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Original article

Endometriosis and the subsequent risk of epithelial ovarian cancer

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ABSTRACT

Objective: There is a possible correlation between endometriosis and an increased risk of epithelial ovarian cancer (EOC), but many uncertainties remain, including race, exposure or surveillance time, and surgical confirmation. Therefore, we carried out a large-scale, nationwide, controlled cohort study in the Taiwanese women to respond to these uncertainties.

Materials and methods: A historical cohort study was performed by linking the National Health Insurance Research Database of Taiwan. Each patient diagnosed with endometriosis ($n = 7537$) between 2000 and 2009 was background matched with up to two women without endometriosis ($n = 15,074$). The total was 136,643 person-years of follow-up and 24 women having new EOC. Cox regression analysis was used to determine the relationship between the EOC incidence rate and an endometriosis status.

Results: The EOC incidence rate of the endometriosis and non-endometriosis women was 3.31 per 10,000 person-years and 0.99 per 10,000 person-years, respectively, contributing to an adjusted hazard ratio (HR) of 3.28 (95% confidence interval, 1.37–7.85). The women with surgical confirmation had a much higher adjusted HR (3.87; 95% confidence interval, 1.58–9.47). No significantly statistical difference of surveillance time between women with and without endometriosis (3.87 years vs. 3.73 years). The occurrence of EOC was not also affected by exposure time of women with endometriosis.

Conclusion: Taiwanese women with endometriosis really had a risk of newly developed EOC, especially those who had a surgical diagnosis, and this three-fold increase of risk was neither influenced by exposure time nor biased by surveillance.

Introduction

Endometriosis, affecting 6–10% of women of reproductive age, is a common gynecological disorder defined by the presence of viable, extrauterine, endometrial glands, and stroma [1]. It can grow or bleed cyclically, and possesses several characteristics of invasive cancer, such as a destructive, invasive, and metastatic nature [2] that subsequently results in pelvic inflammation, adhesion, chronic pain, and infertility, and progresses to biologic malignant tumors [3,4]. The relationship between endometriosis and

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malignant transformation [epithelial ovarian cancer (EOC)] might have been proposed initially as early as 1925 by Sampson [5]. A subsequent study found that cancers arising in endometriosis were not limited to the ovary. The ovary is the most common site (78.7%) [6], and endometriosis at the ovary had a higher risk of EOC compared with the other sites (5% vs. 1%) [7].

Many epidemiologic or molecular studies have indicated that women with endometriosis may have an increased risk of developing EOC [8–28]. However, not all studies supported the positive correlation, thus contributing to many uncertainties. For example, Olson and colleagues [29] did not find any significant association [age-adjusted relative risk 0.8, 95% confidence interval (CI) 0.2–2.4]. Similar results of no association between EOC and endometriosis were also found in studies analyzing patients at an infertility clinic or those who had potential exposure to ovarian inflammatory factors [30–32]. By contrast, two Japanese studies [14,15] reported an especially higher risk of EOC in women with ultrasound-diagnosed ovarian endometrioma [hazard ratios (HR) of 8.95 for all EOCs and 13.5 for specific-type EOCs] than did the majority of other studies [8–13,16–28]. Therefore, it was necessary to carry out an extensive literature search before we tried to conduct the study to investigate the relationship between endometriosis and EOC. We used the term "ovarian cancer risk and endometriosis" (up to February 26, 2014) to search PubMed for relevant English-language articles and identified 278 published articles. Additional reports identified from the articles found during the initial search were reviewed for relevance. We found that nearly all existing evidence was from the Western populations [8–13,16–30], except two above-mentioned studies [14,15]. We analyzed all cohort studies [14,16–18,20,21,27–30], including 133,976 women with endometriosis, and the HR was 1.68 (95% CI 1.52–1.87). The power of the increased risk from this meta-analysis may not be strong to support causality. In addition, biases might further weaken this association [33,34]. For example, the age factor, exposure duration, obstetric and gynecologic history [infertility status, pelvic inflammatory disease (PID), etc.], and Charlson Comorbidity Index (CCI) are all confounding factors associated with either endometriosis or EOC. In fact, not all studies adequately controlled for these confounders. Furthermore, the basic definition of endometriosis varied greatly, from a high possibility of misclassification, such as self-reported endometriosis [29], to a severe selection bias, such as ovarian endometrioma [14,15], which might result in an under- or overestimated risk of developing EOC. Moreover, many authors have used the results (women with diagnosed EOC) to retrospectively investigate the causal factor (women with history of endometriosis) [3].

The other question of whether the exposure time or surveillance affects occurrence of EOC is uncertain. This issue is important, because it influences the final decision-making in the management of women with endometriosis. In addition, the answer to question—whether the risk of EOC is also increased in the Taiwanese population with endometriosis—is unknown, because no study could be referenced. Therefore, we carried out a large-scale, nationwide, controlled cohort study in Taiwan to investigate whether endometriosis women with/without surgical confirmation or the exposure time raises the risk of developing EOC. The findings may help physicians make a better assessment of the risks and benefits associated with surgical management of endometriosis.

Methods

The Taiwanese National Health Insurance (NHI) program was set up in 1995. More than 99% of the residents in Taiwan are enrolled in this program. As of December 2010, it covered >99% of the population (23,074,487 beneficiaries) and contracted with almost all medical hospitals and clinics in Taiwan (25,031 institutions) [35]. The NHI program in Taiwan provides a comprehensive coverage for inpatient and outpatient medical services, including prescription drugs [1]. The National Health Research Institute cooperated with the Bureau of NHI in 2000 to establish an NHI Research Database that would guard the privacy and confidentiality of all beneficiaries and provide health insurance data to researchers who have obtained ethical approval [1]. The Longitudinal Health Insurance Database 2000 (LHID 2000) contains the entire original enrollment and claims data of 1 million beneficiaries, randomly sampled from among the beneficiaries of the NHI Research Database during the period 1996 to 2000. The data of the sampled individuals in the LHID 2000 are representative of all beneficiaries with regard to age, sex, and insurance cost. These data include details of medical orders, procedures, and medical diagnoses with codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modifications* (ICD9-CM), and the identity of all patients in the LHID.

This was a retrospective cohort study (approval for the study was obtained from the local ethics committee; VGHIRB 2012-12-012BC); 191,858 women aged between 20 years and 51 years were identified. Women with a diagnosis of EOC, endometriosis or with a total hysterectomy prior to their diagnosis of endometriosis, and without a visit to an obstetrician or gynecologist during the study period were excluded. To increase the identification validity of the women with endometriosis in the administrative data set, only those women with three or more visits and with a primary diagnosis of endometriosis within 1 year or with one surgically confirmed diagnosis of endometriosis during the period between January 1, 2000, and December 31, 2009 were referred to as women with endometriosis, the exposure group ($n = 7537$).

Each woman in the exposure group was matched with two women in the remaining sample by age, index year, obstetric history, socioeconomic status, work, and urbanization (Fig. 1), because many of these factors were reported to be correlated with the occurrence of invasive EOC [8–10,12,13,16,21–25,30]. The matched women without endometriosis were referred to as the nonexposure group ($n = 15,074$). For the exposure group, the index date was the date of the first visit/admission between 2000 and 2009 that resulted in a diagnosis code for endometriosis (ICD9-CM code 617.0–617.9). For the nonexposure group, the index date was the first visit/admission to an obstetric/gynecological provider during the study period.

Invasive EOC was initially detected in inpatients with a surgicopathological diagnosis and validated using the major disease files (ICD-9-CM 183.0 from the Registry for Catastrophic Illness Patients). Because synchronous endometriosis and EOC is commonly found and the prevalence of endometriosis in invasive EOC may vary in different subtypes of EOC [e.g., clear cell (35–39%), endometrioid (21–27%), serous (3–5%), and mucinous type (3–4%)] [36]—and to clarify the subsequent risk of developing EOC in women with endometriosis—we excluded patients with synchronous endometriosis and EOC. Furthermore, we also excluded those women with a diagnosis of EOC within 1 year after their first diagnosis of endometriosis or the first visit/admission to an obstetric/gynecological provider.

Statistical analysis

Starting from the cohort index date, the study participants were followed until the occurrence of hospitalization with EOC (ICD-9-CM 183.0) or death, whichever came first, or to the end of the study (December 31, 2010) if no EOC or death had occurred. Basic characteristics are presented as a percentage. The incidence of EOC was compared between the women with and without endometriosis using the incidence rate (IR). The Cox proportional hazards