (NAD) intake in CI patients before CI onset and compared it with NAD in healthy subjects. **Methods:** We performed a cross-sectional study on CI patients in 3 hospitals and healthy subjects in the Kobe Orthopedic and Biomedical Epidemiologic (KOBÉ) study. Data from 1,287 subjects (274 CI patients and 1,013 healthy subjects) were used for the analyses. By dividing the CI patients into “increased”, “unchanged”, and “decreased” groups according to their current NAD intake, we compared the NAD intake between these 3 groups and healthy subjects by analyses of covariance and the post hoc test, adjusting for sex, age, surveyed month, body mass index, alcohol drinking history, and smoking history. Under the assumption that the NAD intake in the “unchanged” group was equal to the NAD intake before CI onset, the OR of less NAD intake for CI adjusting for the relevant variables in the “unchanged” group and the healthy subjects was calculated; the cut-off point was chosen using Youden’s index. **Results:** The mean age (mean \pm SD) of the participants was 62.8 ± 9.3 years. One hundred and fifty-one patients (36 women) were included in the “increased” group; 105 (30 women), in the “unchanged” group; 18 (2 women), in the “decreased” group; and 1,013 (706 women), in the “healthy” group. The mean NAD intake was $1,702.5 \pm 670.2$ mL in the “increased” group, $1,494.2 \pm 611.2$ mL in the “unchanged” group, $1,268.0 \pm 596.1$ mL in the “decreased” group, and $1,720.6 \pm 686.0$ mL in the “healthy” group. After adjusting for the relevant variables, a significant difference in NAD intake between the groups was observed ($F = 6.1$, $p < 0.001$), and a post hoc test demonstrated significant differences ($p < 0.05$) in NAD intake between the “healthy” and “unchanged” groups, and between the “increased” and “unchanged” groups. The OR of less NAD intake ($< 1,570$ mL/day, chosen using Youden’s index) for CI was 2.48 (95% CI 1.52–4.07). **Conclusion:** This study showed that daily NAD intake before CI onset in CI patients was less than that in healthy persons, indicating that sufficient intake of NAD may be protective for CI.

Serum Lipopolysaccharide-Binding Protein Levels and the Incidence of Cardiovascular Disease in a General Japanese Population: The Hisayama Study

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Background—Epidemiological studies have reported a link between serum LBP (lipopolysaccharide-binding protein) levels and lifestyle-related diseases. However, there have been no longitudinal studies investigating the association of serum LBP levels and the incidence of cardiovascular disease (CVD) in general populations.

Methods and Results—A total of 2568 community-dwelling Japanese individuals 40 years and older without prior CVD were followed for 10 years (2002–2012). Serum LBP levels were divided into quartiles (quartile 1: 2.20–9.68 $\mu\text{g}/\text{mL}$; quartile 2: 9.69–10.93 $\mu\text{g}/\text{mL}$; quartile 3: 10.94–12.40 $\mu\text{g}/\text{mL}$; quartile 4: 12.41–24.34 $\mu\text{g}/\text{mL}$). The hazard ratios (HRs) and their 95% CIs for the incidence of CVD were computed using a Cox proportional hazards model. During the follow-up period, 180 individuals developed CVD. The age- and sex-adjusted cumulative incidence of CVD increased significantly with higher serum LBP levels (P for trend=0.005). Individuals with higher serum LBP levels had a significantly greater risk of the development of CVD after adjusting for conventional cardiovascular risk factors (quartile 1: HR, 1.00 [reference]; quartile 2: HR, 1.04 [95% CI, 0.60–1.78]; quartile 3: HR, 1.52 [95% CI, 0.92–2.51]; and quartile 4: HR, 1.90 [95% CI, 1.17–3.09]; P for trend=0.01). This association remained significant after additional adjustment for homeostasis model assessment of insulin resistance (P for trend=0.01). However, when additional adjustment was made for high-sensitivity C-reactive protein, the association was attenuated to the nonsignificant level (P for trend=0.08).

Conclusions—The present findings suggest that higher serum LBP levels are associated with increased risk of the development of CVD in the general Japanese population. Low-grade endotoxemia may contribute to the pathogenesis of CVD through chronic systemic inflammation. (*J Am Heart Assoc.* 2019;8:e013628. DOI: 10.1161/JAHA.119.013628.)

Key Words: cardiovascular disease • endotoxemia • epidemiology • follow-up studies • lipopolysaccharide-binding protein

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, accounting for 17.9 million deaths every year and 31% of all global deaths.¹ Atherosclerotic

diseases including stroke and coronary artery disease are the most common forms of CVD.^{2,3} Although it has been widely acknowledged that atherosclerosis is promoted by the chronic inflammation of blood vessels,⁴ the causes of chronic inflammation remain unclear. In recent years, lipopolysaccharide, which is a component of the outer membrane of gram-negative bacteria, has been noted as a potential source of chronic low-grade systemic inflammation.⁵ Gram-negative bacteria colonize as resident microbiota in the human gastrointestinal, genitourinary, and respiratory tracts, and in the oral cavity. Recently, the condition of chronically elevated serum lipopolysaccharide, in which serum levels are 10 to 50 times lower than those for patients with sepsis, has been designated “metabolic endotoxemia.”⁶ Several studies of mice^{7–10} and humans^{11–14} have shown that metabolic endotoxemia is linked with metabolic disturbances such as obesity, insulin resistance, and diabetes mellitus.

LBP (lipopolysaccharide-binding protein), an acute-phase protein with a molecular mass of <60 kDa, binds multimers of

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Accompanying Tables S1 through S5 and Figure S1 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013628>

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Received June 15, 2019; accepted September 25, 2019.

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Original Contribution

Association Between Serum β -Alanine and Risk of Dementia

The Hisayama Study

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Initially submitted December 21, 2018; accepted for publication April 30, 2019.

We examined the association between serum concentrations of β -alanine, a metabolite of carnosine and anserine, and the risk of dementia in a general population of elderly Japanese persons. In 2007, 1,475 residents of Hisayama, Japan, aged 60–79 years and without dementia were divided into 4 groups according to quartiles of serum β -alanine concentrations (quartile 1, lowest; quartile 4, highest) and followed for a median of 5.3 years. During follow-up, 117 subjects developed all-cause dementia (Alzheimer in 77 cases and vascular dementia in 31). The risk of all-cause dementia decreased with increasing serum β -alanine levels after adjustment for potential confounding factors (quartile 2, hazard ratio (HR) = 0.73 (95% confidence interval (CI): 0.45, 1.18); quartile 3, HR = 0.50 (95% CI: 0.28, 0.89); quartile 4, HR = 0.50 (95% CI: 0.27, 0.92); $P = 0.01$ for trend). A similar inverse association was observed for Alzheimer disease (quartile 2, HR = 0.78 (95% CI: 0.44, 1.38); quartile 3, HR = 0.53 (95% CI: 0.26, 1.06); quartile 4, HR = 0.53 (95% CI: 0.25, 1.10); $P = 0.04$ for trend) but not for vascular dementia. We found that higher serum β -alanine levels were significantly associated with lower risks of all-cause dementia and Alzheimer disease. Because serum β -alanine levels reflect intakes of carnosine/anserine, higher intakes of carnosine/anserine might be beneficial for the prevention of dementia.

β -alanine; Alzheimer disease; cohort study; dementia; imidazole dipeptides

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; VaD, vascular dementia.

Dementia is one of the major causes of disability and mortality in the elderly (1). The prevalence and incidence of dementia have been increasing in Japan (2), and the medical and economic burden of dementia on society is a serious problem. However, the causes of dementia, especially Alzheimer disease (AD), remain unclear. Therefore, it is important to identify risk factors or protective factors in order to reduce the burden of dementia.

Growing epidemiologic evidence suggests that some modifiable risk factors—namely, diabetes (3), hypertension (4), cigarette smoking (5), and physical inactivity (6)—are associated with increased risk of dementia. In addition, dietary or nutritional factors are considered possible protective factors against dementia (7–10), and some nutraceuticals have been developed for the prevention and treatment of dementia (10).

Recent studies have shown that carnosine and anserine, which are imidazole dipeptides contained in the skeletal muscles and brain, have some biological functions, including antioxidant, antiglycation, and antiinflammatory activities (11). The content of these imidazole dipeptides has been positively linked with muscle buffering capacity and performance capacity (12). Moreover, supplementation with these dipeptides has been reported to have a beneficial effect on cognitive function in humans (13, 14) and in mice (15). However, the influence of these dipeptides on cognitive function has not been fully investigated in a general population.

Carnosine and anserine are rapidly cleaved into β -alanine and histidine/methyl-histidine after intake. Thus, serum carnosine/anserine levels become undetectable within 6 hours after the intake of these dipeptides, while serum β -alanine levels increase

Genetic risk and incident type 2 diabetes.

Association between genetic risk and development of type 2 diabetes in a general Japanese population: The Hisayama Study

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Context: Although recent genetic studies have identified many susceptibility loci associated with type 2 diabetes (T2D), the usefulness of such loci for precision medicine remains uncertain.

Objective: This study investigated the impact of a genetic risk score (GRS) on the development of T2D in a general Japanese population

NT-proBNP and Risk of Dementia in a General Japanese Elderly Population: The Hisayama Study

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Background—Epidemiological evidence implies a link between heart disease and dementia. However, few prospective studies have assessed the association between serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels and dementia.

Methods and Results—A total of 1635 community-dwelling Japanese elderly aged ≥ 60 years without dementia (57% women, mean age \pm SD 70.8 \pm 7.7 years) were followed up for 10 years. Serum NT-proBNP levels were divided into 4 categories (≤ 54 , 55–124, 125–299, and ≥ 300 pg/mL). The hazard ratios were estimated using a Cox proportional hazards model. During the follow-up period, 377 subjects developed all-cause dementia, 247 Alzheimer disease, and 102 vascular dementia. The age- and sex-adjusted incidence of all-cause dementia was 31.5 per 1000 person-years and increased significantly with higher serum NT-proBNP levels, being 16.4, 32.0, 35.7, and 45.5, respectively (P for trend < 0.01). Subjects with serum NT-proBNP levels of ≥ 300 pg/mL had a significantly higher risk of all-cause dementia (hazard ratio=2.46, 95% CI 1.63–3.71) than those with serum NT-proBNP levels of ≤ 54 pg/mL after adjusting for confounders. Similar risks were observed for Alzheimer disease and vascular dementia. Incorporation of the serum NT-proBNP level into a model with known risk factors for dementia significantly improved the predictive ability for incident dementia (c-statistics 0.780–0.787, $P=0.02$; net reclassification improvement 0.189, $P=0.001$; integrated discrimination improvement 0.011, $P=0.003$).

Conclusions—Higher serum NT-proBNP levels were significantly associated with an increased risk of dementia. Serum NT-proBNP could be a novel biomarker for predicting future risk of dementia in the general elderly population. (*J Am Heart Assoc.* 2019;8:e011652. DOI: 10.1161/JAHA.118.011652.)

Key Words: Alzheimer disease • biomarker • N-terminal pro-B-type natriuretic peptide • prospective cohort study • vascular dementia

Dementia is a major cause of disability among the elderly, and its medical and economic burdens on society have been increasing worldwide.¹ Recent epidemiological studies have reported that lifestyle-related diseases such as

hypertension,² diabetes mellitus,³ and obesity⁴ as well as lifestyle factors such as smoking habits,⁵ dietary patterns,⁶ and physical activity⁷ are associated with the risk of developing dementia. However, the influence of these factors on dementia, especially Alzheimer disease (AD), remains incompletely understood.

Heart disease is a major cause of disability and premature death among the elderly.⁸ Circulatory failure and vascular insufficiency that are caused by heart disease and its risk factors have the potential to impair function in various organs, including the brain. Several prospective studies have shown a close association between chronic heart failure and the risk of dementia.^{9–11} In addition, interventional studies revealed that treatment to increase cardiac output improved the cognitive function in patients with severe heart failure.^{12,13} These findings imply a link between heart disease and dementia.

NT-proBNP (N-terminal pro-B-type natriuretic peptide) is an inactive N-terminal fragment of proBNP with 76 amino acids and is released as a prohormone from ventricular myocytes in response to mechanical stretch and ischemic injury.¹⁴ Serum

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Accompanying Tables S1 through S8 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011652>

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Received November 30, 2018; accepted July 31, 2019.

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Serum Ethylamine Levels As an Indicator of L-Theanine Consumption and the Risk of Type 2 Diabetes in a General Japanese Population: The Hisayama Study

Diabetes Care 2019;42:1–7 | <https://doi.org/10.2337/dc18-2655>

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OBJECTIVE

This study investigated the association between serum ethylamine levels as an indicator of L-theanine consumption and the development of type 2 diabetes in a Japanese community.

RESEARCH DESIGN AND METHODS

A total of 2,253 community-dwelling Japanese individuals aged 40–79 years without diabetes were monitored for 7 years. Serum ethylamine levels were divided into quartiles: ≤ 0.86 , 0.87–2.10, 2.11–5.28, and ≥ 5.29 ng/mL. Kinetic analysis of serum ethylamine concentrations was performed after ingestion of L-theanine-rich green tea products containing 8 mg of L-theanine by 12 healthy volunteers.

RESULTS

During follow-up, 282 subjects developed type 2 diabetes. The age- and sex-adjusted cumulative incidence of type 2 diabetes decreased significantly with elevating levels of serum ethylamine (P for trend = 0.04). This association remained unchanged after adjusting for potential confounding factors. The multivariable-adjusted hazard ratio (HR) for type 2 diabetes was significantly lower in the fourth quartile of serum ethylamine than in the first quartile (HR 0.69, 95% CI 0.49–0.98). This trend of decrease in diabetic risk across serum ethylamine levels was more prominent in middle-aged subjects and in subjects with prediabetes, obesity, or insulin resistance. Kinetic analysis estimated that the minimum concentration at the steady state was >5.90 ng/mL in the case of twice-daily ingestion with an interval of 12 h.

CONCLUSIONS

Higher serum ethylamine was significantly associated with lower risk of the development of type 2 diabetes in a general Japanese population. The measurement of serum ethylamine concentration would be a useful biomarker for the objective estimation of L-theanine consumption.

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Received 29 December 2018 and accepted 15 April 2019

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-2655/-/DC1>.

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Serum Soluble Triggering Receptor Expressed on Myeloid Cells 2 as a Biomarker for Incident Dementia: The Hisayama Study

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Objective: To investigate the association between serum soluble triggering receptor expressed on myeloid cells 2 (sTREM2), a soluble type of an innate immune receptor expressed on the microglia, and the risk of dementia.

Methods: A total of 1,349 Japanese community residents aged 60 and older without dementia were followed prospectively for 10 years (2002–2012). Serum sTREM2 levels were quantified by using an enzyme-linked immunosorbent assay and divided into quartiles. Cox proportional hazards model was used to estimate the hazard ratios (HRs) of serum sTREM2 levels on the risk of dementia.

Results: During the follow-up, 300 subjects developed all-cause dementia; 193 had Alzheimer's disease (AD), and 85 had vascular dementia (VaD). The age- and sex-adjusted incidences of all-cause dementia, AD, and VaD elevated significantly with higher serum sTREM2 levels (all p for trend < 0.012). These associations were not altered after adjustment for confounding factors, including high-sensitive C-reactive protein. Subjects with the highest quartile of serum sTREM2 levels had significantly higher multivariable-adjusted risks of developing all-cause dementia, AD, and VaD than those with the lowest quartile (HR = 2.03, 95% confidence interval [CI] = 1.39–2.97, p < 0.001 for all-cause dementia; HR = 1.62, 95% CI = 1.02–2.55, p = 0.04 for AD; HR = 2.85, 95% CI = 1.35–6.02, p = 0.006 for VaD). No significant heterogeneity in the association of serum sTREM2 levels with the development of dementia was observed among the other risk factor subgroups (all p for heterogeneity > 0.11).

Interpretation: The present findings suggest a significant association between increased serum sTREM2 levels and the risk of developing all-cause dementia, AD, and VaD in the general elderly Japanese population.

ANN NEUROL 2019;85:47–58

The world's socioeconomic burden of dementia has been increasing, but causes of the disease, especially Alzheimer's disease (AD), are still unclear. Inflammatory response may have a crucial role in the early stages of the

pathological cascade of dementia, because the levels of activated microglia and astrocytes increase along with dementia pathology.¹ Recently, whole genome sequencing studies have revealed that rare variants in the triggering

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25385

Received May 22, 2018, and in revised form Nov 22, 2018. Accepted for publication Nov 23, 2018.

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Dairy consumption and risk of functional disability in an elderly Japanese population: the Hisayama Study

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The American Journal of Clinical Nutrition, Volume 109, Issue 6, June 2019, Pages 1664–1671,

<https://doi.org/10.1093/ajcn/nqz040>

Published: 10 May 2019 **Article history** ▼

ABSTRACT

Background

Little is known about the association between dairy intake and risk of functional disability in the elderly.

Objectives

We examined the influence of dairy intake on the development of declining functional capacity and activities of daily living (ADL) in a prospective cohort study of an elderly population.

Methods

A total of 859 community-dwelling Japanese residents, aged ≥ 65 y without functional disability, were followed up for 7 y. Functional capacity impairment was defined as a Tokyo Metropolitan Institute of Gerontology Index of Competence score of ≤ 12 , and ADL disability was defined as a Barthel Index score of ≤ 95 . Dairy intake was evaluated using a 150-item semiquantitative food frequency questionnaire, grouped into quartiles. The RR of dairy intake on incident functional disability was computed using a Poisson regression model.

Results

The multivariable-adjusted RR of impaired functional capacity decreased significantly with increasing dairy intake levels (RR [95% CI]: quartile 1, 1.00 [reference]; quartile 2, 0.85 [0.71, 1.02]; quartile 3, 0.81 [0.68, 0.98]; and quartile 4, 0.74 [0.61, 0.90]; P -trend = 0.001). Regarding the three subscales of functional capacity, the inverse association between dairy intake and risk for impairment of intellectual activity and social role remained significant (P -trend = 0.0009 and 0.02, respectively), but such an association was not observed for instrumental ADL. The multivariable-adjusted risk of ADL disability also decreased weakly but significantly with elevating dairy intake (P -trend = 0.04). A similar association was seen for severity of functional disability (P -trend = 0.002). However, the magnitude of these associations was attenuated after further adjustment for protein intake.

Conclusion

Our findings suggest that higher dairy intake is associated with a lower risk of functional disability and its progression in the elderly, probably via an increase in protein intake.

[dairy intake](#), [functional disability](#), [functional capacity impairment](#), [disability](#), [elderly](#), [cohort studies](#), [Japanese](#)

Introduction

The elderly population is growing rapidly worldwide, in both developed and developing countries (1). Along with the aging of the population, functional disability, which causes dependency, institutionalization, and poor/fatal prognosis, has raised serious social, medical, and economic concerns (2, 3). The burden of functional disability is enormous, especially in developed countries, in which the aging of the population started earlier and the elderly population has thus increased sharply. Epidemiological and clinical studies on the causes and preventive measures of functional disability in the elderly are therefore requisite for appropriate public health policy and planning. Diet is among the modifiable factors that can affect the risk of various diseases (4, 5). It has been reported that dairy intake may contribute to a decreased risk of diseases that cause functional disability and its precursor state, such as dementia (6), cardiovascular disease (7), orthopedic disease (8), and frailty (9). These findings have led to a hypothesis that dairy intake may be associated with a lower risk of functional disability in the elderly. Several community-based studies conducted in Western and Asian countries have examined the association between dairy intake and functional disability (10–13). However, there have been only a few prospective cohort studies on this issue in the elderly, and they did not show clear associations (11, 12). The aim of this investigation was to examine the association between dairy intake and the development of functional disability in a prospective cohort study of a general Japanese elderly population.

Methods

Study population

The Hisayama Study is an ongoing prospective cohort study of cerebrocardiovascular diseases and dementia in a suburban community, the town of Hisayama, which is located adjacent to the metropolitan area of Fukuoka, Japan (14–17). Between October 2005 and August 2006, we performed a screening survey for the current study. The survey was performed in the public hall of Hisayama or in the homes of participants. We also visited hospitals and health care facilities



Article

Effects of Demographic Variables on Subjective Neurocognitive Complaints Using the Neurocognitive Questionnaire (NCQ) in an Aged Japanese Population

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Received: 7 January 2019; Accepted: 30 January 2019; Published: 1 February 2019



Abstract: Objectives: In an aged Japanese population, we investigated associations of demographic variables with subjective neurocognitive complaints using the Neurocognitive Questionnaire (NCQ). Methods: Participants ($N = 649$) provided answers to the NCQ in both 2011 and 2013. Using fully-completed NCQs from 503 participants in 2011, we identified latent factors of subjective neurocognitive complaints using exploratory factor analysis; then examined associations of demographic variables with the identified factors for all 649 participants over the two years. We also examined changes in factor scores over the 2-year period. Results: We identified four factors representing 20 of the 25 NCQ items and labelled them metacognition, emotional regulation, motivation/organization, and processing speed. In a regression model using all participants, we observed linear deterioration with age on emotional regulation and linear-quadratic deterioration with age on the other factors. Less education was associated with more problems for all factors, but we detected no evidence of interaction between age and education. In 314 participants completing both assessments, paired t -tests comparing the 2013 to 2011 responses corroborated the regression results, except for emotional regulation. Conclusions: On the NCQ, older age and less education were associated with more subjective neurocognitive complaints. This is compatible with the association of the same factors with objective cognition and suggests that subjective cognitive complaints complement objective cognition as a prodrome of non-normative cognitive decline.

Keywords: subjective neurocognitive complaint; aging; education; demographic factors; questionnaire; factor analysis

1. Introduction

In older persons, an increase in subjective cognitive complaints are related to a deterioration of simultaneously measured performances on neurocognitive tests [1]. Those with subjective cognitive complaints, even in the absence of current objective cognitive deficits, experience more objective cognitive decline over time [2,3]. These results suggest that subjective cognitive complaints may be a prodrome of non-normative cognitive decline. Although a questionnaire survey on subjective cognitive complaints is a simple and cost-effective method to examine neurocognitive function, few instruments that evaluate subjective cognition are used globally, and there is a dearth of reports on subjective cognition, except for subjective memory complaints [4]. In aging research, subjective cognitive

Blood pressure levels and risk of cardiovascular disease mortality among Japanese men and women: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study)

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Objective: To examine the association of blood pressure (BP) with cardiovascular mortality in real-world settings and investigate whether that association varied by use of antihypertensive medication at baseline.

Methods: Data from 27 728 Japanese men and women, aged 40–79 years, free of stroke, coronary heart disease, cancer, and kidney disease at entry (1988–1990) were used in this study. Mortality surveillance was completed through 2009, resulting in 449 800 person-years of follow-up. Hazard ratios for cardiovascular mortality were analysed by BP category (based on 2018 European guidelines) at admission.

Results: There were 1477 deaths from cardiovascular diseases (CVDs). Relative to high-normal BP at admission, the multivariable hazard ratios (95% confidence intervals) of CVD were 0.85 (0.69–1.04) for optimal BP; 0.96 (0.81–1.15) for normal BP; 1.26 (1.09–1.46) for Grade 1 hypertension; and 1.55 (1.31–1.84) for Grade 2–3 hypertension. A similar linear association was observed among persons not taking antihypertensive medication at admission. Among patients treated for hypertension, a U-shaped association with CVD mortality was observed; hazard ratios = 2.31 (1.25–4.27), 1.68 (1.05–2.69), 1.56 (1.10–2.22), and 1.63 (1.13–2.36), respectively. Similar patterns were observed for stroke and coronary heart disease, although not always statistically significant.

Conclusion: BP categories at baseline were linearly and positively associated with CVD mortality overall and also among participants not taking antihypertensive medication. A higher risk of mortality from CVD was observed among patients already treated for hypertension with optimal and normal BPs than those with high-normal BP, suggesting the importance of careful monitoring of BP and comorbidities of such patients.

Keywords: cerebrovascular disease, epidemiology, follow-up study, hypertension

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; JACC Study, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; SPRINT, Systolic Blood Pressure Intervention Trial

INTRODUCTION

It is well known that high blood pressure (BP) increases the risk of cardiovascular disease (CVD) [1], and that treatment of hypertension reduces that risk [2]. Clinical trials have shown that treating hypertension to below-normal BP levels is better for the prevention of coronary heart disease or stroke among patients with high cardiovascular risk [3]. On the other hand, several prospective cohort studies have shown that among patients treated for hypertension treatment to low BP levels was associated with increased risk of coronary heart disease and/or stroke compared with treatment to moderate BP levels [4–8].

The causal relations need to be determined through randomized controlled trials, as observational study designs have inevitable drawbacks (e.g. confounding factors). As mentioned, some clinical trials have shown the benefit of lowering BP below ‘normal’ levels among strictly selected patients [3]. However, in general practice, patients with hypertension alongside comorbidities such as atherosclerosis, atrial fibrillation, and heart failure are sometimes unintentionally treated to low BP levels, which could lead to an elevated risk of CVD. Clinical trials are typically performed under ‘ideal’ trial conditions (following strict inclusion/exclusion criteria and a rigid protocol), and their results may not be generalizable to general practice in which patients might exhibit hypertension together with such comorbidities as mentioned above. In addition, many

Journal of Hypertension 2019, 37:1366–1371

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Received 8 November 2018 **Revised** 15 January 2019 **Accepted** 27 January 2019

J Hypertens 37:1366–1371 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/HJH.0000000000002073

Among the water-soluble vitamins, dietary intakes of vitamins C, B₂ and folate are associated with the reduced risk of diabetes in Japanese women but not men

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(Submitted 26 December 2018 – Final revision received 21 February 2019 – Accepted 8 March 2019 – First published online 10 June 2019)

Abstract

Recent studies have shown that micronutrients are involved in the pathology of type 2 diabetes. Antioxidant effects of vitamins C and B₂ and homocysteine-lowering effects of vitamins B₆, folate and B₁₂ may have protective roles. However, a few reports have investigated the association between dietary water-soluble vitamin intakes and risk of diabetes. In a prospective study encompassing 19 168 healthy Japanese men and women aged 40–79 years, we examined the associations between dietary intakes of water-soluble vitamins, determined by a validated self-administered FFQ, with the risk of 5-year cumulative incidence of type 2 diabetes by using the logistic regression model. Within the 5-year period, there were 494 self-reported new cases of diabetes. Higher dietary intakes of vitamins C, B₂ and folate were associated with lower risk of incident diabetes only in women, whereas no associations of dietary intakes of vitamins B₁, B₃, B₅, B₆ and B₁₂ were observed in either sex. The multivariable OR in the highest *v.* the lowest quartile of intakes among women were 0.61 (95% CI 0.44, 0.94; *P*-trend = 0.04) for vitamin C, 0.56 (95% CI 0.34, 0.93; *P*-trend = 0.03) for vitamin B₂ and 0.70 (95% CI 0.46, 0.98; *P*-trend = 0.03) for folate. Other than that for sex (*P* < 0.05), the *P*-interactions with age, BMI, smoking status or having a family history of diabetes were >0.10. In conclusion, higher dietary intakes of vitamins C, B₂ and folate, but not other water-soluble vitamins, were associated with reduced risk of type 2 diabetes in Japanese women.

Key words: Water-soluble vitamins: Vitamin B: Vitamin C: Diabetes: Japanese

With its global expanding prevalence⁽¹⁾, especially in Japan⁽²⁾, type 2 diabetes mellitus (T2DM) ranks as one of the top health problems. Previous epidemiological studies reported that improving diet quality should be targeted for the prevention of T2DM^(2–5). A growing body of evidence suggested a considerable role of micronutrients in the pathogenesis and complications of T2DM^(3–5).

The antioxidant properties of vitamin C have been suggested as a plausible mechanism for the reduced risk of T2DM with high vitamin C intakes or plasma concentrations^(6,7). However, a review of observational studies indicated that these associations were evident in some but not in all previous studies⁽⁸⁾. Moreover, no association was reported in a large randomised controlled trial⁽⁹⁾.

On the other hand, the plasma levels in almost all the B-group vitamins have been found lower in diabetic than in non-diabetic individuals^(4,5) as a consequence of diabetes, either because of behavioural changes or changes in metabolism. However, most of the available research on B-group vitamins/T2DM associations has concentrated on vitamins B₆, folate and vitamin B₁₂, and has

shown inconsistent findings^(10–12). Similar large studies to investigate the associations of other B vitamin intakes, such as vitamin B₁ (thiamine), B₂ (riboflavin), B₃ (niacin) and B₅ (pantothenic acid) are scarce^(13–18). Moreover, the previous observations were either for the vitamin B-group status^(11,13,17) or supplemental^(8,9,12,14–16,18) rather than dietary intakes⁽⁷⁾. Therefore, in the present analysis, we aimed to investigate the association between dietary consumptions of the whole set of water-soluble vitamins (B₁, B₂, B₃, B₅, B₆, B₉, B₁₂ and C) and the risk of 5-year cumulative incidence of T2DM among a large cohort of Japanese men and women, hypothesising that intakes of at least some of these water-soluble vitamins could associate inversely with the risk of T2DM.

Methodology

Study population and baseline covariates

A total of 52 658 diabetes-free residents of forty-five Japanese communities aged 40–79 years participated in the Japan

Abbreviation: T2DM, type 2 diabetes mellitus.

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Dietary Inflammatory Index Is Associated with Risk of All-Cause and Cardiovascular Disease Mortality but Not with Cancer Mortality in Middle-Aged and Older Japanese Adults

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ABSTRACT

Background: The Dietary Inflammatory Index (DII) is a comprehensive, literature-derived index for assessing the effect of dietary constituents on inflammatory biomarkers. Several studies have shown an association between DII score and mortality, but there are limited prospective studies in Asian populations.

Objectives: The aim of this study was to investigate the association between DII score and risk of all-cause, total cardiovascular disease (CVD), stroke, coronary heart disease (CHD), total cancer, digestive cancer, and noncancer/non-CVD mortality in the Japanese population.

Methods: A total of 58,782 Japanese participants aged 40–79 y who were enrolled in the Japan Collaborative Cohort Study during 1988–1990 were included in the analysis. DII scores were calculated based on a food-frequency questionnaire. HRs and 95% CIs for mortality according to DII quintiles were estimated using Cox proportional hazards models.

Results: During the median follow-up period of 19.3 y, a total of 11,693 participants died. The multivariable HR for all-cause mortality for the highest compared with the lowest DII quintiles was 1.13 (95% CI: 1.05, 1.21). For CVD mortality, the highest multivariable HRs were 1.30 (95% CI: 1.13, 1.49), 1.29 (95% CI: 1.05, 1.59), and 1.30 (95% CI: 0.96, 1.76) for total CVD, stroke, and CHD, respectively. No significant associations were observed between DII and risk of total cancer, digestive cancer, and noncancer/non-CVD mortality.

Conclusion: Our findings suggest that a higher DII was associated with an increased risk of all-cause and CVD mortality among Japanese adults. *J Nutr* 2019;149:1451–1459.

Keywords: Dietary Inflammatory Index, Japan, mortality, cohort study, cardiovascular disease

Introduction

Serum inflammatory markers may be indicators of mortality. Elevated high-sensitivity C-reactive protein (hs-CRP) levels can predict an increased risk of all-cause and cardiovascular disease (CVD) mortality as well as death from several cancers in the general population (1, 2). In the general Japanese population, higher hs-CRP levels were associated with increased risk of CVD mortality (3). Elevated circulating IL-6 levels were also independently associated with greater risk of all-cause and CVD mortality in the general elderly population (4). Furthermore, the inflammatory markers CRP and IL-6 were shown to be affected by dietary intake as 1 of the lifestyle factors (5, 6).

The literature-derived, population-based Dietary Inflammatory Index (DII) was developed as a comprehensive index to assess the effect of dietary factors on 6 inflammatory biomarkers: IL-1 β , IL-4, IL-6, IL-10, TNF- α , and CRP (7). The DII can be used in epidemiological and clinical studies because it can estimate the inflammatory potential of diet using any competent dietary assessment tool. A higher DII was associated with higher levels of IL-6, TNF- α , homocysteine, and hs-CRP (8–11). Moreover, some meta-analyses of previous cohort studies have shown that a higher DII was associated with increased risk of all-cause and CVD mortality and death from several cancers, such as colorectal, breast, lung, and prostate cancer, in the general population (12–15). However,



Green tea consumption and risk of hematologic neoplasms: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study)

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Received: 29 October 2018 / Accepted: 13 August 2019 / Published online: 26 August 2019
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Abstract

Purpose Experimental studies suggested that green tea may have an anticancer effect on hematologic neoplasms. However, few prospective studies have been conducted.

Methods A total of 65,042 individuals aged 40–79 years participated in this study and completed a self-administered questionnaire about their lifestyle and medical history at baseline (1988–1990). Of these, 52,462 individuals living in 24 communities with information on incident hematologic neoplasms available in the cancer registry, who did not have a history of cancer and provided valid information on frequency of green tea consumption, were followed through 2009. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of hematologic neoplasms according to green tea consumption were analyzed.

Results The incidence of hematologic neoplasms during a median follow-up of 13.3 years was 323. Compared with the never-drinkers of green tea, the multivariate HRs and 95% CIs for total hematologic neoplasms in green tea drinkers of ≤ 2 cups/day, 3–4 cups/day, and ≥ 5 cups/day were 0.65 (0.42–1.00), 0.73 (0.47–1.13), and 0.63 (0.42–0.96), respectively. The association was more prominent for acute myeloid leukemias and follicular lymphomas.

Conclusions The present cohort study suggests a protective effect of green tea against hematologic neoplasms, especially acute myeloid leukemias.

Keywords Epigallocatechin-3-gallate · Hematologic neoplasm · Japan collaborative cohort study for evaluation of cancer risk · Preventive medicine · Green tea · Acute myeloid leukemia

Introduction

Experimental studies have suggested that consumption of green tea may prevent various cancers including hematologic neoplasms [1–3]. Green tea constituents such as epigallocatechin-3-gallate (EGCG) induce apoptosis in a variety of cancer cells including human myeloid leukemia cells [4–6]. EGCG induces apoptosis of acute myeloid leukemia cells by increasing the amount of intracellular reactive oxygen species [6]. However, the epidemiologic evidence is limited and controversial. A previous Japanese cohort study showed that a higher frequency of green tea consumption was associated with a lower risk of hematologic neoplasms [7]. Meanwhile, another Japanese cohort study found no significant association between green tea consumption and the risk of acute myeloid leukemia or myelodysplastic syndromes [8]. Case-control studies conducted in Taiwan [9] and China [10] reported that high intake of green tea was associated with lower risk of leukemias such as myeloid leukemia.

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Associations of Daily Walking Time With Pneumonia Mortality Among Elderly Individuals With or Without a Medical History of Myocardial Infarction or Stroke: Findings From the Japan Collaborative Cohort Study

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Received January 15, 2018; accepted June 3, 2018; released online September 22, 2018

ABSTRACT

Background: The association between daily walking and pneumonia mortality, stratified by the presence of disease conditions, such as myocardial infarction (MI) or stroke, was investigated.

Methods: The study participants were 22,280 Japanese individuals (9,067 men and 13,213 women) aged 65–79 years. Inverse propensity weighted competing risk model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for pneumonia mortality.

Results: After a median of 11.9 years of follow-up, 1,203 participants died of pneumonia. Participants who did not have a history of MI or stroke and who walked for 1 hour/day or more were less likely to die from pneumonia (HR 0.90; 95% CI, 0.82–0.98) than those walked for 0.5 hours/day. A similar inverse association of pneumonia and walking (0.5 hours/day) was observed among participants with a history of MI (HR 0.66; 95% CI, 0.48–0.90). Among the participants with a history of stroke, those who walked for 0.6–0.9 hours/day were less likely to die because of pneumonia (HR 0.65; 95% CI, 0.43–0.98).

Conclusions: Regular walking for ≥ 1 hour/day may reduce the risk of pneumonia mortality in elderly individuals with or without cardiovascular disease history.

Key words: walking; pneumonia; influenza; motor activity; epidemiology

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BACKGROUND

Pneumonia is one of the leading causes of death in developed countries ranking sixth and eight in England¹ and North America,² respectively, among all underlying causes of death. Similarly, the combination of pneumonia and influenza ranks third among the leading causes of death in the Japanese elderly population, accounting for more than 561 deaths per 100,000 population annually.³ Indeed, several systematic reviews suggested that age ≥ 65 years is a risk factor of pneumonia.^{4–6} Previous cohort studies showed that walking⁷ or high-intensity physical activities^{8,9} were associated with a decreased risk of pneumonia. However, the elderly population often has underlying chronic diseases, such as myocardial infarction (MI) or stroke, which may prevent them from walking and increase the risk of pneumonia,^{10,11} and the association of walking with pneumonia

may result from a combination of underlying conditions. Therefore, this study aimed to investigate whether daily walking time was associated with pneumonia mortality in Japanese participants aged 65–79 years with or without a medical history of MI or stroke.

METHODS

Study population and data collection

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), which was established in 1988–1990, has been described in detail elsewhere.^{12,13} Briefly, 110,585 inhabitants (46,395 men and 64,190 women) aged 40–79 years from 45 areas in Japan were enrolled into the study. In the present study, the overall number of baseline participants (aged 65–79 years) was 29,956 (12,196 men and 17,760 women). Data were

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The members of the JACC Study Group are provided in the appendix.

Self-Reported Eczema in Relation with Mortality from Cardiovascular Disease in Japanese: the Japan Collaborative Cohort Study

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Aim: Previous studies suggested a positive association between eczema and cardiovascular disease (CVD), probably through enhanced systemic inflammation. However, several studies reported null findings about eczema and CVD, so the evidence is still controversial.

Methods: We asked 85,099 participants (35,489 men and 49,610 women), aged 40 to 79 years, without a history of CVD or cancer at baseline between 1988 and 1990, to complete a lifestyle questionnaire, including information eczema frequency (seldom, sometimes or often).

Results: During the 6,389,818 person-years of follow-up, there were 1,174 deaths from coronary heart disease (CHD), 979 from heart failure, 366 from cardiac arrhythmia, 2,454 from total stroke, 1,357 from ischemic stroke, 1,013 from hemorrhagic stroke, and 201 from aortic aneurysm or dissection. The multivariable-adjusted model showed that individuals who “sometimes” or “often” had eczema had 0.82 (95%confidence interval (CI): 0.69–0.97) or 1.26 (95%CI: 1.01–1.56) times the risk of mortality from CHD, respectively, compared to those who “seldom” did. Individuals who “often” had 1.30 (95%CI: 1.05–1.61) times the risk of mortality from CHD, compared to those who “seldom or sometimes” did. There was no association of eczema with mortality from other CVD, or no interaction between eczema and sex or age, in relation to any CVD mortality risk.

Conclusions: Self-reported frequent eczema was associated with increased risk of mortality from CHD, but not other major CVD, in a Japanese general population. Since steroid usage was not considered, future studies should include it as a potential confounding factor.

See editorial vol. 26: 760-761

Key words: Eczema, Cardiovascular disease, Atherosclerosis, CHD, Population-based study

Introduction

Chronic inflammation is an important risk factor for cardiovascular disease (CVD)¹⁻⁵. Chronic inflammatory diseases, such as systemic lupus erythematosus⁶, rheumatoid arthritis⁷, psoriatic arthritis⁸, and inflammatory bowel disease^{9, 10}, may be associated with an increased risk of CVD.

Eczema, which is also a chronic inflammatory disorder, appears to affect adults as well as children¹¹⁻¹³. Some studies associate eczema with CVD risk, probably through inflammation^{14, 15}. However,

several studies have reported null findings about eczema and CVD^{16, 17}, so the association is still controversial. In addition, existing reports using population-based cohort studies are mainly from Western countries; no Japanese cohort study has investigated the association between eczema and risk of CVD.

Therefore, we aimed to prospectively examine the association of eczema with mortality from several major CVDs, including CHD, heart failure, stroke and aortic aneurysm, using a Japanese population-based cohort study. Furthermore, we examined whether the effect is modified by age or sex.

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Received: August 14, 2018 Accepted for publication: December 12, 2018

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Original Article

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Television Viewing Time and Breast Cancer Incidence for Japanese Premenopausal and Postmenopausal Women: The JACC Study

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Received December 21, 2018

Accepted March 16, 2019

Published Online March 21, 2019

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Purpose

The evidence on effects of TV viewing time among premenopausal and postmenopausal women for breast cancer risk remains controversial and limited.

Materials and Methods

A prospective study encompassing 33,276 (17,568 premenopausal, and 15,708 postmenopausal) women aged 40-79 years in whom TV viewing time, menstrual, and reproductive histories were determined by a self-administered questionnaire. The follow-up was from 1988 to 2009 and hazard ratios (HRs) with 95% confidence intervals (CIs) of breast cancer incidence were calculated for longer TV viewing time in reference to shorter TV viewing time by Cox proportional hazard models.

Results

During 16.8-year median follow-up, we found positive associations between TV viewing time and breast cancer incidence with a borderline significant trend among total women and a significant trend among postmenopausal women. Among total women, the multivariable HRs (95% CIs) for risk of breast cancer in reference to < 1.5 hr/day of TV viewing time were 0.89 (0.59-1.34) for 1.5 to < 3.0 hr/day, 1.19 (0.82-1.74) for 3.0 to < 4.5 hr/day, and 1.45 (0.91-2.32) for ≥ 4.5 hr/day (p for trend=0.053) and among postmenopausal women, the corresponding risk estimates were 1.10 (0.42-2.88), 2.54 (1.11-5.80), and 2.37 (0.92-6.10) (p for trend=0.009), respectively.

Conclusion

Prolonged TV viewing time was associated with increased risk of breast cancer, especially among postmenopausal women.

Key words

Television viewing time, Breast neoplasms, Incidence, Cohort study, Postmenopausal, Body mass index, Japan

Introduction

Television (TV) viewing time is a sedentary time along with less activity and it is an important leisure behavior in women daily routines [1,2]. The average hours spent in watching TV has been reported to be about 5 hr/day in the US adults and 3-4 hr/day in Japanese adults [3,4].

Breast cancer is the most common cancer among Japanese women (19.0% of female cancers) [5], and have markedly

increased in Asia in recent years [6]. Physical activity has been shown inversely associated with risk of breast cancer [5-10]; whereas sedentary behaviors were associated with the increased risk [7,11]. The increased risk of breast cancer with sedentary behaviors was evident for both occupational sitting time [12,13] and leisure sedentary time including TV watching time [11], with a higher risk with the occupational sitting time than leisure sedentary time, as indicated in a meta-analysis of 21 observational studies [14]. However, another meta-analysis of 43 observational studies confirmed