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The Joint Effect of Diabetes and Blood Transfusion on Ischemic Heart Disease Mortality in a Cohort Study in Japan

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Abstract

In order to investigate the joint effect of history of diabetes and blood transfusion on ischemic heart disease mortality, we analyzed data for 7,759 subjects enrolled in a cohort study in Fukuoka Prefecture, Japan. All deaths due to ischemic heart disease were recorded. The Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) of ischemic heart disease with history of diabetes and blood transfusion. We also tested the null hypothesis of the multiplicative model to assess the potential joint effect of these two factors. During 102,800 person-years of follow-up, we observed 66 deaths due to ischemic heart disease. Adjusted HRs of diabetes only as well as transfusion only showed no statistical association, with HRs of 0.93 and 1.18, respectively. In contrast, an increased HR of 9.49 (95% CI: 2.82–32.00) was observed in subjects having both diabetes and blood transfusion, suggesting a positive interaction between them on the risk of death from ischemic heart disease (p=0.02). To conclude: We identified a multiplicative effect of history of diabetes and blood transfusion on the risk of death from ischemic heart disease.

Key words: diabetes, blood transfusion, ischemic heart disease, joint effect

❖ Introduction

In Japan, the mortality rate from cardiovascular disease has shown an ongoing decline over recent decades, but cardiovascular disease nevertheless remains the second leading cause of death following cancer. Interestingly, the mortality rate of ischemic heart disease, the most frequent subtype of cardiovascular disease, has shown a steady increase in the Japanese population[1], and the prevention of this condition must therefore be considered an important public health concern.

Reported risk factors of ischemic heart disease include a combination of various factors, including tobacco smoking, hypertension, and diabetes among

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others[2–5]. Evidence for the association between diabetes and cardiovascular disease in general and ischemic heart disease in particular has been documented[4, 5], with most epidemiological studies showing an approximately two-fold increase in risk for ischemic heart disease in diabetic subjects. Recently, a history of blood transfusion was also shown to significantly increase the risk of death from both stroke and coronary heart disease[6]. To date, however, the joint effect of these two factors on the risk of ischemic heart disease has not been investigated.

Here, we investigated the joint effect of history of diabetes and blood transfusion on the mortality of ischemic heart disease in a prospective cohort study in Japan.

❖ Materials and Methods

Study population

Study subjects were the participants of the Miyako Study, a cohort study conducted in four areas of Fukuoka Prefecture, Japan. Details of the present cohort study have been described elsewhere[7, 8]. Briefly, the baseline survey was conducted from 1986 to 1989. We invited all inhabitants aged 30 to 79 years living in A town, B village, and selected districts of C city and D town (15,417 subjects in total) to participate in a self-administered questionnaire survey. Response rate was 86.1%, equivalent to 13,270 subjects, who constituted the cohort. Baseline characteristics of the subjects were obtained through self-administered questionnaires. All subjects were asked to provide information about health-related factors, including smoking, alcohol, diet, disease history and others.

We then followed these 13,270 subjects for vital status. Data were updated annually with the collaboration of the respective municipal office until the end of 1999 in one of the study areas and until the end of 2003 in the other three. Subjects who moved out of the study areas were censored. For deaths, the underlying cause of death during the study period was ascertained from death certificates and coded according to the International Classification of Diseases and Injuries (ICD), 9th Revision (ICD-9). In the present analyses, we assessed all causes of death through ICD-9 codes, with all deaths due to ischemic heart disease defined as codes 410 to 414.

The research protocol of the study was approved by the Ethics Committee of Medical Care and Research of the University of Occupational and Environmental Health, Kitakyushu, Japan.

Assessment of exposure and other covariates

A history of diabetes and blood transfusion as well as other covariates were assessed using a self-administered questionnaire at the study baseline. Diabetes history was determined based on the response to the question "Have you ever been told you had or received any treatment for diabetes?" and a history of blood transfusion by a positive response to the question "Have you ever had a blood transfusion?".

In addition to age at baseline and sex, the following variables were also considered potential confounders: body mass index (computed as weight in kilograms divided by the square of height in meters), tobacco smoking habit (never smoker, former smoker, current smoker, and missing), alcohol habit (never drinker, daily drinker, occasional drinker, and missing), history of hypertension, daily vegetable consumption and daily fruit consumption, and study area (A town, B village, C city and D town).

Exclusion

One study area (A town) was excluded from analysis because a history of blood transfusion was not investigated (5,098 subjects). We also excluded subjects with a history of stroke (62 subjects), coronary heart disease (244 subjects), or cancer diagnosed before the study baseline (107 subjects). Analysis was thus performed in 7,759 subjects (3,420 males and 4,339 females).

Statistical analysis

The number of person-years of follow-up for each subject was counted from the study baseline until the date of death, date of migration from a study area or end of follow-up, whichever came first. Actual mortality per 100,000 person-years from deaths due to ischemic heart disease was calculated, and 95% confidence intervals (95% CI) were estimated based on the Poisson distribution. Baseline characteristics of all study subjects were compared using the chi-square test for categorical variables and the t-test for continuous variables. The Cox proportional hazards model was then used to estimate hazard ratios (HR) and their 95% CI of mortality for a history of diabetes only, a

Table 1 Characteristics[1] of 7,759 subjects at baseline study

Characteristics	Males	Females	*p* value[2]
Number of subjects	3,420	4,339	
Number of deaths	32	34	0.47
Mean age (SD)[3]	51.3 (13.2)	52.2 (13.6)	0.61
Body mass index (SD)[3]	22.8 (2.7)	22.6 (3.0)	0.83
Current tobacco smoking (%)	49.1	7.4	<0.01
Daily alcohol consumption (%)	47.2	4.3	<0.01
History of hypertension (%)	12.8	12.5	0.73
History of diabetes (%)	5.7	2.6	<0.01
History of transfusion (%)	10.0	8.9	0.10
Daily intake of vegetable (%)	25.6	37.2	<0.01
Daily intake of fruit (%)	6.1	14.6	<0.01

[1]Information obtained through self-reporting in the baseline questionnaire; [2]Test for homogeneity of characteristics between males and females based on chi-square test for categorical variables and t-test for continuous variables; [3]SD: Standard deviation.

history of blood transfusion only, and a history of these factors combined. The multivariate HRs were adjusted for the potential confounding factors mentioned above. Patterns of Schoenfeld[9] residuals with time, considered to identify possible violations of the proportional hazards model, were found to be valid in our analysis. To assess the interaction between the two factors above, we tested the null hypothesis of the following multiplicative model:

$$HR_{AB} = (HR_A \times HR_B) / HR_{00},$$

where HR_{00} was the background HR of subjects unexposed to either A and B factor, assumed to be equal to one (reference); HR_A and HR_B were the observed HRs of subjects exposed to A or to B factor only, respectively; and HR_{AB} was the observed HR of subjects exposed to both A and B factor.

All statistical analyses were performed using the Stata version 9.0 software package (Stata Corporation, USA)[10]. All *p* values and confidence intervals were based on two-sided tests.

❖ Results

A total of 102,800 person-years were counted over an average of 13.8 years of follow-up in 7,759 subjects. Thirty-two deaths from ischemic heart disease occurred in males and 34 in females. Table 1 shows selected characteristics of study participants at baseline by sex. Among them, 5.7% of males and 2.6% of females reported a history of diabetes, and 10.0% and 8.9% reported a history of blood transfusion, respectively. No sex differences were seen for age or body mass index (p=0.61 and 0.83, respectively). Proportion for current tobacco use as well as daily alcohol intake were much higher in males than females (p<0.01), whereas females tended to consume more vegetables and fruit (p<0.01). No sex differences were seen in proportions of hypertension or blood transfusion history (p=0.73 and 0.10, respectively), but a higher proportion of diabetes was seen in males (p<0.01).

Table 2 presents the number of deaths due to ischemic heart disease and age-specific mortality rate per 100,000 person-years. No deaths occurred among those aged 30 to 39 years, while most deaths occurred at age 60 and over.

Table 3 shows the ischemic heart disease mortality rate per 100,000 person-years for subjects having diabetes only, blood transfusion only, both, or neither, as well as the multivariate HRs compared to those with neither. The multivariate HR of diabetes only as well as of transfusion only showed no statistical association, with HRs of 0.93 and 1.18, respectively. In contrast, subjects having both diabetes and blood transfusion had an increased HR of 9.49 (95% CI: 2.82–32.00). The observed effect of these factors (HR=9.49) was greater than the anticipated multiplicative effect that would be expected to be about 1.18 × 0.93 = 1.10, suggesting a positive interaction between them on the risk of death from ischemic heart disease (p-value for rejecting the multiplicative model

Table 2 Age-specific mortality (95% CI[1]) per 100,000 person-years of ischemic heart disease among 7,759 subjects

Age at death	Person-years	No of deaths	Mortality (95% CI)
30–39	7,884	0	–
40–49	23,084	3	13 (3–37)
50–59	26,687	4	15 (4–38)
60–69	23,869	14	59 (32–98)
70–79	15,475	15	97 (54–159)
≥ 80	5,801	30	517 (349–738)
Total	102,800	66	64 (50–81)

[1]CI: confidence interval estimated based on the Poisson distribution.

Table 3 Mortality rate per 100,000 person-years and adjusted hazards ratios (HR[1]) of diabetes and transfusion and their joint effect on the death from ischemic heart disease

	Without diabetes		With diabetes	
	Without transfusion	With transfusion	Without transfusion	With transfusion
Number of deaths	53	7	3	3
Number of subjects	6,757	695	271	36
Person-years	90,455	8,669	3,326	350
Mortality rate (95% CI)	59 (44–77)	81 (32–166)	90 (19–263)	857 (176–2,505)
Age-,sex-adjusted HR (95% CI)	1.00 (reference)	1.12 (0.51–2.46)	1.04 (0.32–3.34)	9.68 (2.93–32.03)
Multivariate HR (95% CI)	1.00 (reference)	1.18 (0.54–2.61)	0.93 (0.29–3.00)	9.49 (2.82–32.00)[2]

[1]Multivariate HR adjusted for sex, age, body mass index, tobacco smoking habit, alcohol habit, history of hypertension, vegetable and fruit intake, and study area; [2]Observed effect of diabetes and blood transfusion (HR=9.49) was greater than anticipated multiplicative effect (1.18 × 0.93 = 1.10), suggesting a multiplicative effect with p=0.02 for rejecting the multiplicative model.

was 0.02).

With regard to the importance of hypertension history as a risk factor for this condition, 12.8% and 12.5% males and females, respectively, reported a history of hypertension. The multivariate HR reflecting the risk of blood hypertension in the study was 2.67 (1.58–4.49) (data not shown).

❖ Discussion

In this study, we examined the joint effect of diabetes and blood transfusion on the mortality of ischemic heart disease in a prospective cohort study in Japan. To our knowledge, this study is the first to report a multiplicative effect between these two factors on the risk of this condition.

Our results showed no significant association with ischemic heart disease mortality in subjects having diabetes or blood transfusion only. In contrast, a number of epidemiological studies have reported a significant association between ischemic disease and diabetes, with patients with both having an approximately two-fold increase in the risk of death of coronary heart disease[3, 11]. Complications are common in long-term diabetes patients, including atherosclerosis, and the occurrence of ischemic heart disease in these patients is therefore likely. With regard to a history of blood transfusion, in contrast, we found only one cohort study in Japan showing a significant increase in the risk of stroke as well as cardiovascular disease[6]. The authors speculated on the involvement of transfusion-mediated immunomodulation and chronic inflammation caused by various transfusion-transmitted infectious agents, but the mechanisms underlying this putative association are not well understood. A number of studies have suggested that allogeneic blood transfusion has immunosuppressive effects in recipients[12–14], and hence may increase the risk of hypertension or atherosclerosis, both of which are known as traditional risk factors for ischemic heart

disease. In addition, treatment involving blood transfusion has been considered a major transmission route for hepatitis C virus (HCV)[15]. The screening of donated blood for HCV began with a first generation assay in 1989, and an association between a history of blood transfusion before 1990 and liver cancer has been reported[15].

The concept of joint effect of two factors has been somewhat controversial in the epidemiologic literature[16, 17]. The selection of an additive or multiplicative model to estimate the interaction should be done in accordance with the way that risk is measured, with absolute risk requiring an additive model and relative risk a multiplicative model[17]. In this study, we used the Cox regression, an implicitly exponential model, to compare the probability of events in the exposed and unexposed groups. Hence, this is inherently a multiplicative model.

The findings of this study have important clinical consequences; specifically, they should be considered in any decision to conduct blood transfusion in diabetic subjects. When considered essential, the use of derived blood products in place of whole blood is recommended.

The major strength of this study was its prospective design and conduct among a general population. Exposure information was collected before the subsequent diagnosis of any ischemic heart disease, avoiding the exposure recall bias inherent to case-control studies.

A limitation of the study was its assessment of risk factors as well as other covariates at baseline by self-questionnaire only. We did not carry out glucose tolerance testing to confirm diabetes. Moreover, no information was available on abnormal blood lipids. High levels of total cholesterol, LDL-cholesterol and triglycerides increase the risk of this condition. Further, a history of blood transfusion was not investigated in one study area (A town), which led to the exclusion of one-third of the study population. Thus, selection bias may have occurred.

In summary, we identified a multiplicative effect of a history of diabetes and blood transfusion on the risk of death from ischemic heart disease. Because this is the first investigation to examine the joint effect of these factors, the findings need to be confirmed in additional cohort studies.

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❖ References

1) Health and Welfare Statistics Association: Journal of Health and Welfare Statistics. Vol. 47. Tokyo: Health and Welfare Statistics Association; 2000.
2) Martiniuk AL, Lee CM, Lam TH, et al.: The fraction of ischaemic heart disease and stroke attributable to smoking in the WHO Western Pacific and South-East Asian regions. Tob Control 15, 181–188 (2006).
3) Woodward M, Zhang X, Barzi F, et al.: The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. Diabetes Care 26, 360–366 (2003).
4) Chyun DA, Young LH: Diabetes mellitus and cardiovascular disease. Nurs Clin North Am 41, 681–695 (2006).
5) Resnick HE, Howard BV: Diabetes and cardiovascular disease. Annu Rev Med 53, 245–267 (2002).
6) Yamada S, Koizumi A, Iso H, et al.: History of blood transfusion before 1990 is a risk factor for stroke and cardiovascular diseases: the Japan collaborative cohort study (JACC study). Cerebrovasc Dis 20, 164–171 (2005).
7) Mizoue T, Tokui N, Nishisaka K, et al.: Prospective study on the relation of cigarette smoking with cancer of the liver and stomach in an endemic region. Int J Epidemiol 29, 232–237 (2000).
8) Pham TM, Fujino Y, Ide R, et al.: Prospective study of vegetable consumption and liver cancer in Japan. Int J Cancer 119, 2408–2411 (2006).
9) Kleinbaum DG: Survival Analysis. A self-Learning Text. New York: Springer; 1997.
10) StataCorp: Stata Statistical Sofware: Release 9. College Station. Texas; 2005.
11) Stamler J, Vaccaro O, Neaton JD, et al.: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor

Intervention Trial. Diabetes Care 16, 434–444 (1993).
12) Blumberg N, Heal JM: Immunomodulation by blood transfusion: an evolving scientific and clinical challenge. Am J Med 101, 299–308 (1996).
13) Brand A: Immunological aspects of blood transfusions. Blood Rev 14, 130–144 (2000).
14) Klein HG: Immunomodulatory aspects of transfusion: a once and future risk? Anesthesiology 91, 861–865 (1999).
15) Fujino Y, Mizoue T, Tokui N, et al.: A prospective study of blood transfusion history and liver cancer in a high-endemic area of Japan. Transfus Med 12, 297–302 (2002).
16) Ahlbom A, Alfredsson L: Interaction: A word with two meanings creates confusion. Eur J Epidemiol 20, 563–564 (2005).
17) Darroch J: Biologic synergism and parallelism. Am J Epidemiol 145, 661–668 (1997).