의학석사 학위논문

The impact of lifestyle behaviors on the acquisition of pandemic (H1N1) 2009 influenza infection: a case-control study

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2013 년 2 월

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A thesis of the Degree of Master of Science

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The impact of lifestyle behaviors on the acquisition of pandemic (H1N1) 2009 influenza infection: a case-control study

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ABSTRACT

Introduction: A novel strain of influenza A H1N1 identified in Mexico and the United States (U.S.) in 2009 spread globally. There is not much data about which people have increased susceptibility to H1N1 infection among the healthy population. The aim of this study was to compare lifestyle behaviors and health habits in subjects with and without a diagnosis of the pandemic 2009 influenza (H1N1) virus infection.

Methods: We conducted a case-control study in a secondary care hospital in South Korea between November 2009 and August 2010. We enrolled cases with H1N1 infection confirmed by a positive result of real-time reverse transcriptase polymerase chain reaction (RT-PCR); in addition, four age- and sex-matched controls with no history of H1N1 infection or severe acute respiratory illness during the H1N1 pandemic in South Korea, were enrolled (1:4 matching).

Results: During the study period, 34 cases and 136 age- and sex-matched controls were enrolled. The history of contact with H1N1 patients was more predominant among the cases than the controls ($p<0.001$). The case group had a significantly higher percentage of current smoker ($p=0.004$) and a lower frequency of regular physical activity compared to the control group ($p<0.001$). The case group also reported regular vitamin intake per week less than that of the control group. In the multivariable analysis, when history of contact with H1N1 patients was adjusted for, current smoker (adjusted OR

4.418, 95% CI 1.012-19.256; p=0.048) and regular physical activity (adjusted OR 0.051, 95% CI 0.012-0.209; p<0.001) were independently associated with H1N1 infection.

Conclusions: This study shows that regular physical activity has an effect of preventing H1N1 infection and current smokers have increased risk of H1N1 infection

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Keywords: influenza A virus, H1N1 subtype, life style, exercise, smoking

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CONTENTS

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LIST OF ABBREVIATIONS

BMI body mass index

CDC Centers for Disease Control and Prevention

RT-PCR real-time reverse transcriptase polymerase chain reaction

URTI upper respiratory tract infection

U.S. United States

INTRODUCTION

A novel strain of influenza A H1N1 identified in Mexico and the United States (U.S.) in 2009 spread globally, and many countries experienced their first wave of infection from the spring of 2009 to the end of 2009 (1). The cumulative number of infected people has increased rapidly and the Centers for Disease Control and Prevention (CDC) estimated that 60 million cases of pandemic H1N1 occurred in the U.S. since the spring of 2009 (2).

It appeared that the risk factors for severe disease following H1N1 virus infection were similar to those for seasonal influenza infection which include chronic medical conditions, some cognitive conditions, and immunodeficiency after a series of teleconferences organized by the World Health Organization (3). In addition, several new risk factors such as pregnancy (4), obesity, and tuberculosis (5, 6) were also detected. However, there is not much data about which people have increased susceptibility to H1N1 infection among the healthy population.

Several studies have showed that lifestyle behaviors such as cigarette smoking, physical activity, and stress have an impact on respiratory infections. Cigarette smoking is well known to be a major risk factor for respiratory tract infections. The mechanism of increased susceptibility to infections in smokers is multifactorial, and one of the mechanism is alteration of the structural and immunological host defenses (7). An association between physical activity and upper respiratory infection also has been documented. Nieman suggested that moderate levels of physical activity are associated with a reduced risk of upper respiratory tract infection (8). In addition, chronic stress is known to be associated with suppression of both cellular and humoral measures of immune function (9), and self-reported perceived stress is associated with an increased

risk of upper respiratory tract infection (10). However, there is no research about the relationship between lifestyle behaviors and H1N1 infection.

The aim of this study was to compare lifestyle behaviors (smoking, alcohol consumption, physical activity, and sleep time) and health habits such as use of vitamin supplements in subjects with and without a diagnosis of H1N1 virus infection.

PATIENTS AND METHODS

1. Participants

A case-control study was conducted at the Seoul Metropolitan Government Seoul National University Boramae Medical Center, a secondary care hospital in South Korea. Between November 2009 and March 2010, cases aged 18 years or over with pandemic 2009 influenza (H1N1) virus infection confirmed by a positive result from real-time reverse transcriptase polymerase chain reaction (RT-PCR) with a nasopharyngeal or oropharyngeal swab among patients who had visited the hospital because of suspicion of influenza were enrolled. We recruited four age and sex-matched controls for each confirmed case of H1N1 influenza from one high school, one college, healthcare personnel, and adults who visited the same hospital for health screening between June 2010 and August 2010. Controls had no history of H1N1 infection or severe acute respiratory illness from September 2009 to March 2010 (the period of H1N1 pandemic in South Korea) by self-reports. All participants signed a written informed consent sheet and agreed to participate in the study.

2. Analysis

All participants were asked to fill out a questionnaire. It asked participants about demographic information such as age, sex, height, body weight, body mass index (BMI) and co-morbidities, and whether they had a history of contact with H1N1 patients or not and how often they had experienced common cold a year. It also evaluated lifestyle behaviors such as smoking status, alcohol intake (frequency per week and amount), physical activity

(type, frequency per week, and duration), stress (numeric rating scale), and sleeping duration (wake-up time and bedtime) and health habits such as the use of vitamin supplements (type and frequency per week) and frequency of meal relating to nutritional status. Variables on the questionnaire were compared between the cases and the controls with the Student's *t* test or the Mann-Whitney *U* test for continuous variables and with the χ^2 test or Fisher's exact test for categorical variables in univariate analyses. Multivariable logistic regression analysis was also done. A *p* value of less than 0.05 was regarded statistically significant. Statistical analyses were done with SPSS 17.0(Chicago, IL, USA) and STATA 11.1 (StataCorp, Tex, USA).

RESULTS

During the period of the enrollment, 34 cases diagnosed as H1N1 infection by RT--PCR and 136 age--and sex--matched controls were enrolled. The median age was 41 years (range, 18 to 72) and 58.9% were female. Table 1 shows the baseline characteristics among the cases and the controls. There were no significant differences in the body mass index, comorbid diseases (diabetes mellitus, hypertension and asthma), and in the frequency of the common cold per year between the two groups. There were no pregnant women. The history of contact with H1N1 patients was more predominant among the cases than the controls. (p<0.001)

Table 1. Baseline characteristics

	Case No. = 34	Control No. = 136	p value
Age (median, range)	41 (18-76)	41 (19-72)	0.668[a]
Male Sex (%)	15 (44.1)	60 (44.1)	1.000[b]
Height (mean ± SD)	163.6±8.6	165.9±8.6	0.179[a]
Weight (mean ± SD)	62.1±10.0	63.4±12.0	0.524[a]
BMI, Kg/m2 (mean ± SD)	22.4±5.1	22.4±4.7	0.998[a]
Hypertension (%)	3 (9.4)	13 (10.1)	0.999[d]
Diabetes mellitus (%)	2 (6.3)	1 (0.8)	0.101[d]
Asthma (%)	2 (6.3)	2 (1.6)	0.177[d]
History of contact with H1N1 patients	20 (58.5)	12 (8.8)	<0.001[b]
Common cold, freq/year (median, IQR)	2.7 (1-3)	2.2 (1-2.4)	0.073[c]

No.: Number
SD: standard deviation
IQR: interquartile range
a: Student's *t*-test
b: Chi-square test
c: Mann-Whitney U test
d: fisher's exact test

With regard to lifestyle behaviors and health habits, the case group had a significantly higher percentage of current smokers (p=0.004) (Table 2). The case group also had a lower frequency of regular physical activity compared to the control group (p<0.001), and there was an inverse trend between the frequency of regular physical activity and the acquisition of H1N1 infection (p for trend<0.001, Figure 1). Physical activities included weight training (23.6%), walking (20%), golf (16.4%), running (10.9%), climbing (10.9%), and swimming (9.1%)

Table 2. Lifestyle behaviors and health habits

	Case No.=34	Control No.=136	p value
Smoking			
Current smoker (%)	12 (35.3)	18 (13.7)	0.004[b]
Pack-year, median (IQR)	5.7 (0-8.4)	2.9 (0-0)	0.268[c]
Physical activity			
Frequency per week, median (IQR)	0.6 (0-1)	2.5 (1-4)	<0.001[c]
≥ Once a week (%)	8 (26.7)	51 (85)	<0.001[a]
≥ Three times a week (%)	2 (6.7)	30 (50)	<0.001[a]
Use of vitamin supplements (%)	13 (41.9)	64 (77.1)	<0.001[a]
Frequency per week, median (IQR)	0 (0-3)	3 (1-7)	0.001[b]
Meal			
Frequency per day, median (IQR)	2.7 (2-3)	2.7 (2-3)	0.855[c]
Three times a day (%)	23 (69.7)	93 (69.9)	0.980[a]
Alcohol intake (g/day)			
g/day, median (IQR)	6.2 (0-10.8)	8.0 (0-9.9)	0.925[c]
Frequency per week, median (IQR)	0 (0-1.5)	0 (0-2)	0.828[c]
Sleep time (hour/day)			
Duration (hour/day), median (IQR)	6.52 (6-7.9)	6.6 (6 -7)	0.480[c]
Go to bed after 0AM (%)	10 (30.3)	27 (20.9)	0.252[a]
Stress (numeric rating scale, 0-10)	5.7±1.9	5.3±2.1	0.287[a]

a: Student's t-test
b: Chi-square test
c: Mann-Whitney U test

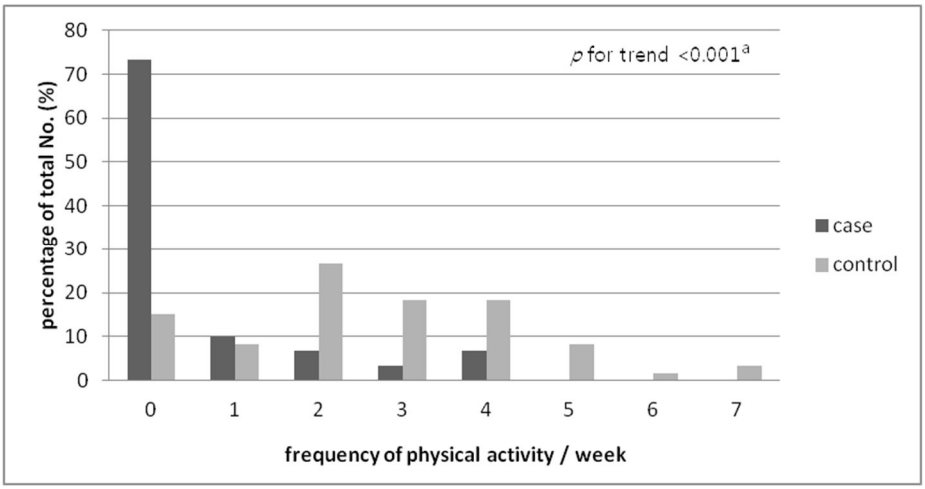

Figure 1. Relationship between physical activity and H1N1 infection

The case group had a lower frequency of regular physical activity compared to the control group (p<0.001), and there was an inverse trend between the frequency of regular physical activity and the acquisition of H1N1 infection (p for trend<0.001).
a: Trend tests were done by using STATA command 'tabodds'.

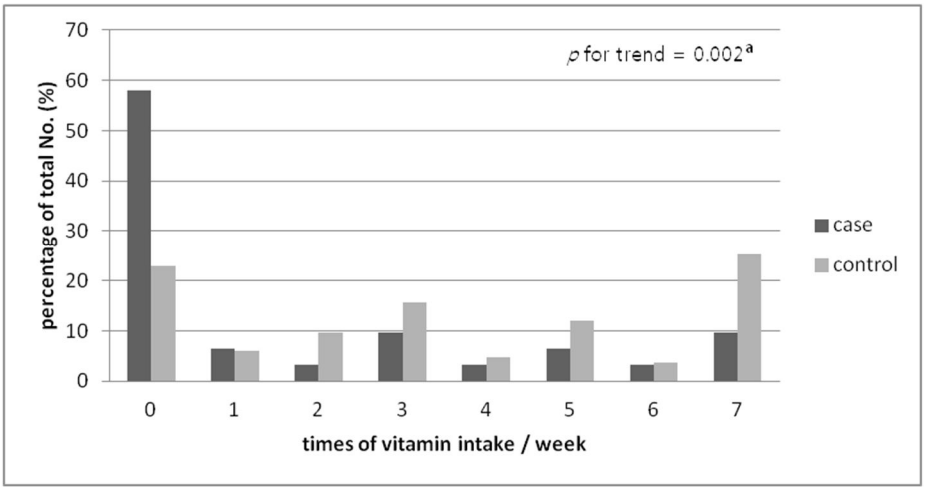

Figure 2. Relationship between vitamin intake and H1N1 infection

The cases reported more often regular vitamin intake per week than the controls, and there was an inverse trend between the frequency of vitamin intake and the acquisition of H1N1 infection (p for trend=0.002).
a: Trend tests were done by using STATA command 'tabodds'.

The cases also reported regular vitamin intake per week more than the controls (Table 2), and there was an inverse trend between the frequency of vitamin intake and the acquisition of H1N1 infection (p for trend=0.002, Figure 2).

There were no significant differences found for the frequency of meals per day, alcohol intake, stress intensity, and sleep time (Table 2).

In multivariable analysis, when history of contact with H1N1 patients (adjusted OR 10.630, 95% CI 2.674-42.260; p=0.001) was adjusted for current smoker (adjusted OR 4.418, 95% CI 1.014-19.256; p=0.048) and regular physical activity (at least once per week) (adjusted OR 0.051, 95% CI 0.012-0.209; p<0.001), they were independently associated with H1N1 infection (Table 3).

Table 3. Multivariable analysis to identify independent preventive or risk factors of H1N1 infection acquisition

Variable	p-value	OR[a]	95% CI
History of contact with influenza patients	0.001	10.630	2.674-42.260
Regular physical activity	<0.001	0.051	0.012-0.209
Current smoking	0.048	4.418	1.014-19.256
Use of vitamin supplements	0.992	0.994	0.275-3.586

OR: odds ratio
CI: confidence interval
a: multivariable logistic regression

DISCUSSION

In our case-control study, regular physical activity and smoking were associated with acquisition of H1N1 infection. Our study compared lifestyle behaviors and health habits in people with and without H1N1 infection. Although there have been various studies evaluating the impact of lifestyle in patients with respiratory disease such as chronic bronchitis, emphysema, and upper respiratory infection, to our knowledge, there has been no study about those in patients with H1N1 infection.

Previous studies have reported the beneficial effects of physical activity on H1N1 infection or other upper respiratory tract infection (URTI), in which the mechanism has been explained by the immunological effects of exercise. Previous studies suggested that exercise was associated with a lesser decline in circulating T cell function related to viral clearance , specific antibody production and neuroendocrinological changes in immune system.(11-15).. However, there are also studies suggesting contrary results such as a J-curve relationship (8). The J-curve relationship means that as the amount of exercise increases, the risk decreases initially but increases after some level (8). In our study, we were able to find the beneficial effects of physical activity on H1N1 infection, which supports the results of earlier studies (8, 16). People who reported regular physical activity at least once per week had a significantly lower chance of acquiring H1N1 infection in our study (adjusted OR 0.051, 95% CI 0.012-0.209; $p<0.001$). Median frequency of physical activity in the control group was higher than that in the case group, at 2.5 and 0.6 per week, respectively ($p<0.001$), and there was a significant trend for a decreased risk in H1N1 acquisition as the frequency of the physical activity per week increased (p for trend <0.001), although there were no subjects, in our study,

whose physical activity level corresponded to that of a marathon runner who had an increased risk of URTI in the study suggesting the J-curve relationship (8).

Current smoking was another independent risk factor for H1N1 infection in our study. It was comparable to previous studies evaluating the relationship between smoking and influenza (17). Kark et al. showed that female smokers in the Israeli Army had a 60% risk of influenza compared to 41.6% in nonsmokers (OR 1.44, 95% CI 1.03-2.01) (18). They also described in another study that 68.5 % of 168 smokers had a H1N1 infection compared to 47.2 % of the nonsmokers (p<0.0001) (19). The study showed that smoking was a major determinant of morbidity in epidemic H1N1 infection and might contribute substantially to incapacitation in outbreaks in heavy smokers (19). Mechanisms increasing the risk of infections by smoking include structural changes in the respiratory tract and a decrease in the immune response (7). Structural changes include peribronchiolar inflammation and fibrosis, increased mucosal permeability, impairment of the mucociliary clearance, changes in pathogen adherence, and disruption of the respiratory epithelium (20). They may alter both susceptibility to contract infection and the course of an infectious disease and compromise the host's ability to mount appropriate immune and inflammatory responses (21). Meliska et al. and Hersey et al. reported that natural killer cytotoxic activity increased substantially in smokers who quit compared to current smokers (22, 23). This could be one of the mechanisms by which current smokers have a higher risk than that of never- or ex-smokers.

Micronutrients such as vitamins have an impact on susceptibility to infection, and there has been considerable interest regarding the association of vitamin and URTI such as influenza. Vitamin D has been found to modulate macrophages' response, preventing them from releasing too many

inflammatory cytokines and chemokines (24). An animal model system has demonstrated enhanced lung pathology in an influenza virus-infected vitamin C-deficient mouse model (25). One randomized controlled trial showed a significant lower rate of development for self-reported cold and influenza symptoms (26). In this study, there was an inverse association between lower H1N1 infection acquisition and the frequency of vitamin supplements even after adjustment for history of contact with H1N1 patients (Figure 2), although statistical significance was lost after adjustment for smoking and physical activity.

Besides physical activity, smoking, vitamin intake, and contact history with H1N1 patients, there are several factors related to H1N1 infection in other studies. A cross-sectional survey evaluating the characteristics of H1N1 outbreaks among healthcare personnel (HCP) (27) showed that the female gender, an age <40 years, chronic underlying diseases, and having infected household members were associated with H1N1 infection. Obesity also was detected as a risk factor for H1N1 infection. A recent study from California described that half of Californians ≥20 years of age hospitalized with H1N1 infection were obese (28), and after adjusting for co-morbidities and other risk factors, extreme obesity (BMI>40) was independently significantly associated with death due to 2009 H1N1 infection. However, this study did not show a relationship between BMI and H1N1 infection.

This study has several limitations. First, there were significant differences in the history of contact with cases of H1N1 infection between the cases and the controls. In fact, the contact history is an important risk factor in the acquisition of H1N1 infection (29, 30). However, in this study, smoking and lower physical activity were independent risk factors for H1N1 infection even after adjusting for history of contact with H1N1 patients. Second, the number of cases enrolled was small. This one-center prospective study could be

initiated at the late phase of the pandemic in Korea after receiving the approval of ethical board. However, we attempted to compensate for this weakness by increasing the number of controls. Third, the period of enrollment was different between the cases and the controls. Since whether a person experienced the acquisition of H1N1 can be determined after the pandemic ended, control persons were enrolled after the enrollment of the cases. It might have brought recall bias. Fourth, there could be healthy volunteer bias (31, 32) as many controls were healthcare personnel or people who visited hospitals for health screening. Finally, it is possible that some of controls might have experienced mild H1N1 infection without influenza-like symptoms, because controls were enrolled by self-reports of no history of H1N1 infection, not confirmed by serologic testing for H1N1 infection.

In conclusion, our study showed that regular physical activity had a preventive effect and current smoking had a harmful effect on H1N1 infection.

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국문 초록

서론 2009년 멕시코와 미국에서 새롭게 발견된 신종 인플루엔자 H1N1은 전세계적으로 퍼지면서 대유행을 일으키면서 이와 관한 많은 연구가 진행되었다. 그러나 건강한 사람들 중에서 어떠한 사람이 H1N1 감염의 위험이 높은지에 대한 연구는 거의 없는 상황이다. 본 연구의 목적은 일반 인구에서 생활 습관이 H1N1 인플루엔자 감염에 어떠한 영향을 미치는지 확인해보고자 하는 것이다.

방법 2009년 11월부터 2010년 8월까지 서울에 위치한 한 2차병원에서 환자 대조군 연구를 시행하였다. 환자군은 RT-PCR로 H1N1 감염이 확인된 환자들을 대상으로 하였으며 대조군은 설문지를 통하여 H1N1이 유행하던 시기에 H1N1의 감염의 병력이 없고 급성호흡기계 질환을 경험하지 않았던 사람을 대상으로 환자군과 성별과 나이를 일치시켜 1:4로 모집하였다.

결과 연구 기간 동안 34명의 환자군과 136명의 대조군이 모집되었다. 과거 H1N1 환자와의 접촉력은 환자군에서 유의하게 높았다(p<0.001). 환자군은 대조군과 비교하여 유의하게 높은 흡연자의 비율을 보였으며(p=0.004), 또한 적은 운동 횟수를 보고하였다(p<0.001). 환자군은 또한 정기적으로 비타민제를 복용하는 사람이 대조군보다 적었다. 다변량 분석을 시행하였을 때,

흡연은 H1N1 감염의 위험을 증가시켰으며(adjusted OR 4.418, 95% CI 1.014-19.256; p=0.048) 정기적인 운동은 그 위험을 낮추는 것을 확인하였다(adjusted OR 0.051, 95% CI 0.012-0.209; p<0.001).

결론 본 연구 결과 정기적인 운동은 H1N1 감염의 위험을 낮추며 흡연은 H1N1 감염의 위험을 높인다는 것을 확인하였다.

주요어 : 2009 H1N1 인플루엔자, 생활 습관, 운동, 흡연

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