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A large scale population-based cohort study on the risk of ovarian neoplasm in patients with type 2 diabetes mellitus

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HIGHLIGHTS

- Investigations on the risk of ovarian cancer in type 2 diabetes are inconclusive due to certain methodological concerns.
- A recent meta-analysis suggested a 17% increase in risk of ovarian cancer in type 2 diabetes.
- This large study provides little support for the association of type 2 diabetes with risk of ovarian cancer.

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ABSTRACT

Objective. To investigate whether the risk of developing ovarian cancer is elevated in women with diabetes mellitus.

Methods. The study is a population-based cohort study. Women with type 2 diabetes ($n = 319{,}310$) and age-matched controls ($n = 319{,}308$) were selected from the ambulatory care claims and beneficiary registry in 2000, respectively. Selected patients were linked to the in-patient claims (2000–2008) to identify admissions due to ovarian (ICD-9-CM: 183.xx) cancer. The person-year approach with Poisson assumption was used to estimate the incidence density rate. The age-specific hazard ratios (HRs) of ovarian cancer in relation to diabetes were calculated using multivariate Cox proportional hazard regression model.

Results. The overall incidence density rate of ovarian cancer was estimated at 1.87 (95% confidence interval (CI) 1.70–2.05) per 10,000 patient-years for patients with diabetes. The corresponding figures for controls were slightly lower at 1.79 per 10,000 patient-years. The incidence density of ovarian cancer was increased with age in diabetes but not in controls. The covariate-adjusted HR for ovarian cancer was statistically compared with null (adjusted HR = 1.06, 95% CI = 0.92–1.22) in women with diabetes. Moderately elevated HR was noted in women with diabetes aged <50 (adjusted HR = 1.17, 95% CI = 0.82–1.65) and in women with diabetes aged >65 (adjusted HR = 1.10, 95% CI = 0.92–1.42). The null association between diabetes and ovarian cancer remains true regardless of the disease duration of diabetes.

Conclusion. This large-scale cohort study provides little support on the putative association between type 2 diabetes and the risk of ovarian cancer.

Introduction

Diabetes mellitus (DM) is a worldwide epidemic. Marked changes in human health behavior and lifestyle have resulted in increasing incidence and prevalent rates of DM [1]. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and is predicted to be 4.4% in 2030 [2]. The number of people with diabetes is increasing because of population growth, aging, urbanization, nutritional changes, and increasing prevalence of obesity and physical inactivity [2,3].

Patients with type 2 DM have increased the risk of developing certain cancers. In 2009, the American Cancer Society and American Diabetes Association reviewed the scientific evidence on the relationship between DM and cancer risk and concluded that the relative risks

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imparted by diabetes (primarily type 2 DM) are the greatest (approximately twofold or higher) for cancers of the liver, pancreas, and endometrium and lesser (approximately 1.2-fold to 1.5-fold) for cancers of the colon/rectum, breast, and bladder. The increased risk for developing other cancers (e.g., lung) does not appear to be associated with diabetes. Whether diabetes is associated with the risk of developing kidney cancer and non-Hodgkin's lymphoma is inconclusive [4]. The potential link between type 2 DM and ovarian cancer has rarely been investigated, and the results are inconclusive. A recent study that reviewed 7 case–control studies and 11 cohort studies summarized their study findings to evaluate the epidemiological associations between diabetes and ovarian cancer [5]. Combining data from all 18 studies, diabetes was found to be associated with a modestly increased risk of ovarian cancer. The summarized relative risk of ovarian cancer incidence was estimated at 1.17 (95% confidence interval (CI), 1.02–1.33). Only one case–control study [6] and one cohort study [7] showed a significantly increased risk for ovarian cancer in patients with diabetes. In addition to such inconsistency in findings, the results of previous studies also varied with respect to age range of diabetic patients, potential confounders, and method of diabetes ascertainment. For cohort studies, the follow-up duration also varied, ranging from 3.5 years to 11.8 years. The dissimilarities in findings made it difficult to interpret the summarized results on the relationship between diabetes and ovarian cancer. Moreover, very few studies [8,9] censored follow-up at the time of bilateral oophorectomy, which in turn became a source of bias that could have attenuated an association because of misclassifications made over time. No analyses on age-specific and disease duration-specific risks of ovarian cancer in relation to diabetes were performed by previous studies, primarily because of the limited sample size [6–9].

In accordance with the global trend for DM, more than 70% increase in the total diabetic population or a 35% increase in the standardized prevalence rate was observed in Taiwan from 2000 to 2009 [10]. A recent study that investigated the incidence of epithelial ovarian cancer in Taiwanese women from 1979 to 2008 reported that the age-adjusted incidence of epithelial ovarian cancer were 1.01, 1.37, 2.37, 3.24, 4.18, and 6.33 per 100,000 person-years at every five-year period from 1979 to 2008 [11]. The figures highlighted the clinical and public health importance of both diabetes and ovarian cancer in Taiwan. By using a national representative sample of patients with diabetes, we conducted a long-term follow-up study to investigate the age-specific and disease duration-specific risks of ovarian cancer in women with diabetes.

Material and methods

Source of data

The data analyzed in this study were retrospectively retrieved from the claims of the National Health Insurance Research Database (NHIRD) provided by the Bureau of National Health Insurance (BNHI). The NHIRD provided all inpatient and ambulatory medical claims for around 99% of Taiwanese people [12]. To ensure the accuracy of claim files, the BNHI performs quarterly expert reviews on a random sample for every 50 to 100 ambulatory and inpatient claims [13]. Therefore, information from the NHIRD on diabetes and cancer diagnoses is considered to be complete and accurate [14]. We used several NHIRD data sets in this study, including ambulatory care visit claims, inpatient claims, major illness/injury certificates, and registry for beneficiaries. Access to research data has been reviewed and approved by the Review Committee of the National Health Research Institutes.

Study design and populations

Our study utilizes a population-based cohort design. Details of the NHI claim data and the methods of selection used for patients with diabetes and control subjects were described in our previous report [15]. Briefly, we considered a patient to be diabetic if she or he was diagnosed as having diabetes (ICD-9-CM: 250 or A-code: 181) in 2000 and again within the subsequent 12 months ($n = 715{,}734$). To avoid accidental inclusion of miscoded patients, we selected only patients with first and last outpatient visits at least 30 days apart ($n = 639{,}804$).

To accurately estimate the incidence rate of ovarian cancer, we excluded patients who were admitted to the hospital for any malignant neoplasm (ICD-9-CM: 140–208) between 1997 and the date of initial ambulatory care visit (i.e., the indexed date) for diabetes treatment in 2000. Because major illness/injury certificates are issued to all patients with malignant neoplasms in Taiwan, we excluded only cancer patients with a major illness/injury certificates prior to the index date ($n = 24{,}272$) in order to avoid incorrect exclusion of cancer patients. For the specific purpose of this study, we selected only females with diabetes and excluded males with diabetes ($n = 289{,}915$). Females aged 20 years or less ($n = 5592$) were also excluded to ensure that the patients had type 2 DM. We further excluded women who had bilateral oophorectomy ($n = 715$). Thus, the final cohort consisted of 319,310 female patients with diabetes. The date of the first outpatient visit in 2000 was the index date for each patient.

The control subjects were identified from the RB. We excluded patients with claims for ambulatory care for diabetes or hospitalized for any type of malignancy (ICD-9-CM: 140–208) along with patients with major illness/injury certificates issued between 1997 and 1999. We selected age-matched and sex-matched control subjects by using the frequency matching procedure. Given that information on the age or sex of 661 patients with diabetes is missing, we selected only 614,871 control subjects. We again limited our control subjects to females ($n = 319{,}308$). The index date for subjects in the control group was the date of their enrollment to NHI. If their date of enrollment was before January 1, 2000, the index date was set to January 1, 2000, which was the starting point for the follow-up of controls.

End-points and covariates

We used the unique personal identification number (PIN) of each insurer in both groups. We then linked the PIN of each insurer to the inpatient claims of 2000 to 2008 to identify the primary or secondary diagnoses of ovarian cancer (ICD-9-CM: 183), which was the endpoint in this study. To avoid incorrect assessment of malignant neoplasm, we included only patients who possessed major illness/injury certificates for admissions. The day of hospitalization of the patients was considered the date when the clinical endpoint of interest occurred. The study period was from January 1, 2000, to December 31, 2008.

The geographic location of each individual's NHI unit, either the location of employment or residential area, was classified as north, central, south, or east or according to the level of urbanization (i.e., urban or rural), as per the National Statistics of Regional Standard Classification [16]. Information on a study subject's underlying illness was retrieved from the inpatient and outpatient claims from the first day of 1997 to the index date of 2000. Recorded illnesses included endometriosis (ICD-9-CM: 617.9), cardiovascular disease (ICD-9-CM: 410–414), pelvic inflammatory disease (ICD-9-CM: 614–616), chronic liver disease (ICD-9-CM: 571–572), and rheumatic disease (ICD-9-CM: 714) [17]. In the analysis of ovarian neoplasm in relation to diabetes, we calculated the Charlson's score to indicate an individual's level of co-morbidity. The Charlson comorbidity index is a weighted summary measure of clinically important concomitant diseases that has been adapted for use with ICD-9-CM coded administrative databases [18,19]. Patients with diabetes are more likely to frequently seek medical care compared with their control counterparts, leading to a spuriously elevated risk of ovarian neoplasm in diabetes. Therefore, we also adjusted for the frequency of outpatient visits for each study subject to avoid disease surveillance bias.