学位論文内容の要旨

博士の専攻分野の名称　博士（医　学）　氏 名　Titilola Serifat Braimoh

学 位 論 文 題 名

EFFECTS OF MATERNAL SECONDHAND SMOKE EXPOSURE AND GENE POLYMORPHISMS OF *CYP1A1, EPHX1* AND *NAT2* ON INFANT BIRTH SIZE

（妊婦の受動喫煙曝露と *CYP1A1, EPHX1* , *NAT2* 遺伝子多型が出生時体格に及ぼす影響）

BACKGROUND: The recent high prevalence of low birth weight (LBW, defined as birth weight <2500g) in Japan compared to other developed countries is a major public health concern. Nonsmoking pregnant women are at risk of secondhand smoke (SHS) exposure especially at home due to the high prevalence of smoking among Japanese men. Results of the effects of secondhand smoke (SHS) exposure on infant birth weight observed in previous studies are inconclusive. Also, not all mothers who were prenatally exposed to SHS gave birth to LBW babies. This suggests that genetic susceptibility may be playing a role.

OBJECTIVE: The main aim of this study was to investigate the moderating role of maternal genetic susceptibility in the association of secondhand smoke exposure with infant birth size

METHODS: A prospective cohort study involving 1336 nonsmoking native Japanese pregnant women enrolled for antenatal care at hospitals within Hokkaido Prefecture from 2003 to 2007 was conducted. Self-administered questionnaires and birth records were used for gathering information on maternal and infants' characteristics and lifestyle behaviors. Cotinine measurements were carried out by analyzing biochemically maternal blood specimen using enzyme-linked immunosorbent assay (ELISA) technique. Genetic analyses included extraction of genomic DNA from maternal blood specimen collected at delivery and genotyping using real-time polymerase chain reaction (PCR) technique. Descriptive statistics, analysis of variance (ANOVA), ROC curve and multiple linear regression models were used for the statistical analyses. All statistical analyses were performed using SPSS for Windows, version 16.0.

RESULTS: Exposure to SHS had a marginal association with reductions in the mean birth weight (-32g, SE, 21; $P = 0.07$) and birth length (-0.4cm, SE, 0.2; $P = 0.09$) after adjusting for the confounding variables. Independently, *Tyr/His113* and *His/His113*

genotypes of *EPHX1 Tyr113His* had an adverse effect on the mean birth weight (-59g, *P* = 0.039 and 92g, *P* = 0.003 respectively). However, in the presence of SHS exposure, *CYP1A1*2C* variant genotype conferred an adverse effect on the birth size of the infants of the exposed mothers (mean birth weight reduction = -88g, SE, 37; *P* = 0.019 and birth length reduction = -0.9cm, SE, 0.4; *P* = 0.025). The exposed women with *EPHX1 Tyr113His* homozygous recessive genotypes also had the lowest mean birth weight and birth length (-154g, SE, 42; *P* < 0.001 and 1.1cm, SE, 0.4; *P* = 0.010) respectively. For NAT2*7, the mean reduction in birth weight was 51g (SE, 24; *P* = 0.034) for the exposed slow acetylators.

EPHX1 Tyr113His and *NAT2*7* had a combined effect on the birth weight, birth length and head circumference (145g, SE, 48; *P* = 0.003; 1.1cm, SE, 0.5; *P* = 0.003; 0.9cm, SE, 0.5; *P* = 0.052 respectively) among the exposed *EPHX1* homozygous recessive group and *NAT2*7* slow acetylation genotype. Also, SHS exposure with a combination of *EPHX1 His/His 113* and *NAT2*7* fast acetylation genotype groups reduced birth weight by 180g (SE, 70; *P* = 0.010). Interaction of both genes with SHS exposure had a stronger effect on birth weight. The unexposed showed no statistically significant association between any of the genotypes and birth size reduction.

DISCUSSION: The consistent vulnerability of CYP1A1*2C variant genotypes (A/G +G/G), EPHX1 Tyr113His His/His113 and NAT2*7 slow alleles to the negative effects of tobacco smoke implies a relationship between metabolic genes and SHS exposure. *CYP1A1* is a phase 1 gene whereas *EPHX1* and *NAT2* perform dual functions (activation and detoxification) in xenobiotic metabolism depending on the substrate. The ability of an individual to convert the toxic metabolites of cigarette smoke into less harmful compounds is crucial for reducing their adverse effects on birth outcomes. The missense mutation which occurred in *EPHX1 Tyr113His* at codon 113 of exon 3, however, may lead to a decrease in enzyme activity while that of *CYP1A1*2C* variant genotypes may increase enzyme activity.

This is the first study to demonstrate a significant association between *CYP1A1*2C, EPHX1 Tyr113His* and *NAT2*7* mutant alleles and SHS exposure with infant birth size in the Japanese population.

CONCLUSION: This study has demonstrated that maternal genetic factor (*EPHX1 Tyr113His, NAT2*7* and *CYP1A1*2C*) play an important modifying role in the association between maternal exposure to SHS during pregnancy and birth size among Japanese subjects.