Journal of Diabetes and Its Complications 30 (2016) 1217–1222

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Reproductive factors and risk of type 2 diabetes in an occupational cohort of Chinese women

Aimin Yang [a,b], Simin Liu [b,c], Ning Cheng [d], Hongquan Pu [e], Min Dai [f], Jiao Ding [e], Juansheng Li [a], Haiyan Li [e], Xiaobin Hu [a], Xiaowei Ren [a], Jie He [f], Tongzhang Zheng [b,*], Yana Bai [a,*]

[a] Department of Epidemiology and Statistics, School of Public Health, Lanzhou University, Lanzhou, Gansu 730000, China
[b] Department of Epidemiology, School of Public Health, Brown University, Providence, RI 02912, USA
[c] Department of Medicine (Endocrinology), Rhode Island Hospital and the Alpert Medical School, Brown University, Providence, RI 02901, USA
[d] Center of Medical Laboratory, Lanzhou University, Lanzhou, Gansu 730000, China
[e] Workers' Hospital of Jinchuan Group Co., Ltd., Jinchang, Gansu 737103, China
[f] Cancer Hospital, Chinese Academy of Medical Sciences, Beijing 100021, China

ARTICLE INFO

Article history:
Received 28 April 2016
Received in revised form 7 June 2016
Accepted 8 June 2016
Available online 14 June 2016

Keywords:
Menarche
Menopause
Type 2 diabetes
Reproduction
Risk factors

ABSTRACT

Aims: Hormonal milieu has long been known to play an important role in the development of type 2 diabetes (T2D). The aims of this study are to investigate the roles of menstrual and reproductive factors in relation to T2D risk in an occupational cohort of Chinese women; and to explore the role of endogenous estrogen in T2D development.
Methods: We conducted a cross-sectional analysis of baseline data from 16114 women (11051 premenopausal and 5063 postmenopausal) aged ≥20 years who participated in the ongoing prospective occupational cohort study. Multivariable logistic regressions were modeled to evaluate the associations of reproductive factors with T2D risk.
Results: Early menarche at age (≤12 versus 15–16 years) was associated with increased T2D risk (odds ratio [OR]: 1.60, 95% confidence interval [CI]: 1.16–2.22). After multiple adjustment including age, BMI and occupation, postmenopausal status was positively associated with T2D risk (OR: 1.54, 95% CI: 1.10–2.14). Reproductive life span was significantly associated with T2D risk ($P = 0.02$), albeit displaying a U-shape relationship. Similarly, age at menopause was also associated with T2D risk in the same U-shaped as with reproductive life span ($P = 0.03$). Further, years since menopause ($P = 0.003$), but not history of cycle regularity and hormone use, was associated with increased T2D risk.
Conclusion: Reproductive factors were associated with T2D supporting the notion that either a short or prolonged exposure to endogenous estrogen affects T2D risk in Chinese women. Reproductive factors should be added to risk stratification when counseling women about their risk of developing diabetes.

1. Introduction

Estrogens have long been considered to have beneficial effects on insulin secretion and glucose homeostasis (Cignarella & Bolego, 2010; Godsland, 2005; Mauvais-Jarvis, Clegg, & Hevener, 2013; Tiano & Mauvais-Jarvis, 2012). In postmenopausal women, estrogen replacement therapy reduces risk of type 2 diabetes (T2D) (Kanaya, Herrington, Vittinghoff, et al., 2003; Margolis, Bonds, Rodabough, et al., 2004), although endogenous estrogen levels have been associated with an increased T2D risk (Kalyani, Franco, Dobs, et al., 2009). Associations between reproductive factors and risk of chronic disease are usually attributed to a short or prolonged exposure to endogenous estrogens (Elks, Ong, Scott, et al., 2013). Mounting evidence on reproductive factors such as age at menarche, menopausal status, age at menopause, reproductive life span, years since menopause, and cycle irregularity all point to an important role of endogenous estrogens in T2D development.

Menarche is an indicator of puberty that signals the initiation of reproductive lifespan in a woman. Some (Baek, Lim, Kim, et al., 2015; He, Zhang, Hunter, et al., 2009; Lakshman, Forouhi, Luben, et al., 2008; Stöckl, Döring, Peters, et al., 2012) but not all previous studies (Chen, Zhang, Yeung, et al., 2011; Qiu, Chen, Wen, et al., 2013) have suggested that earlier age at menarche is directly associated with an increased T2D risk. Elevated body-mass index (BMI) or obesity, which are major predictors of T2D (Adair & Gordon-Larsen, 2001; Narayan, Boyle,

Declaration of Interests: The data collection was funded in part by the Jinchuan Nonferrous Metals Corporation (JNMC) but JNMC had no part in the data analysis for this study or the drafting of this paper, nor did they review the results before submission. The authors alone are responsible for the content and writing of the paper.
* Correspondence to: Y. Bai, Department of Epidemiology and Statistics, School of Public Health, Lanzhou University, South Donggang Xi Road 199, Lanzhou, 730000 China. Tel./fax: +86 931 8915 526; or T. Zheng, Department of Epidemiology, School of Public Health, Brown University, 121 South Main Street, Providence, RI 02912, USA. Tel./fax: +1 401 863 6365.
E-mail addresses: tongzhang_zheng@brown.edu (T. Zheng), baiyana@lzu.edu.cn (Y. Bai).

http://dx.doi.org/10.1016/j.jdiacomp.2016.06.011
1056-8727/

Thompson, et al., 2007), are also known to correlate closely with earlier age at menarche (Pierce & Leon, 2005). It remains unclear whether age at menarche independently influences T2D risk, and whether older age at menarche is associated with lower diabetes risk. At the other end of the reproductive lifespan, menopause is an important indicator for significant changes in endogenous hormonal milieu in a woman, although the effects of which on T2D risk remain controversial (Brand, van der Schouw, Onland-Moret, et al., 2013; Heianza, Arase, Kodama, et al., 2013; Kivimäki, Lawlor, Smith, et al., 2008; Lee, Hayashi, Mishra, et al., 2013). Whether menopause itself or older age is a risk factor for T2D still needs to be assessed. Reproductive life span is a marker of total duration of endogenous estrogen exposure, however, few studies have been conducted to examine its relationship with diabetes risk (Brand et al., 2013). Years since menopause and cycle irregularity were also associated with metabolic syndrome or T2D (Brower, Brennan, Pall, et al., 2013; Dishi, Enquobahrie, Abetew, et al., 2011; Solomon, Hu, Dunaif, et al., 2001; Yan, Liu, Zhao, et al., 2015).

Previous studies were predominantly conducted among postmenopausal women. Thus, there is an important gap in knowledge relating reproductive factors to T2D risk across the lifespan particularly in younger women. Moreover, few studies have been conducted in Chinese women who have undergone significant social economic and nutrition transition in recent decades. We have previously observed that exposed to metal and other occupational factors appeared to affect T2D risk and age at menopause (Wang, Wang, Cheng, et al., 2015; Yang, Cheng, Pu, et al., 2015). The objectives of the current study were to understand the associations of reproductive factors with T2D risk among Chinese women; and to explore the role of endogenous estrogen in T2D development.

2. Material and methods

2.1. Study population

This was a cross-sectional study using the baseline data of the Jinchang Cohort Study in Jinchang city, China. The Jinchang Cohort Study is an ongoing prospective cohort study of about 45000 workers that are engaged in mining, concentrating, metallurgy, and deep processing. The design and methods of the Jinchang Cohort Study have been detailed elsewhere (Bai, Yang, Pu, et al., 2014). Briefly, we began the baseline health survey from June 2011 to December 2013, after which all workers in the cohort participated in medical exams every other year that include in-person interviews, comprehensive physical exams, lab-based tests, and biosample collection. Overall, 93.7% (42122/44947) of all workers older than 20 years were included in the cohort, which includes 26008 (61.7%) males and 16,114 (38.3%) females. Thus, a sample of 16,114 female workers with mean age of 45.8 ± 11.8 years constituted present study. The study was approved by the Ethical Committees of the Public Health School of Lanzhou University.

2.2. Data collection

We conducted the baseline survey via in-person interviews by trained interviewers using a standardized and structured questionnaire that included questions pertaining to reproductive information, an assessment of lifetime occupational history, medical history, family history of diabetes, and other demographic, socioeconomic, and lifestyle factors (smoking and drinking). At baseline, clinical data were obtained from physical and biochemical examinations where participants also provided biological samples stored for future work. The comprehensive physical examination was performed by clinicians, which included a measurement of weight, height, and blood pressure. BMI was calculated as weight in kilograms divided by the square of height in meters. Tobacco smoke was categorized as current, former, and non-smoker. Current smokers were defined as those who smoked at least one cigarette per day in the last six months. Former smokers were defined as those who used to be smokers, but who had smoked less than one cigarette per day or stopped smoking for at least the past six months. The rest of the participants were defined as non-smokers. The biochemical examinations were performed using a clinical chemistry automatic analyzer (Hitachi 7600-020, Kyoto, Japan) during the morning, including fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-cholesterol), and low-density lipoprotein cholesterol (LDL-cholesterol). Abnormal lipid measurements were defined as (CDS, 2004): TG ≥ 1.70 mmol/L (150 mg/dL) or HDL-cholesterol < 1.0 mmol/L (39 mg/dL).

2.3. Menstrual and reproductive factors

We assessed the menstrual and reproductive information with a self-reported questionnaire at the time of the baseline survey. Female participants were asked about age at menarche (At what age did your first menstrual period begin?), history of cycle regularity, number of delivery, and hormone use (including hormone replacement therapy or oral contraceptives). Age at menopause was defined as the age at the last period prior to 12 months of amenorrhea in women who experienced natural menopause. Reproductive life span was defined menopausal age minus menarcheal age. Years since menopause was calculated by subtracting age of menopause from age at study enrollment.

2.4. Definition of T2D and hypertension

Type 2 diabetes was defined as fasting plasma glucose ≥ 126 mg/dL (≥7.0 mmol/L) or those who were on anti-diabetic medications at the time of the baseline interview (ADA, 2014). Hypertension was defined as systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg, or self-reported treatment for hypertension.

2.5. Metal exposure levels assessment

In this occupational-based study, female workers are possibly exposed to nickel as well as several other metals, including cobalt, copper, arsenic, and chromium. Estimation of likely metal exposure levels for each subject was based on their occupation/process of production in the company. Detailed methods in assessing metal exposure have been described elsewhere (Yang et al., 2015). Briefly, occupation was divided into three categories, namely office workers (low metal exposure levels), mining/production workers (intermediate metal exposure levels) and smelting/refining workers (high metal exposure levels). Assignment of female workers into these three categories was determined using data collected from the occupational history assessment from the baseline questionnaire.

2.6. Statistical analysis

Basic characteristics of women in the study were described and stratified by menopausal status (pre, post), and reproductive life span. Means and standard deviations (SD) or frequency distributions were calculated continuous variables or categorical variables. We performed the logistic regression analysis to estimate the odds ratios (OR) of T2D and categorized age at menarche (≤12, 13–14, 15–16, 17–18, ≥19 years), menopausal status (pre or post), reproductive life span (<30, 30–35, >35 years), years since menopause (≤5, 6–10, 11–15, 16–20, ≥21 years), cycle regularity (yes, no), and hormone use (yes, no). These categories were chosen to be clinically meaningful or equally spaced.

Analyses were adjusted for potential confounders in three consecutive models. The first one was unadjusted model. Next, we adjusted for age. In the final multivariable model, we added other potential confounders including education (1–9, 10–12, ≥13 years), marital status (single, married, divorced or widowed), BMI (<18.5, 18.5–25, 25–30, ≥30 kg/m^2), occupation (office, mining/production, smelting/refining), tobacco smoke (never, current, former), alcohol drinking (never, 1–14, >14 drinks/week), times of delivery (0, 1, 2, ≥3), age at first delivery