

Original Article



Risk factors in progression from endometriosis to ovarian cancer: a cohort study based on medical insurance data

An Jen Chiang^{1,2}, Chung Chang,³ Chi-Hsiang Huang,³ Wei-Chun Huang,^{4,5,6}
Yuen-Yee Kan,⁷ Jiabin Chen^{8,9}

¹Department of Obstetrics and Gynecology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

²Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan

³Department of Applied Mathematics, National Sun Yat-sen University, Kaohsiung, Taiwan

⁴Critical Care Center and Cardiovascular Medical Center, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

⁵Department of Physical Therapy, Fooyin University, Kaohsiung, Taiwan

⁶School of Medicine, National Yang-Ming University, Taipei, Taiwan

⁷Department of Obstetrics and Gynecology, Yuan's General Hospital, Kaohsiung, Taiwan

⁸Multidisciplinary Science Research Center, National Sun Yat-sen University, Kaohsiung, Taiwan

⁹Da-Yeh University, Changhua, Taiwan

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Correspondence to

Jiabin Chen

Multidisciplinary Science Research Center,
National Sun Yat-sen University, 70 Lienhai
Road, Kaohsiung 80424, Taiwan.

E-mail: jiabinchung@gmail.com

Chung Chang

Department of Applied Mathematics, National
Sun Yat-sen University, 70 Lienhai Road,
Kaohsiung 80424, Taiwan.

E-mail: cchang@math.nsysu.edu.tw

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cited.

ORCID iDs

An Jen Chiang

<https://orcid.org/0000-0001-6892-8559>

Jiabin Chen

<https://orcid.org/0000-0002-6859-4293>

ABSTRACT

Objective: The objective was to identify risk factors that were associated with the progression from endometriosis to ovarian cancer based on medical insurance data.

Methods: The study was performed on a dataset obtained from the National Health Insurance Research Database, which covered all the inpatient claim data from 2000 to 2013 in Taiwan. The International Classification of Diseases (ICD) code 617 was used to screen the dataset for the patients who were admitted to hospital due to endometriosis. They were then tracked for subsequent diagnosis of ovarian cancer, and available biological, socioeconomic and clinical information was also collected. Univariate and multivariate analyses were then performed based on the Cox regression model to identify risk factors. C-index was calculated and cross validated.

Results: A total of 229,617 patients who were admitted to hospital due to endometriosis from 2000 to 2013 were included in the study, out of whom 1,473 developed ovarian cancer by the end of 2013. A variety of factors, including age, residence, hospital stratification, premium range, and various comorbidities had significant impact on the progression ($p < 0.05$). Among them, age, urbanization of residence, hospital stratification, premium range, post-endometriosis childbearing, pelvic inflammation, and depression all had independent, significant impact ($p < 0.05$). The validated C-index was 0.69.

Conclusion: For a woman diagnosed with endometriosis, increased age, residing in a highly urbanized area, low or high income, depression, pelvic inflammation, and absence of childbearing post-endometriosis all put her at high-risk to develop ovarian cancer. The findings may be of help to gynecologists to identify high-risk patients.

Keywords: Endometriosis; Ovarian Neoplasms; Risk Factors; Cohort Studies

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: C.A.J., C.C., C.J.; Data curation: C.C., H.C.H., C.J.; Formal analysis: H.C.H.; Funding Acquisition: C.A.J., C.C.; Investigation: C.A.J., C.C., H.C.H., H.W.C., K.Y.Y., C.J.; Methodology: C.C., H.C.H., C.J.; Project administration: C.A.J., C.C., C.J.; Resources: C.A.J., H.W.C., K.Y.Y.; Software: C.C., H.C.H.; Supervision: C.A.J., C.C., C.J.; Validation: H.C.H.; Visualization: H.C.H., C.J.; Writing - original draft: C.J.; Writing - review & editing: C.A.J., C.C., C.J.

INTRODUCTION

Endometriosis is a condition in which endometrial glands and stroma grow outside of the endometrial lining and uterine musculature [1,2]. It affects 1% to 10% women of reproductive age and can be associated with substantial morbidity such as pelvic pain and infertility [3,4]. Although a benign gynecologic disorder itself, endometriosis puts one at risk for ovarian cancer [5-7].

Ovarian cancer is the second leading cause of death among gynecologic cancers worldwide [8]. Unfortunately, most women are diagnosed at an advanced stage, and the 5-year survival rate ranges from 30% to 90% while the recurrence rate, 20% to 75%, according to the stage of the disease [9]. The global burden of ovarian cancer is immense, not only to patients and their families, but also to healthcare institutes and social economies.

The link between endometriosis and ovarian cancer has been well established although the exact mechanisms underlying the progression are not entirely understood. There is some evidence that atypical endometriosis may represent a transition to carcinoma, while 2 histotypes of ovarian cancer, clear cell and endometrioid carcinomas, are particularly associated with endometriosis [10,11]. On top of pathogenesis, there may also remain other factors that potentially affect the progression from endometriosis to ovarian cancer, and, unfortunately, few studies have established convincing results. This study therefore was aimed to identify risk factors that were associated with the progression from endometriosis to ovarian cancer based on a cohort.

MATERIALS AND METHODS

The study was based on the National Health Insurance Research Database (NHIRD, case number: NHIRD-104-071). The dataset used covered all the inpatient claim data from 2000 to 2013 in Taiwan. The study was approved by the Internal Review Board of Kaohsiung Veterans General Hospital (IRB number: VGHS15-EM4-01) and was in accordance with the Declaration of Helsinki.

The International Classification of Diseases (ICD) code 617 (617.0 through 617.9) was used to screen the dataset for the patients who were admitted to hospital due to endometriosis. The search resulted in 233,277 patients. They were then tracked for subsequent diagnosis of ovarian cancer (ICD code 183.0–183.9), and available biological, socioeconomic, and clinical information was also collected. Then 144 patients were excluded from the study since they had been diagnosed with ovarian cancer before being hospitalized for endometriosis and 887 were later excluded due to scanty information available. The patient information collected included age, urbanization of residence [12], premium ranges [13], hospital stratification, a wide range of comorbidity such as coronary heart disease, diabetes, depression and dementia, malignancies other than ovarian cancer, and post-endometriosis parity. A list of variables used can be found in **Table 1**.

All the statistical analysis was carried out with the statistical computing and graphic drawing language, R (R Core Team, Vienna, Austria; <http://www.Rproject.org>) [14]. The univariate and multivariate analyses were performed based on the Cox regression model. The nomogram was drawn with an R package, rms. In calculating the concordance statistic

Table 1. Characteristics of the cohort in study

| Variables (n=229,617) | Medium (range) |
|---------------------------------------|--------------------|
| Age (yr) | 41.07 (2.24–96.41) |
| Time to ovarian cancer (day) | 2,438 (0–5,113) |
| Post-endometriosis ovarian cancer (%) | 0.64 |
| Hospital stratification (%) | |
| Medical centers | 49.28 |
| Regional hospitals | 37.32 |
| District hospitals | 12.58 |
| Local hospitals | 0.82 |
| Urbanization (%) | |
| Highly urbanized | 35.71 |
| Moderately urbanized | 32.03 |
| Newly urbanized | 15.40 |
| Rural areas | 11.02 |
| Others* | 5.84 |
| Premium range (monthly income, NTD) | |
| >15,840 and ≤25,000 | 15.56 |
| ≤15,840 | 47.73 |
| >25,000 | 36.71 |
| Comorbidity | |
| Myocardial infarction | 0.14 |
| Congestive heart failure | 0.42 |
| Peripheral vascular disease | 0.11 |
| Cerebrovascular diseases | 1.18 |
| Dementia | 0.05 |
| Chronic pulmonary disease | 1.08 |
| Rheumatologic disease | 0.45 |
| Peptic ulcer disease | 2.02 |
| Mild liver disease | 0.40 |
| Diabetes | 2.76 |
| Diabetes with chronic complications | 0.38 |
| Hemiplegia/paraplegia | 0.17 |
| Renal disease | 0.41 |
| Moderate/severe liver disease | 0.15 |
| AIDS | 0.00 |
| Parkinson's disease | 0.09 |
| Stroke | 1.18 |
| Coronary heart disease | 1.21 |
| Immune rheumatism | 0.45 |
| Depression | 1.36 |
| Hypertension | 5.22 |
| Hyperlipidaemia | 1.53 |
| Pelvic inflammation | 6.36 |
| Childbearing post endometriosis | 9.65 |

AIDS, acquired immune deficiency syndrome; NTD, New Taiwan Dollar.

*Others includes areas with aged population, agrarian towns and cities, and remote areas.

(C-index), cross validation was performed for 50 times, and at each time, 4/5 of the patients were randomly chosen as the training set and 1/5, testing set. Details of making the nomogram and calculating the C-index with the validation process are provided in the supplementary files (**Supplementary Data 1, 2, and Supplementary Table 1**).

RESULTS

A total of 229,617 patients who were admitted to hospital due to endometriosis from 2000 to 2013 in Taiwan were included in the study. Out of these patients, 1,473 eventually developed ovarian cancer by the end of 2013. Demographic information of all the patients, including

Table 2. Significant factors in univariate analysis

| Variables | Hazard ratio | p | 95% confidence interval |
|---------------------------|--------------|--------|-------------------------|
| Age (yr) | 1.06 | <0.001 | 1.06–1.07 |
| Hospital stratification | | | |
| Medical centers | Reference | | |
| Regional hospitals | 0.61 | <0.001 | 0.54–0.68 |
| District hospitals | 0.46 | <0.001 | 0.54–0.56 |
| Local hospitals | 0.19 | <0.001 | 0.06–0.58 |
| Urbanization | | | |
| Highly urbanized | Reference | | |
| Moderately urbanized | 0.80 | <0.001 | 0.70–0.90 |
| Newly urbanized | 0.72 | <0.001 | 0.61–0.85 |
| Rural areas | 0.72 | <0.001 | 0.60–0.87 |
| Others* | 0.81 | 0.070 | 0.64–1.02 |
| Premium range (NTD/month) | | | |
| >15,840 and ≤25,000 | Reference | | |
| ≤15,840 | 1.25 | <0.001 | 1.08–1.44 |
| >25,000 | 1.23 | <0.001 | 1.10–1.38 |
| Comorbidity | | | |
| Congestive heart failure | 2.46 | <0.001 | 1.50–4.03 |
| Cerebrovascular diseases | 1.79 | <0.001 | 1.27–2.52 |
| Peptic ulcer disease | 1.83 | <0.001 | 1.41–2.38 |
| Mild liver disease | 1.89 | 0.030 | 1.07–3.34 |
| Diabetes | 1.99 | <0.001 | 1.60–2.47 |
| Renal disease | 2.87 | <0.001 | 1.80–4.57 |
| Stroke | 1.79 | <0.001 | 1.27–2.52 |
| Depression | 1.86 | <0.001 | 1.35–2.56 |
| Hypertension | 2.05 | <0.001 | 1.74–2.41 |
| Pelvic inflammation | 1.85 | <0.001 | 1.58–2.17 |
| Childbearing | 0.33 | <0.001 | 0.25–0.44 |

NTD, New Taiwan Dollar.

*Others includes areas with aged population, agricultural towns and cities, and remote areas.

distribution of age, occurrence rate and time-to-event of ovarian cancer, urbanization of residence, premium range and all the comorbidities, is summarized in **Table 1**.

Univariate analysis was performed as a preliminary screen for factors that impacted the progression to ovarian cancer. All the available variables were tested and a p-value of 0.05 was used as the threshold to select for significant factors. A variety of factors, including age, residence, hospital stratification, premium range, and various comorbidities were shown in the tests to have significant impact on the progression. A complete list of these factors is summarized in **Table 2**.

Multivariate analysis was then performed on the above factors to identify independent risk factors in the progression. As shown in **Table 3**, age, urbanization of residence, hospital stratification, premium range, post-endometriosis childbearing, pelvic inflammation and depression all had independent, significant impact on the progression to ovarian cancer.

The above independent factors were combined together and a nomogram was calculated in **Fig. 1** in order to show the predicted risk of a patient with endometriosis to progress to ovarian cancer at various time points. In the nomogram, the first line of points gives the weights of each risk factor while the line of total points, obtained by adding up the weights of all the risk factors, is used to locate the survival probability with ovarian cancer as the end event at a given time point. Therefore, for a woman aged at 50 (with 50 points), diagnosed with endometriosis at a medical center (hospital stratification 1, corresponding to 21 points),

Table 3. Independent risk factors in multivariate analysis

| Variables | Hazard ratio | p | 95% confidence interval |
|---------------------------|--------------|--------|-------------------------|
| Age (yr) | 1.06 | <0.001 | 1.06–1.07 |
| Hospital stratification | | | |
| Medical centers | Reference | | |
| Regional hospitals | 0.64 | <0.001 | 0.57–0.72 |
| District hospitals | 0.50 | <0.001 | 0.41–0.61 |
| Local hospitals | 0.28 | 0.030 | 0.09–0.86 |
| Urbanization | | | |
| Highly urbanized | Reference | | |
| Moderately urbanized | 0.85 | 0.010 | 0.75–0.96 |
| Newly urbanized | 0.77 | <0.001 | 0.66–0.91 |
| Rural areas | 0.79 | 0.010 | 0.65–0.95 |
| Others* | 0.87 | 0.240 | 0.69–1.10 |
| Premium range (NTD/month) | | | |
| >15,840 and ≤25,000 | Reference | | |
| ≤15,840 | 1.27 | <0.001 | 1.10–1.46 |
| >25,000 | 1.23 | <0.001 | 1.10–1.38 |
| Comorbidity | | | |
| Depression | 1.67 | <0.001 | 1.21–2.30 |
| Pelvic inflammation | 2.73 | <0.001 | 2.32–3.22 |
| Childbearing | 0.69 | 0.010 | 0.52–0.92 |

NTD, New Taiwan Dollar.

*Others includes areas with aged population, agricultural towns and cities, and remote areas.

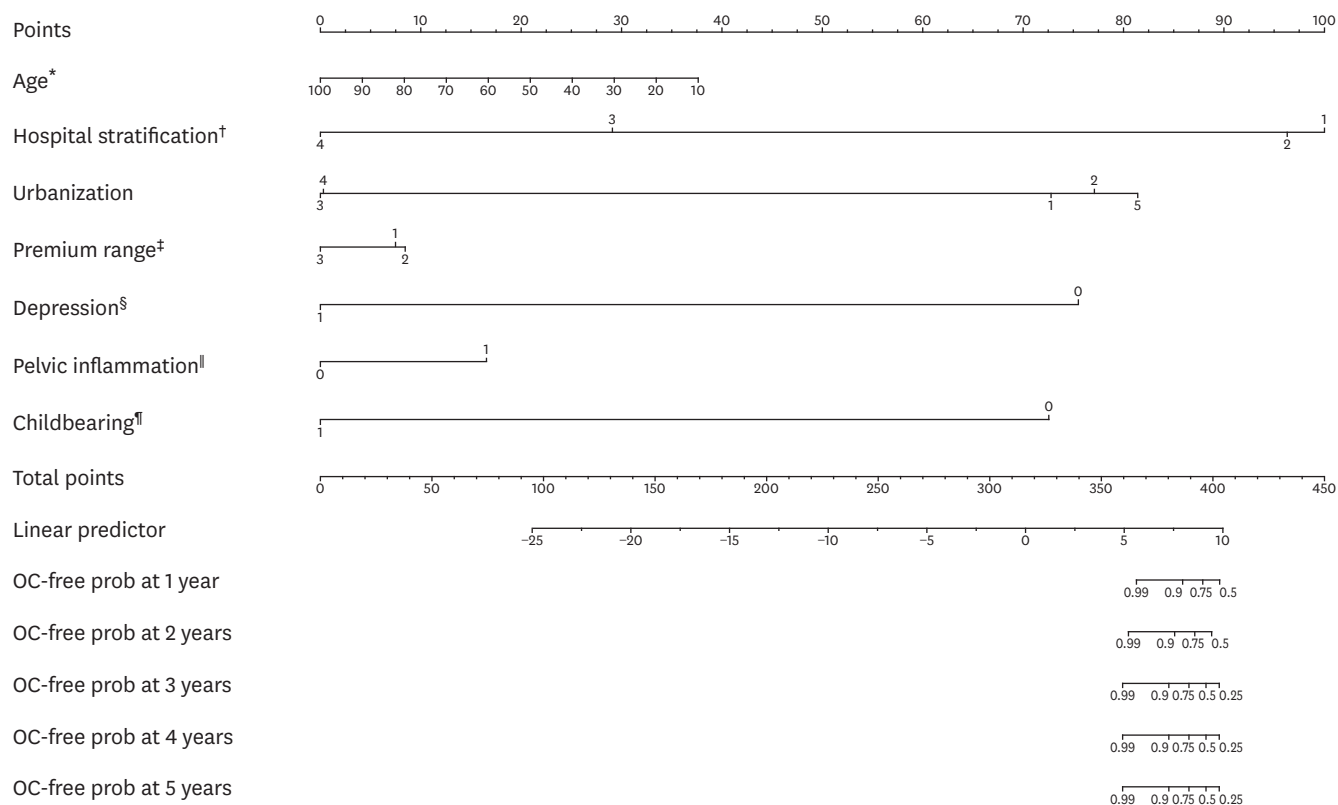


Fig. 1. Nomogram of risk factors in the progression from endometriosis to ovarian cancer.

OC-free prob, ovarian cancer-free probability; NTD, New Taiwan Dollar.

The scales of the risk factors are as follows: *Age: continuous; †Hospital stratification: 1, medical center; 2, regional hospitals; 3, district hospitals; 4, local hospitals; ‡Premium range in NTD: 1, >15,840 and ≤25,000; 2, ≤15,840; 3, >25,000; §Depression: 0, none; 1, history of depression; ||Pelvic inflammation: 0, none; 1, history of pelvic inflammation; ¶Childbearing: 0, none after endometriosis; 1, history of birth-giving after endometriosis.

living in a highly urbanized area (urbanization 1, corresponding to 4 points), paying at the highest premium range (with 3 points), with a history of depression (with 9 points) and pelvic inflammation (with 17 points), and without a history of giving birth (with 6 points), she has a total points of 110, and that puts her probability of surviving 5 years post-endometriosis diagnosis without developing ovarian cancer at 0.95. The reliability of such a probability may be tested by calculating the C-index, which tests the risk factors for their predictivity of ovarian cancer occurrence following diagnosis of endometriosis. We performed the calculation with 5-fold cross validation and the validated C-index was 0.69.

DISCUSSION

Many studies have established that endometriosis is a precursor of ovarian cancer, and many more are directed to explore the factors that trigger the former to take a turn for malignant transition. The present study, although not touching on molecular or pathologic mechanisms of the transition, identified factors associated with the progression from endometriosis to ovarian cancer, and was thus helpful with identification of high-risk patients.

The study started with a cohort of patients who were hospitalized due to endometriosis. We did not resort to patient surveys on medical history as patients' own recollection may not be entirely accurate. After all, aside from errors in memories, some affected by endometriosis may not even be aware of it as many may have none or little morbidity. Nor did we resort to out-patient records to screen for endometriosis patients because, unfortunately, there was usually substantial overlap of symptoms between endometriosis and other causes, and out-patient records would not be enough to ascertain the diagnosis of endometriosis [15]. By starting with the in-patient cohort, we could be assured that the subsequent analysis was firmly based on clear diagnosis of endometriosis.

We identified a few independent factors that were associated with the progression of endometriosis to ovarian cancer, and some of them had been previously suggested to be linked to incidence of ovarian cancer. Depression is a common public health problem and has been found to be associated with a variety of health concerns such as obesity and metabolic dysfunction while a few studies also linked it with an increased risk of ovarian cancer [16-18]. In addition, pelvic inflammatory disease has also been associated with higher risk of ovarian cancer and there is some evidence that it may be histotype specific [19,20].

Among the other risk factors were those associated with one's biological and socioeconomic status. Higher age, residing in a highly urbanized area and both low and high income all facilitated the progression to ovarian cancer. The socioeconomic status of the patients in this study was embodied by their medical insurance premiums, and the lower cutoff value used here, 15,840 New Taiwan Dollar (NTD), corresponded to the amount of monthly income at the level of the government-stipulated minimum wage for full-time employees in Taiwan, and the higher cutoff, 25,000 NTD, was previously described to indicate high socioeconomic status [13]. Although the classifications here were based on local standards, the findings associated with the classifications may still bring insights for other regions around the world. After all, what the findings pointed to was not any absolute amount of income, but one's socioeconomic status in a society. We argue that higher age is associated with diseases of any kind and the other factors may have something to do with a highly stressed environment while the stress may be caused by urbanization, work pressure that is potentially associated

with both high and low income, poor living conditions associated with low income and unhealthy lifestyles associated with high income. The results highlighted the importance to watch one's living condition and life styles in prevention of the malignant transformation.

The last but the not least risk factor was absence of childbearing after endometriosis. It is estimated that 90% of the women with infertility has endometriosis [1]. Childbearing after hospital discharge post-endometriosis suggests remission of the disorder, and it is therefore reasonable to deduct that treatment for endometriosis, especially those focused on infertility, may help prevent the progression to malignancy.

The predictivity of the risk factors was illustrated visually with the nomogram and statistically with C-index. The nomogram demonstrated the probability of any given patient with endometriosis to develop ovarian cancer at a given year when her points of all the factors were added up. Such a risk measurement shall be of help to gynecologists when assessing patient risk as well as to patients themselves seeking for medical consultation. In addition, the C-index calculated in the study was also validated, i.e., the patients were randomly classified into a training set and a testing set, and the procedure was repeated for 50 times. The validated C-index highlighted the predictivity of the risk factors.

There were a few limitations to the study. First, it was a retrospective study and thus had limitations inherent in all such studies. Second, although based on a large sample size ($n=229,617$), it lacked details on clinical characteristics such as subtypes of endometriosis, diagnostic tools, histological information of ovarian cancer and cancer stage. Furthermore, there have been a growing body of studies on the accuracy of ICD codes [21,22], and unfortunately, the study was based on ICD codes to identify diseases of interest, and was thus subject to the errors and limitations of the ICD coding system. In addition, the overall incidence of ovarian cancer is low and only 0.64% of the cohort eventually developed the disease. The imbalance between those with ovarian cancer and those without might have resulted in bias in the conclusion.

In conclusion, for a woman diagnosed with endometriosis, increased age, residing in a highly urbanized area, low or high income, depression, pelvic inflammation, and absence of childbearing post-endometriosis all put her at high-risk to develop ovarian cancer. The findings may be of help to gynecologists to identify high-risk patients.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1

Nomogram codes.

[Click here to view](#)

Supplementary Data 2

C-index calculation and cross validation.

[Click here to view](#)

Supplementary Table 1

Example of the data format used to plot the nomogram

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