American Journal of Epidemiology

Vol. 152, No. 7
Printed in U.S.A.

Influenza Vaccination and the Risk of Primary Cardiac Arrest

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Influenza epidemics are associated with an excess of mortality not only from respiratory diseases but also from other causes, and cardiovascular mortality increases abruptly during influenza epidemics, with little evidence of a lag period. In a population-based case-control study, the authors examined whether influenza vaccination was associated with a reduced risk of out-of-hospital primary cardiac arrest (PCA), a major contributor to cardiovascular mortality in the community. Cases of PCA (n = 342) without prior heart disease or life-threatening comorbidity that occurred in King County, Washington, were identified from paramedic incident reports from October 1988 to July 1994. Demographically similar controls (n = 549) were identified from the community by using random digit dialing. Spouses of subjects were interviewed to assess treatment with influenza vaccine during the previous year and other risk factors. After adjustment for demographic, clinical, and behavioral risk factors, influenza vaccination was associated with a reduced risk of PCA (odds ratio = 0.51, 95 percent confidence interval: 0.33, 0.79). The authors suggest that while the association of influenza vaccination with a reduced risk of PCA is consistent with cohort studies of influenza vaccination and total mortality, further studies are needed to determine whether the observed association reflects protection or selection. *Am J Epidemiol* 2000;152:674–7.

cardiac arrest; influenza; vaccination

Influenza epidemics are associated with excess morbidity and mortality, not only from respiratory diseases but also from other causes (1–4), and influenza vaccination is recommended to prevent these clinical outcomes (5). The contribution of influenza to clinical events, including clinical cardiovascular diseases, frequently is not recognized (6, 7). The number of deaths attributable to influenza but assigned another cause far exceeds the number of deaths registered as related to influenza (8). In a meta-analysis of 20 cohort studies among the elderly, the pooled estimate of influenza vaccine efficacy for preventing death was 68 percent (95 percent confidence interval (CI): 56 percent, 76 percent) (9).

Previous studies did not examined whether influenza vaccination is associated with reduced cardiovascular mortality. Because cardiovascular mortality increases abruptly during influenza epidemics, with little evidence of a lag period, we analyzed data from a population-based case-control study to determine whether influenza vaccination during the previous year was associated with a reduced risk of primary cardiac arrest (PCA), a major contributor to cardiovascular mortality in the community.

MATERIALS AND METHODS

Study setting

Details of the study design and data collection are presented elsewhere (10). Briefly, from paramedic incident reports, cases of out-of-hospital PCA attended by paramedics in King County, Washington, from October 1988 to July 1994 were identified. PCA cases were defined by the occurrence of a sudden pulseless condition and the absence of evidence of a noncardiac condition as the cause of cardiac arrest (11). In addition to emergency service incidence reports, we reviewed death certificates, medical examiner reports, and autopsy reports, when available, to confirm the absence of evidence of a noncardiac condition, such as pneumonia, asthma, or respiratory failure, as the cause of cardiac arrest. As expected, medical examiner reports with or without autopsy reports were available for only 23 percent of the cases.

Selection of cases and controls

We excluded PCA cases if they had had prior clinically recognized heart disease, such as angina pectoris, myocardial infarction, coronary bypass surgery and graft, angio-

Received for publication August 12, 1999, and accepted for publication January 12, 2000.

Abbreviations: CI, confidence interval; PCA, primary cardiac arrest.

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plasty, congestive heart failure, arrhythmias, cardiomyopathy, congenital or valvular disease, or life-threatening comorbidities, such as cancer or end-stage lung, liver, or renal disease. Since we relied on information from surrogate respondents to assess previous exposures, we further restricted the PCA cases to patients who were married and were aged 25–74 years. The spouses of 360 (86 percent) of the 418 eligible cases agreed to participate in an in-person interview. The mean age of the cases was 59 years, 80 percent were male, 94 percent were White, and 61 percent had at least a high school education.

For each PCA case, one to two controls, matched for age (within 7 years) and sex, were selected from the community by using random digit dialing (12). Potential controls who had had previous clinically recognized heart disease or life-threatening comorbidity or who were not married were excluded from the study. The spouses of 576 (71 percent) of the 816 eligible controls identified by random digit dialing participated in the in-person interview.

Data collection

Data on the subjects' vaccination status were collected from both case and control spouses by using a standardized questionnaire. For each subject, information was collected on whether the subject had received an influenza vaccination during the previous 12 months and, if so, when the vaccination had been given. We did not collect information on whether the subject had received influenza vaccination during the years prior to that period.

The interview also covered other risk factors for PCA, including age, sex, race, weight, and height; physician-diagnosed diabetes mellitus, hypertension, and hypercholesterolemia; cigarette smoking; physical activity; alcohol and caffeine consumption; dietary intake of saturated fat and n-3 fatty acids from seafood; family history of myocardial infarction or sudden death in a first-degree relative; education; employment; and general health status (10).

To assess the reliability of spouse reports, we interviewed 56 survivors of PCA and their spouses and 531 controls and their spouses independently (13). There was excellent agreement between the influenza vaccination reports of spouses and those obtained from subjects themselves (for cases, kappa = 1.0, 95 percent CI: 1.0, 1.0; and for controls, kappa = 0.88, 95 percent CI: 0.85, 0.93). The agreement for other risk factors was good to excellent (13).

Statistical analysis

We used conditional logistic regression to assess the association of influenza vaccination during the previous year with the risk of PCA after adjustment for potential confounding factors. We also explored whether the association varied according to the presence of other risk factors. Eighteen cases and 32 controls were excluded from the analyses due to missing data on influenza vaccination status. The effect of missing data on covariates was examined through the approach of multiple imputation (14), and the missing data had little effect on the findings.

RESULTS

Controls who were vaccinated were older; were more likely to have had hypertension, diabetes, and a family history of myocardial infarction or sudden death; and were more likely to be a former smoker, but were less likely to be male and currently employed than were controls who were not vaccinated (table 1). Vaccinated controls also expended more kilocalories in physical activity, weighed less, and consumed less caffeine than did unvaccinated controls. On the other hand, the prevalences of current smoking, good-to-excellent reported health status, and higher educational attainment (for both controls and their spouses) and the amount of alcohol consumed were similar among vaccinated and unvaccinated controls.

The prevalence of influenza vaccination during the previous year was lower among the cases of PCA than among the controls (23 vs. 32 percent, respectively) (table 2). After adjustment for the matching variables (age and gender) and current smoking, former smoking, hypertension, diabetes, weight, height, family history, educational attainment, employment status, habitual physical activity, fat intake, and general health status, influenza vaccination during the previous year was associated with a reduced risk of primary cardiac arrest (odds ratio = 0.51, 95 percent CI: 0.33, 0.79). Further adjustment for alcohol and caffeine consumption, n-3 polyunsaturated fatty acid intake, and race altered the findings only slightly.

There was little evidence that the association between influenza vaccination and the risk of PCA varied among

TABLE 1. Clinical characteristics associated with influenza vaccination, King County, Washington, October 1988 to July 1994

Clinical characteristic†	Influenza vaccination‡	
	Yes (*n* = 174)	No (*n* = 375)
Age (years (mean) (SD§))	63 (9)	56* (10)
Male (%)	71	82*
Current smoker (%)	9	11
Former smoker (%)	49	40*
Hypertension (%)	34	20*
Diabetes mellitus (%)	6	2*
Family history (%)	45	37
Weight (pounds¶ (mean) (SD))	175 (35)	179 (34)
Health status ≥ good (%)	94	96
Education > high school (%)	78	77
Spouse education > high school (%)	76	74
Employed (%)	48	74
Physical activity (kcal/week (mean) (SD))	1,431 (1,415)	1,234 (1,691)
Fat intake scale score (mean (SD))	21 (4)	21 (4)
Dietary n-3 intake (mean g/month (SD))	6 (6)	5 (5)
Alcohol consumption (mean g/day (SD))	11 (15)	11 (20)
Caffeine consumption (mean mg/day (SD))	283 (300)	352 (447)

* $p < 0.05$.

† There were missing values for smoking (*n* = 2), hypertension (*n* = 6), diabetes mellitus (*n* = 2), family history (*n* = 3), weight (*n* = 44), and fat intake scale (*n* = 22).

‡ During prior year among controls.

§ SD, standard deviation.

¶ 1 pound = 0.454 kg.

TABLE 2. Influenza vaccination during the previous year and risk of primary cardiac arrest, King County, Washington, October 1988 to July 1994*

Influenza vaccination	Cases (%) (n = 342)	Controls (%) (n = 549)
Yes	23	32
No	77	68

* Odds ratio = 0.51, 95% CI: 0.33, 0.79. Adjusted for matching factors (age and gender), current smoking, former smoking, hypertension, diabetes, weight, height, habitual physical activity, saturated fat intake, family history of myocardial infarction or sudden death, educational attainment, employment, and general health status.

subjects with other risk factors, including older age, male gender, cigarette smoking, hypertension, diabetes, low educational attainment, unemployed status, and fair or poor health status (data not shown), although the statistical power to assess potential interactions between vaccination and other risk factors was limited.

DISCUSSION

Several limitations need to be considered when interpreting these findings. Treatment with influenza vaccination during the previous year was assessed through spouse reports, and medical records were not available to validate these reports. However, the reliability of spouse reports was excellent for both cases and controls. Additionally, we did not assess influenza vaccination in previous years, and, therefore, we could not assess the impact of previous vaccinations.

We sought to minimize potential confounding in both the design and the analysis of the study data, but it remains possible that uncontrolled confounding accounted for our findings. For example, if influenza vaccination was associated with unmeasured differences in health care or health behaviors that reduce the risk of PCA, these differences might account for our findings. Nevertheless, given the available information on potential confounders and the magnitude of the observed effect, we suggest that it is unlikely that uncontrolled confounding accounted for the finding.

The focus of our study was on persons who experienced PCA as their incident clinical cardiac event, in part to minimize potential confounding from previous heart disease. For this reason, we restricted our study population to persons without previous clinically recognized heart disease and life-threatening comorbidity. On the other hand, persons at risk for incident clinical coronary heart disease because of older age, diabetes mellitus, and other risk factors were included in the study population. For these reasons, our findings do not address whether influenza vaccination is associated with a reduced risk of PCA among patients with clinically recognized heart disease or major comorbidity.

To our knowledge, this is the first study to examine the association of previous influenza vaccination with the risk of primary cardiac arrest. However, the magnitude of the risk reduction observed herein is consistent with a meta-analysis of studies that examined the effect of influenza vaccination on total mortality (9). Additionally, a population-based study demonstrated an association between recent acute respiratory tract infection and the risk of acute myocardial infarction (15).

Finally, there are plausible mechanisms related to both the respiratory and systemic effects of influenza for a possible association (16). For example, influenza impairs pulmonary function and, thus, may reduce myocardial oxygen supply, and it also results in systemic effects, such as fever and tachycardia, that increase myocardial oxygen demand (17). Additionally, influenza may influence risk through the inflammatory response to the infection, either systemically through an effect on inflammatory markers or locally through changes in the heart, such as subclinical myocarditis (18).

For now, additional epidemiologic studies, particularly among older populations and other persons at risk for PCA, are needed to explore further whether the observed association of influenza vaccination with a reduced risk of PCA reflects selection or protection. If confirmed in other studies and other populations, the association is likely to have important implications for clinical care and public health, given the magnitude of the effect and the contribution of PCA to coronary heart disease mortality, particularly among high-risk populations.

ACKNOWLEDGMENTS

Supported by grants from the National Heart, Lung, and Blood Institute (HL-41993), the University of Washington Clinical Nutrition Research Unit (DK-35816), and the Medic One Foundation, Seattle, Washington.

Presented in part at the 4th International Conference on Preventive Cardiology, Montreal, Quebec, Canada, March 1997.

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