International Journal of Hygiene and Environmental Health 219 (2016) 850–856

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Cadmium and lead exposure and risk of cataract surgery in U.S. adults

Weiye Wang[a], Debra A. Schaumberg[b,c], Sung Kyun Park[a,d,*]

[a] Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI 48109-2029, USA
[b] Department of Ophthalmology & Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City, UT 84132, USA
[c] Global Medical Affairs, Shire, Lexington, MA 02421, USA
[d] Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI 48109-2029, USA

ARTICLE INFO

Article history:
Received 27 May 2016
Accepted 14 July 2016

Keywords:
Cataract
Cadmium
Smoking
Mediation analysis
NHANES

ABSTRACT

Cataract is a major cause of visual dysfunction and the leading cause of blindness. Elevated levels of cadmium and lead have been found in the lenses of cataract patients, suggesting these metals may play a role in cataract risk. This study aimed to examine the associations of blood lead, blood cadmium and urinary cadmium with cataract risk. We identified 9763 individuals aged 50 years and older with blood lead and cadmium levels, and a randomly selected subgroup of 3175 individuals with available urinary cadmium levels, from the National Health and Nutrition Examination Surveys (NHANES) from 1999 to 2008 (mean age = 63 years). Participants were considered to have cataract if they self-reported prior cataract surgery in NHANES's vision examination. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using survey logistic regression models. We identified 1737 cataract surgery cases (the weighted prevalence = 14.1%). With adjustment for age, race/ethnicity, gender, education, diabetes mellitus, body mass index, cigarette smoking (serum cotinine and pack-years) and urine hydration, every 2-fold increase in urinary cadmium was associated with a 23% higher risk of cataract surgery (OR = 1.23, 95% CI: 1.04, 1.46, p = 0.021). We found no associations of cataract surgery with blood cadmium (OR = 0.97, 95% CI: 0.89, 1.07) and blood lead (OR = 0.97, 95% CI: 0.88, 1.06). Mediation analysis showed that for the smoking-cadmium-cataract pathway, the ratio of smoking's indirect effect to the total effect through cadmium was more than 50%. These results suggest that cumulative cadmium exposure may be an important under-recognized risk factor for cataract. However, these findings should be interpreted with a caution because of inconsistent results between urinary cadmium and blood cadmium.

1. Introduction

Cataract is one of the major causes of visual impairment and the leading cause of blindness. Approximately 10.8 million people worldwide had cataract-induced vision loss in 2010 (Bourne et al., 2013). The prevalence of cataract in the United States in 2010 was 17% in people aged 40 years or older and more than 50% in people aged 70 years or older (Friedman et al., 2012). The physiopathology of cataract is not fully understood (Bobrow et al., 2015). It is believed that oxidative stress may initiate cataract formation through modification of lens epithelium: the excessive generation of reactive molecules can cause oxidative damage to functional DNA, proteins and lipids in lens cells, overwhelm the antioxidant defense system (such as superoxide dismutase, catalase, lipid peroxidases), impair DNA repair mechanisms, enhance apoptosis of lens epithelial cells, and induces protein and lipid aggregation in lens (Spector, 1995; Truscott, 2005; Thiagarajan and Manikandan, 2013; Manayi et al., 2015; Phaniendra et al., 2015; Babizhayev, 2011; Bobrow et al., 2015). Previous studies reported that concentrations of serum anti-oxidative enzymes and products of oxidative stress were relevant to the risk of cataract, although the association might vary across different subtypes (Beebe et al., 2010; Chang et al., 2013; Cui et al., 2013; Thiagarajan and Manikandan, 2013; Zoric et al., 2008).

Exposure to heavy metals, such as lead and cadmium, can lead to oxidative stress through depletion of glutathione and thiol pool and inhibition of the antioxidant defense systems (Ercal et al., 2001; Jomova and Valko, 2011; Valko et al., 2016). Several studies found elevated levels of lens lead and cadmium in patients who suffered cataract, especially among smokers (Cekic, 1998; Harding, 1995; Mosad et al., 2010; Rácz and Erdöhelyi, 1988; Ramakrishnan et al., 1995). One study reported cadmium might induce cell death in human lens epithelial cells (Kalariya et al., 2010). Few epidemiologic studies have examined the association of cataract with lead or cadmium. Only one study reported an association between cumu-

* Corresponding author: Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Heights, SPH-II, M5541, Ann Arbor, MI, 48109, USA.

E-mail addresses: weiyew@umich.edu (W. Wang), dschaumberg0@shire.com (D.A. Schaumberg), sungkyun@umich.edu (S.K. Park).

http://dx.doi.org/10.1016/j.ijheh.2016.07.012
1438-4639/

lative lead exposure (measured by bone lead levels) and cataract in a subset of 642 male participants from the Normative Aging Study (NAS) (Schaumberg et al., 2004). Potential associations between heavy metals and other age-related eye diseases such as age-related macular degeneration (AMD) have also been reported (Erie et al., 2009). Recently, several studies using national survey data from the United States (Wu et al., 2014) and Korea (Hwang et al., 2015; Kim et al., 2014; Park et al., 2015) reported a positive association between blood or urinary cadmium and blood lead and AMD. Another small scale case-control study involving 12 patients also showed a positive association between cadmium levels in aqueous humor and AMD (Jünemann et al., 2013). However, we are unaware of previous epidemiologic studies evaluating the association between cadmium exposure and cataract and could find no reference to it on PubMed, although previous studies have suggested that cigarette smoking, one of the major sources of cadmium exposure, is strongly associated with cataract (Kelly et al., 2005; Ye et al., 2012).

In this study, our primary goal is to assess the associations of lead and cadmium exposure with cataract among adults aged 50 years and older using data from the 1999–2008 National Health and Nutrition Examination Survey (NHANES). Furthermore, we evaluated the potential mediation effect of cadmium on the smoking-cataract pathway.

2. Methods

2.1. Study population

This study was based on NHANES, a national program of cross-sectional studies designed to analyze the physical status of the U.S. general population. Each cycle of NHANES is a cross-sectional survey. Each cycle is independent and includes different US representative samples. Survey protocols were approved by the National Center for Health Statistics Research Ethics Review Board, and all participants have provided written informed consent. Since cataract usually occurs in older population (young-onset cataracts are more likely to be non-age-related), we limited our study to 12781 participants aged 50 and older, from cycle 1999–2000 to cycle 2007–2008. Among these subjects we excluded 1522 individuals with missing value in blood lead or blood cadmium, and 667 subjects lacking cataract surgery information. After additional exclusion of subjects missing important covariates such as educational level, body mass index (BMI), history of diabetes, pack-years of cigarette smoking, and serum cotinine, 9763 individuals remained in our final dataset for analysis of blood lead and blood cadmium.

By design, urinary cadmium was only assessed in one-third of the NHANES sample, randomly selected from all eligible participants. We identified 3175 individuals aged 50 and older as the study population for analysis of urinary cadmium. Population characteristics are almost identical between two study groups.

2.2. Cataract identification

Participants aged 12 years and older were asked whether they have had eye surgery for cataracts, before undertaking detailed vision examination, according to the NHANES' Vision Procedures Manual (US Dept of Health and Human Services, 2005). Because an increasing rate and lower threshold of cataract surgery in U.S., (Bobrow et al., 2015; Lundström et al., 2015) self-reported cataract surgery may roughly represent the existence of clinically significant cataract. This method was used in a previous study (Zhang et al., 2012). Participants who answered "yes" were considered as cataract cases. Those who were completely blind or had severe eye infection were excluded.

2.3. Blood lead, blood cadmium and urinary cadmium measurements

Blood lead and blood cadmium were measured at the Division of Laboratory Sciences, National Center for Environmental Health, the Centers for Disease Control and Prevention by a simultaneous multi-element atomic absorption spectrometer (SIMAA 6000; PerkinElmer, Norwalk, CT) with Zeeman background correction in NHANES 1999–2002 and by an inductive coupled plasma mass spectrometry (ICP-MS) (ELAN 6100; PerkinElmer, Shelton, CT) in NHANES 2003–2008. Urinary cadmium was measured by ICP-MS (ELAN 6100; PerkinElmer, Shelton, CT) in all NHANES cycles. A detailed protocol can be found in the NHANES Laboratory/Medical Technologist Procedures Manual (LPM) (US Dept of Health and Human Services; Hyattsville, MD, 2005). The lower detection limit for blood cadmium was 0.20 μg/L and for urinary cadmium was 0.04 μg/L in NHANES 1999–2008. The lower detection limits for blood lead were 0.30 μg/dL in NHANES 1999–2004, 0.25 μg/dL and 0.30 μg/dL in NAHNES 2005–06 and 0.25 μg/dL in NHANES 2007–08. Values below the detection limits were divided by the square root of two. Among the total 9763 observations with blood cadmium and lead levels, 644 (6.60%) and 7 (0.07%) were below the detection limits; among the 3175 subset with urinary cadmium levels, 59 (1.86%) were below the detection limits.

Urinary lead data was available in the NHANES cycles used in the present study but was not included in our analysis. Urinary lead is not considered a reliable biomarker for total body burden: it mainly secondarily reflects lead level in blood and soft tissues and bone, and even such reflection is still unreliable due to a large variation within and between individuals (Sommar et al., 2014).

2.4. Other covariates

Socio-demographic variables such as age (year), gender (male/female), race/ethnicity (Non-Hispanic White, Mexican American, Non-Hispanic Black and other) and educational level (<high school, high school, some college and above) were obtained using computer-assisted personal interview methods. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Diabetes status (self-reported diagnosis or have taken insulin/diabetic pills, yes/no) was included since previous studies reported association between diabetes mellitus and cataracts (Thompson and Lakhani, 2015). Since cataract was highly related to smoking habits (Kelly et al., 2005; Ye et al., 2012), we included two smoking variables: pack-years of cigarettes and serum cotinine levels (ng/dL); the former indicates direct smoking amounts, whereas the latter indicates amounts of both direct and second-hand smoking (Lindsay et al., 2014). Urinary creatinine (mg/dL) was added to adjust for urine dilution in the urinary cadmium models. Since previous literature also suggested an association between cataract and antioxidant vitamin intakes (Cui et al., 2013), which may be associated with heavy metal body burdens (Mosad et al., 2010), we further included daily intake of vitamin A (mg), vitamin C (mg) and vitamin E (mg) by calculating the sum of dietary and supplement intakes in a sensitivity analysis.

2.5. Statistical analysis

We used SAS 9.2 (SAS Institute Inc., Cary, NC. USA) and R 3.2.2 (https://www.r-project.org/) for all statistical analyses. All p-values for significance were 2-tailed ($P < 0.05$). We combined 5 two-year cycles of NHANES dataset (1999–2008) for analysis. According to NHANES Analytic and Reporting Guidelines (Johnson et al., 2013), we calculated new sample weights for all 9763 observations to reduce sampling bias, by using the mobile examination center (MEC) exam weight (WTMEC2YR) for blood lead