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A case–control study of the association between urinary cadmium concentration and endometriosis in infertile Japanese women

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ABSTRACT

Cadmium may act like an estrogen and be a potential risk factor for estrogen-related diseases such as breast cancer and endometriosis. Here, we tested the hypothesis that higher cadmium exposure is associated with endometriosis among infertile Japanese women in a hospital-based case–control study. We recruited consecutive female patients aged 20–45 years who had complained of infertility and presented to a university hospital in Tokyo. The subjects were interviewed and provided a urine sample prior to a laparoscopic diagnosis of endometriosis between January 2000 and December 2001. The severity of endometriosis was then dichotomized into controls (stage 0 and I) and cases (stage II–IV). We finally measured urinary total cadmium concentration in 54 cases and 74 controls as a biomarker of long-term cumulative exposure. Odds ratios were adjusted for average menstrual cycle length, body-mass index and smoking status using unconditional logistic regression. Results showed no association between endometriosis and urinary cadmium concentration. Medians (interquartile ranges) of urinary cadmium concentration in cases and controls were 0.53 (0.40–0.73) and 0.54 (0.34–0.76) $\mu\text{g/g}$ creatinine, respectively (P for difference = 0.88). Adjusted odds ratio (95% confidence interval) for the highest versus lowest tertile of urinary creatinine-adjusted cadmium concentration was 0.86 (0.30 to 2.49, P for trend = 0.79). Our results do not support the hypothesis that higher urinary cadmium concentration is associated with the risk of endometriosis.

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1. Introduction

Cadmium, a toxic and highly bioaccumulative heavy metal, may act like an estrogen. Cadmium has displayed estrogenic properties in both in vivo and in vitro studies (Henson and Chedrese, 2004; Safe, 2003; Stoica et al., 2000; Takiguchi and Yoshihara, 2006). For example, Johnson et al. (2003)

reported that cadmium increased uterine weight and promoted hyperplasia of mammary glands in female rats. This hypothesized role of cadmium in the etiology of estrogen-related diseases such as breast cancer and endometriosis has recently focused attention on its estrogenic activity (Antila et al., 1996; Heilier et al., 2006, 2004; McElroy et al., 2006; Nagata et al., 2005).

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Humans are exposed to cadmium on a daily basis, mainly via cigarette smoking and the consumption of environmentally contaminated rice and other foods (Ikeda et al., 2005, 2006). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) proposed a provisional tolerable weekly intake (PTWI) for cadmium aimed at preventing renal tubular dysfunction of 7 $\mu\text{g/kg/day}$ (JECFA, 2003); however, this PTWI takes no account of the estrogenic effects of cadmium.

Although the association between estrogen-related diseases and cadmium exposure has been examined in a number of epidemiological studies, findings to date have been inconsistent (Antila et al., 1996; Heilier et al., 2006, 2004; McElroy et al., 2006; Nagata et al., 2005). A recent population-based case-control study in the US showed that increased urinary levels of cadmium were significantly associated with increased breast cancer risk (McElroy et al., 2006). Further, a significant positive association was found between urinary cadmium and serum testosterone concentrations in postmenopausal Japanese women (Nagata et al., 2005). On the other hand, a small case-control study in Helsinki found no significant difference in breast fat cadmium concentration between breast cancer patients and controls (Antila et al., 1996), nor was any difference seen in blood or urine concentrations between endometriosis cases and controls (Heilier et al., 2006, 2004).

Endometriosis, a common benign disease in women of childbearing age, is characterized by the ectopic growth of endometrial-like tissue leading to the painful condition of dysmenorrhea and other reproductive disorders (Cramer and Missmer, 2002). In one study, the prevalence of largely asymptomatic endometriosis found in women undergoing tubal ligation was about 4%, ranging from 1% to 7% (Missmer and Cramer, 2003). Although little is known about the pathological mechanism of endometriosis, epidemiological studies have suggested an association with several estrogen-dependent factors, namely early menarche, shorter menstrual cycle length, and lower parity (Cramer and Missmer, 2002; Missmer and Cramer, 2003; Vigano et al., 2004). Based on this, endometriosis is likely a sensitive detector of the effect of xenoestrogen in humans.

Here, we tested the hypothesis that a higher urinary cadmium concentration, known as an appropriate biomarker for long-term exposure (ATSDR, 1999), is associated with endometriosis risk in a case-control study in infertile Japanese women.

2. Materials and methods

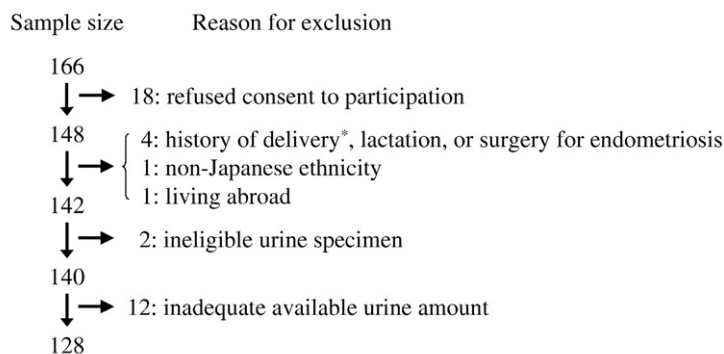
2.1. Subjects

Subjects were recruited from among 166 consecutive female patients aged 20 to 45 years who had complained of infertility and had consulted the Department of Obstetrics and Gynecology of Jikei University School of Medicine for treatment for infertility. A total of 148 women provided written informed consent to participate. Women who had previously given birth ($n=1$) or had lactated, as well as those who had undergone surgery for endometriosis ($n=1$) or had history of miscarriage longer than 3 months ($n=2$) were excluded. One woman of non-Japanese ethnicity and a second who lived abroad were also excluded, finally leaving 142 women eligible. Of these, 140 who submitted an eligible urine sample and underwent laparoscopic examination between January 2000 and December 2001 were available for analysis. Nine patients did not actually complain of infertility according to their questionnaire responses but were included to increase statistical power. Twelve subjects were not used for analysis because of an inadequate available urine amount, leaving the analysis finally restricted to 128 subjects as shown in Fig. 1. The present study was approved by the Institutional Review Boards (ethics committees) of the Jikei University School of Medicine and National Cancer Center (Tokyo, Japan).

The severity of endometriosis was diagnosed using laparoscopy and classified into five stages based on the revised American Fertility Society classification (American Fertility Society, 1985) as stage 0 ($n=55$), I ($n=19$), II ($n=10$), III ($n=22$), and IV ($n=22$). Subjects were then dichotomized into controls (stage 0 and I, $n=74$) and cases (stage II–IV, $n=54$) (Tsukino et al., 2005, 2006).

Participants were interviewed before laparoscopic examination by a single trained interviewer using a structured questionnaire to collect information on demographic factors, age, height, weight, personal and family medical, reproductive and menstrual history, oral contraceptive use, food- and alcohol-consumption frequency, and smoking history. The questionnaire and participant profile have been described in detail elsewhere (Tsukino et al., 2005, 2006).

Participants also collected a first morning urine sample into a paper cup, which was then transferred into a plastic



*Including fetal death after gestation for three or more months.

Fig. 1 – Exclusion flow and evolution of sample size.

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