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Passive smoking and influenza-like illness in housewives: A perspective of gene susceptibility

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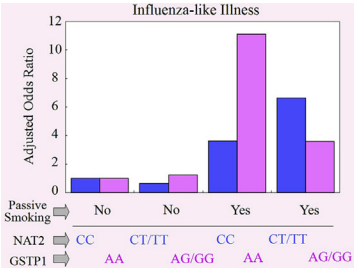
HIGHLIGHTS

- Relation between smoking and influenza-like illness (ILI) is under discussion.
- Interaction effects between smoking and gene polymorphisms were not reported.
- We investigated the association between passive smoking and ILI risk in housewives.
- Passive smoking was associated with an increase of ILI frequency in housewives.
- Genotypes of rs1041984 and rs1695 had interaction effects with passive smoking.

GRAPHICAL ABSTRACT



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ABSTRACT

Relation between influenza-like illness (ILI) and passive smoking remains a debate of subject. We aimed to determine an association of passive smoking with ILI risk of housewives in North China, and the modification effects of gene polymorphisms related to the metabolisms of smoking pollutants. We included 379 housewives for a cross-sectional study in Shanxi Province, China, including 118 with ILI frequency of "≥1 times per year" as the case group and 261 with ILI frequency of "<1 time per year" in the past 10 years as the control group. We collected their information on frequencies of passive smoking and ILI by questionnaires, as well as their single nucleotide polymorphisms (SNPs) of genes related to Phase I and Phase II metabolisms of smoking pollutants. Our results revealed a significant Spearman correlation between frequencies of ILI and passive smoking ($r = 0.406$, $p < 0.001$). Frequency of passive smoking was associated with an increased risk of ILI with adjusted OR [6.75 (95% confidence interval: 3.98–11.4)]. Dose-response association between the passive smoking and ILI risk was observed with or without adjusting for confounders. Mutant types of rs1041983 (*N*-acetyltransferase 2 gene, NAT2) had a synergetic effect with passive smoking on ILI frequency, while mutant types of rs1695 (glutathione S-transferase P1 gene, GSTP1) had an antagonistic effect. Overall, our study results supported the

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hypothesis that passive smoking was positively associated with ILI frequency in housewives and this effect was modified by gene polymorphisms of Phase II metabolism genes (NAT2 and GSTP1).

1. Introduction

Influenza-like illness (ILI) is a common respiratory syndrome caused by numerous respiratory viruses (Peng et al., 2012), which has resulted in substantial morbidity and mortality each year (Ng and Gordon, 2015). Tobacco smoking has been attracting wide public concerns because of its adverse health effects caused by various toxic pollutants generated from tobacco combustion (Dye and Adler, 1994; Arcavi and Benowitz, 2004; McGhee et al., 2005; Ras et al., 2009; Heishman et al., 2010). It has been reported that active smoking was associated with an elevated risk of ILI (Finklea et al., 1969; Kark and Lebiush, 1981; Kark et al., 1982; Roelands et al., 2009). Moreover, smokers with influenza infections had more severely adverse effects (i.e. more cough, acute and chronic sputum production, breathlessness, and wheezing) (Kark et al., 1982). Still, some other studies didn't support this point of view (Cruijff et al., 1999; Chu, 2015). For example, Cruijff et al. didn't observe a significant correlation between smoking and either serological or clinical influenza by a randomized clinical trial in Netherlands (Cruijff et al., 1999). It's therefore necessary to investigate the relation between smoking and ILI risk by more epidemiological studies in different populations.

The underlying mechanisms of the tobacco smoking-induced ILI risk are incompletely understood. Structural and immunologic alterations in the respiratory tract induced by pollutants generated during smoking are two major mechanisms (Arcavi and Benowitz, 2004). Structural alteration mainly results in an increase of the peri-bronchiolar inflammation, impairment of the mucociliary clearance, and disruption of the respiratory epithelium (Dye and Adler, 1994), and immunologic alteration primarily decreases the systematic immune capacity (Sopori et al., 1998; Wang et al., 2015b). During the two above alterations, oxidative stress and inflammation effect were important pathways (Chalmers, 1999; Wu and Metcalf, 2014; Wang et al., 2015b). In addition to the free radicals from tobacco combustion, smoking pollutants (e.g. PAHs and nicotine) can generate reactive oxygen or nitrogen radicals (ROS or RNS) during their metabolism processes (Bostrom et al., 2002; Crowley-Weber et al., 2003), further activating the inflammation effects (Nel et al., 2006). Gene polymorphisms can influence population susceptibility to smoking pollutants. For example, cytochrome P450 genes (e.g., CYP1A1 and CYP1B1) were reported to play an important role in metabolizing PAHs (Kawajiri et al., 1990; Bennett et al., 1999), and PAH detoxification was partly affected by glutathione *S*-transferase (GST) genes (e.g., GSTM1 and GSTT2) (Ketterer et al., 1992; Kihara and Noda, 1995). To our knowledge, an association between smoking pollutants and the SNPs of genes encoding Phase I and Phase II metabolism enzymes on ILI risk has not been investigated, as well as an interaction effect between smoking and SNPs.

Passive smoking is also an important issue for public health, as well as active smoking. Population with passive smoking may not well establish their immune adaptation function to smoking pollutants. It was reported that children with passive smoking exposure who are hospitalized with influenza have more severe illness (Wilson et al., 2013). China has the largest number of tobacco smokers in the world with ~300 million citizens of active smoking, and more seriously, and ~540 million citizens suffering from passive smoking (Ministry of Health, 2012). For Chinese women, exposure to environmental tobacco smoke was related to elevated risks of all cause mortality and mortality due to lung cancer and cardiovascular disease (Wen et al., 2006). It is estimated that more than 100,000 Chinese citizens die annually of diseases due to passive smoking (Ministry of Health, 2007). However, the relationship between ILI risk and passive smoking has been rarely investigated for Chinese population.

Housewives in the rural area of North China spend more time on the housework due to their lifestyle and historical culture. Husbands' smoking has been found to induce an increased risk of non-smoking women to deliver neural tube defects-affected infants (Li et al., 2013). Poor ventilation condition in the rural areas, especially in heating season in North China, can enhance their exposure level to indoor passive smoking (Li et al., 2011, 2013). We also observed that the fever or flu during early pregnancy was also strongly correlated with risks of neural tube defects (Li et al., 2007; Wang et al., 2015a). Thus, we hypothesize that exposure to passive smoking were associated with ILI risk, and this association was modified by gene polymorphisms related to the metabolisms of smoking pollutants. Therefore, the aims of our study were to investigate: (1) the association of exposure to passive smoking with ILI risk in housewives; (2) the interaction effects between passive smoking and genes related to the metabolisms of pollutants from tobacco smoking on ILI risk.

2. Materials and method

2.1. Study population

This study was conducted in Pingding County Hospital in Shanxi Province of northern China as a cross-sectional study. The detailed information about how to recruit housewives was described in our previous study (Wang et al., 2016a, 2016c). Briefly, when a woman is admitted to the hospital for childbirth in northern China, one or two older housewives (the mother or mother-in-law) usually come to the hospital and assist with the delivery. We invited housewives to take part in our study if they satisfied the requirements including: (1) they were residents of Pingding County (rather than immigrants); (2) there were no significant changes in their living conditions over the past 10 years; (3) they were aged 30 years or older. Because the timing of the births was not controlled, the housewives selected to assist with the deliveries were considered as a randomized sampling of local housewives. The study protocol was approved by the institutional review board of Peking University, and signed consents were obtained from all subjects.

2.2. Questionnaire design

Data were collected via face-to-face interviews by local healthcare workers. The questionnaire included information on influenza frequency in the past ten years ("<1 time per year", "1–3 times per year", or ">3 times per year"), age, occupation (farmer or non-farmer), education ("primary or lower", "junior high", "high school or junior college", or "above junior college"), active smoking (yes or no). The following two questions were asked if they don't have active smoking: passive smoking (yes or no), and frequency of