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Association of measles and mumps with cardiovascular disease: The Japan Collaborative Cohort (JACC) study

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ABSTRACT

Objective: Although it has been suggested that exposure to infections during childhood could decrease risk of atherosclerotic cardiovascular disease (CVD), the evidence is scarce. We investigated the association of measles and mumps with CVD.
Methods: 43,689 men and 60,147 women aged 40–79 years at baseline (1988–1990) completed a lifestyle questionnaire, including their history of measles and mumps, and were followed until 2009. Histories of infections were categorized as having no infection (reference), measles only, mumps only, or both infections. Hazard ratios (HR) for mortality from CVD across histories of infections were calculated.
Results: Men with measles only had multivariable HR (95% confidence interval) of 0.92 (0.85–0.99) for total CVD, those with mumps only had 0.52 (0.28–0.94) for total stroke and 0.21 (0.05–0.86) for hemorrhagic stroke, and those with both infections had 0.80 (0.71–0.90) for total CVD, 0.71 (0.53–0.93) for myocardial infarction, and 0.83 (0.69–0.98) for total stroke. Women with both infections had 0.83 (0.74–0.92) for total CVD and 0.84 (0.71–0.99) for total stroke. We also compared subjects with measles only or mumps only (reference) and those with both infections. Men with both infections had 0.88 (0.78–0.99) for total CVD. Women with both infections had 0.85 (0.76–0.94) for total CVD, 0.79 (0.67–0.93) for total stroke, 0.78 (0.62–0.98) for ischemic stroke and 0.78 (0.62–0.98) for hemorrhagic stroke.
Conclusions: Measles and mumps, especially in case of both infections, were associated with lower risks of mortality from atherosclerotic CVD.

1. Introduction

It has been suggested that infection can impact atherosclerotic cardiovascular disease (CVD) either deleteriously or positively [1]. The former proposes that inflammation caused by chronic infections with pathogens such as *Chlamydia pneumonia* and herpes simplex virus type I can accelerate atherosclerosis [1–6]. The latter suggests that infections suffered during childhood can protect from atherosclerosis [1]. The 'hygiene hypothesis' is a possible mechanism underlying this effect [1,7,8]. Improved hygiene decreases the opportunities for infections, which are necessary for normal development of the immune system. Weakened immune systems lead to decreased production, as well as inactivation, of regulatory T cells, which control the balance of T helper cell types, Th1 and Th2. As a result, inflammation at the arterial wall is not well controlled, leading to the development of atherosclerosis. Therefore, people with a history of infections may have a lower risk of CVD, especially atherosclerotic diseases such as stroke and myocardial infarction, compared to those without previous infections. However, to the best of our knowledge, only one previous study, which used a retrospective design and had a small number of participants, has suggested that viral or bacterial infections could protect against CVD [1].

To confirm the protective effect of infections against CVD, this study prospectively examined whether a history of measles and mumps, diseases typically seen in children, alters the risk of mortality from CVD before the era of measles, mumps, and rubella (MMR) vaccination [1,9].

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2. Methods

2.1. Study population

The details of the Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks have been described previously [10]. Briefly, this study conducted a baseline survey from 1988 through 1990 in 45 areas in Japan. Participants completed self-administered questionnaires on their lifestyle and medical history with respect to previous CVD and cancer. The participants comprised 110,585 subjects (46,395 men and 64,190 women) aged 40–79 years. Participants were not vaccinated for measles and mumps, as the MMR vaccine was not introduced in Japan until 1989 [11]. This study excluded 6749 subjects (2706 men and 4043 women) due to missing information on their history of measles and mumps infections. Therefore, a total of 103,836 subjects (43,689 men and 60,147 women) were included in the study. The ethics committees of the Nagoya University School of Medicine and the Osaka University Graduate School of Medicine approved the present study.

2.2. Mortality surveillance

This study conducted systematic mortality surveillance by reviewing death certificates, which were transferred to their respective public health centers. After that, mortality data were gathered at the Ministry of Health and Welfare, where the underlying causes of death were coded for the National Vital Statistics according to the International Classification of Diseases. All deaths within the cohort were ascertained by death certificates from public health centers. Subjects who died after they had moved from their original community were treated as censored cases. The participants were followed up until the end of 2009. In addition to mortality from total CVD, follow-up endpoints included mortality from total stroke, ischemic stroke, hemorrhagic stroke, and myocardial infarction. Death from total CVD was defined as ICD-10 codes I00–I99, total stroke as I60–I69, ischemic stroke as I63 or I69.3, hemorrhagic stroke as I60–I62 or I69.0–I69.2, and myocardial infarction as I21–I23.

2.3. Main exposure: History of measles and mumps

Subjects were asked to provide information about their history of measles and mumps. Specifically, they were asked in the questionnaires, 'Have you ever had the following infectious diseases?: Measles, Mumps'. First, to examine the association of measles and mumps with CVD, participants were classified into the following four groups for comparison: those without a history of measles or mumps (reference group), those with a history of measles only, those with mumps only, and those with a history of both measles and mumps. In addition, to examine whether there is an additional decrease in risk by increased number of infections, we compared participants with a history of a single infection (measles only or mumps only) and those with a history of a double infection (both measles and mumps).

2.4. Potential confounding factors

Potential confounding factors were measured via self-reporting at baseline. They included age (years), body mass index (sex-specific quintiles), history of hypertension (yes or no), history of diabetes (yes or no), history of CVD (coronary heart disease and stroke), family history of CVD (yes or no), alcohol intake (never, ex-drinker, or current drinker with an ethanol intake of 1–22, 23–45, 46–48, or ≥69 g per day), smoking status (never, ex-smoker, or current smoker of 1–19 or ≥20 cigarettes per day), walking frequency (rarely, 30, 30–60, or ≥60 min per day), participation in sports (rarely, 1–2, 3–4, or ≥5 h per week), perceived mental stress (low, medium, or high), and education (elementary school, junior high school, high school, and college or higher).

2.5. Statistical analysis

The person-years of follow-up were calculated from the baseline in 1988–1990 to the first endpoint: death, moving from the community, or the end of follow-up. Multiplicative interactions with sex were tested using a cross-product term. Since there were statistically significant interactions between a history of infections and sex in relation to total stroke and hemorrhagic stroke, sex-specific analysis was conducted. Sex-specific mean values and the prevalence of selected factors were calculated and compared among the four groups using ANOVA and χ^2 tests, respectively. Sex-specific Kaplan–Meier's survival curves for men and women were constructed. Sex-specific hazard ratios (HRs) and their 95% confidence intervals (CIs) of mortality outcomes were calculated after adjustment for age and other potential confounding factors using Cox proportional hazard models. The proportional hazards assumption was tested and was not violated. SAS version 9.3 software (SAS Institute Inc., Cary, NC) was used for statistical analyses. All statistical tests were two-tailed, with values of $P < 0.05$ regarded as significant.

3. Results

Table 1 shows the baseline characteristics with respect to a history of measles or mumps. The higher the number of infections (no infection, measles only or mumps only, and both measles and mumps) in a participant's history was, the younger and less hypertensive both men and women were, the less often they took part in sports, and the higher education level they had. Compared with participants without a history of measles or mumps, those with a history of measles or mumps were more likely to have a family history of CVD and high perceived mental stress. In addition, as for men, the higher the number of infections was, the higher body mass index and the lower prevalence of a history of CVD they had. As for women, those with a history of infections were more likely to have a history of CVD than those without a history of infections.

During 1,690,123 person-years of follow-up of 103,836 subjects (43,689 men and 60,147 women), this study documented 7816 deaths from total CVD (4029 men and 3787 women), 3396 from total stroke (1729 men and 1667 women), 1955 from ischemic stroke (1062 men and 893 women), 1335 from hemorrhagic stroke (612 men and 723 women), and 1212 from myocardial infarction (694 men and 518 women).

Fig. 1 presents the survival curves for each category. The larger decline in survival rate was observed for both men and women without a history of infections than those with a history of infections. Table 2 shows sex-specific, age-adjusted, and multivariable HRs (95% CI) for cause-specific mortality according to infection history. In general, compared with participants without a history of infections, the hazard ratios of cause-specific mortality in those with a history of measles or mumps were likely to decrease. Men and women with measles or mumps displayed significantly lower risks (95% CI) than those without any infection after adjustment for potential confounding factors. It made no difference whether or not a history of CVD was included in potential confounding factors. Men with a history of measles only had hazard ratios of 0.92 (0.85–0.99) for total CVD, those with a history of mumps only had hazard ratios of 0.52 (0.28–0.94) for total stroke and 0.21 (0.05–0.86) for hemorrhagic stroke, and those with a history of both measles and mumps had hazard ratios of 0.80 (0.71–0.90) for