

Research Paper

The Risk of Gynecologic and Urinary Tract Cancer with Pelvic Inflammatory Disease: A Population-Based Cohort Study

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Abstract

Purpose: The aim of the study was to determine the association between pelvic inflammatory disease (PID) and breast, colorectal, gynecologic and urinary tract cancer.

Methods: The source of data was a longitudinal dataset compiled by the Longitudinal Health Insurance Database 2000 (LHID2000) which was collected by the National Health Insurance program. Cases of PID, at least two outpatient visits and one admission, were diagnosed from 2000 to 2013. The data for controls, age matched women who were not diagnosed with PID from 2000 to 2013, were also obtained.

Results: A total of 47,333 PID cases and 189,332 for control group were included in the study. The ectopic pregnancy incidence rate (per 10000 person months) was 1.912 and 0.595 in the PID and control group, respectively; the rate ratio was 3.211 (confidence interval, CI = 2.931-3.519). There were significantly different in gynecologic cancers and urinary tract cancers between the PID and control group; the rate ratios (95% C.I.) were 1.903 (1.672-2.166) and 1.566 (1.211-2.025), respectively.

Conclusion: Our study found that PID was associated with increased risks of gynecologic and urinary tract cancer but not colorectal or breast cancer. The information may lead to a strategy for cancer prevention and a reasonable healthcare usage through understanding PID epidemiology and controlling the inflammatory responses.

Key words: breast, colorectal, gynecologic, urinary tract cancer, pelvic inflammatory disease

Introduction

Pelvic inflammatory disease (PID) is an infection-induced inflammation disease of the female upper genital tract. It involves any combination of the uterine endometrium, fallopian tubes, ovaries and

pelvic peritoneum [1]. Long-term complications of PID and adverse sequelae after PID are concerned in clinical care for its inflammation resulting in tubal scarring and damage which lead to reproductive

disability, such as ectopic pregnancy and infertility [2].

Cancer linked to inflammation was perceived since the 19th century [3]. Inflammation in selected organ may increase the risk of cancer [3]. Cancer-related inflammation links to genetic instability by inflammatory mediators [3]. Molecular pathways, which link inflammation and cancer, have been reported [4-6]. Tumor microenvironment is an indispensable participant in the neoplastic process, proliferation and migration; some of the signaling molecules of the innate immune system are co-opted by tumor cells. Therefore, inflammation is a crucial component of tumor progression [4]. Inflammatory cells and cytokines in tumors could contribute to tumor growth, progression, and immunosuppression [5]. The mediators and cellular effectors of inflammation play important roles for local environment of tumors [6]. Inflammation has been established as an enabling characteristic of cancer and as a hallmark of cancer by molecular biology evidence [7].

Epidemiology researches for the association of PID with cancers have been investigated [8]; researches involving PID in association with a certain type of gynecologic cancers have been proposed. However, the results are not all consistent [8-16]. More investigations are required to clarify the risk of diseases for PID patients [13]. Understanding PID epidemiology leads to reasonable healthcare usage.

The aim of the present study was to investigate

the risks of breast cancer, colorectal cancer, gynecologic cancer and urinary tract cancer in the female patients with PID by a population-based cohort study.

Materials and Methods

Data source

The source of data was a longitudinal dataset compiled by the Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 contains registration and claim data of 1,000,000 individuals, randomly sampled from registry file of 2000, collected by the National Health Insurance program. There were no significant differences between the patients in the LHID2000 and the original National Health Insurance Research Database (NHIRD) in general distribution. (https://nhird.nhri.org.tw/en/Data_Subsets.html). The NHIRD contains comprehensive information regarding clinical detailed and diagnostic codes based on the International Statistical Classification of Diseases and Related Health Problems codes (ninth revision, clinical modification), namely ICD-9-CM codes.

Study population

This is a retrospective cohort study. Flow chart of this study was shown in Figure 1. Cases of PID were diagnosed, individuals with ICD-9-CM code 614,615 (at least two outpatient visits and one admission), from 2000 to 2013 in the national health insurance dataset according to the characteristic criteria of national guidelines for PID. Those PID cases diagnosed before 2002, after 2012 or not been full-matched were excluded. The data for controls, age matched women who were not diagnosed with PID from 2000 to 2013, were also obtained.

The main outcomes of our study included ectopic pregnancy (ICD-9: 633), colorectal cancer (ICD-9: 154), breast cancer (ICD-9: 174), gynecologic cancer (ICD-9: 179-184) and urinary tract cancer (ICD-9: 188-189). The considered variables of our study included age at baseline (matching variable), urbanization (urban, suburban, rural), income (non-low, low income), outpatient visit within 2 years before baseline (0, 1-13, 14-27, 28-55, >=56), length of hospital stay within 2 years before baseline (0, 1-6, 7-13, >=14). The co-morbidities were also concerned in this study, including asthma (ICD-9:

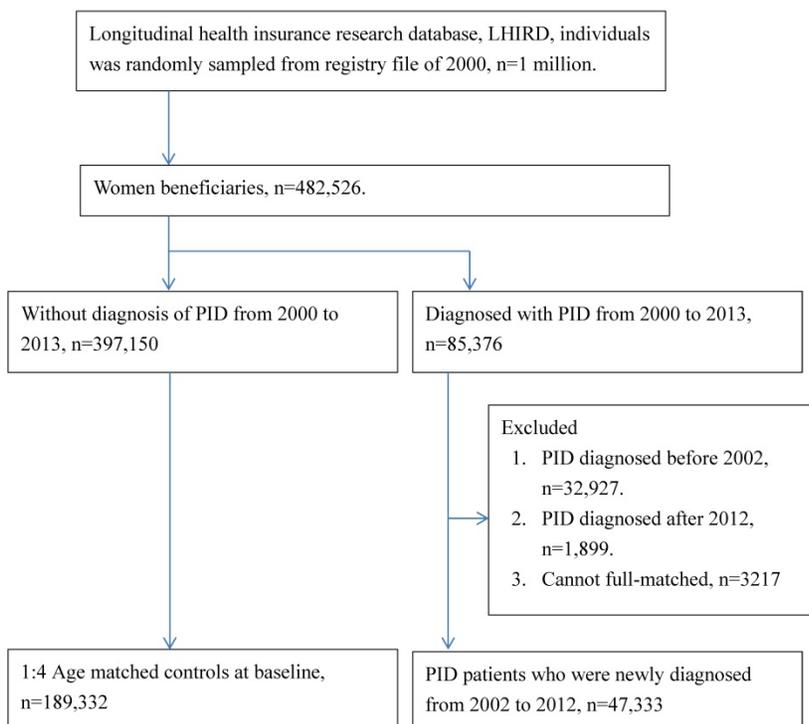


Figure 1. Flow chart of this study. PID, pelvic inflammatory disease

493), atopic dermatitis (ICD-9: 691.0), chronic liver disease (ICD-9: 571), peptic ulcer (ICD-9: 531-534), zoster (ICD-9: 053, 054), hepatitis B virus infection (ICD-9: 070.2, 070.3, V02.61), hepatitis C virus infection (ICD-9: 070.44, 070.51, 070.54, 070.7, V02.62), gout (ICD-9: 274), chronic lung diseases (ICD-9: 490-492 495 496, 500-508), cerebrovascular diseases (ICD-9: 430-438), ischemic heart diseases (ICD-9: 410-414), congestive heart failure (ICD-9: 428, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 429.4, 398.91), renal failure (ICD-9: 40301, 40401, 40403, 40411, 40413, 40491, 40493, 584, 585, 586), urinary tract infection (ICD-9: 590, 595, 597, 5990).

Follow up

For each specific main event, the prevalent cases were excluded from the baseline. All cases, including the PID and control, were followed up until event occurrence, death, or end of study (Dec, 2013).

Statistical analysis

The two-tailed student t test and chi-square test were used for comparing the difference of continue and category variables between PID and control group. The time to event analysis was performed to estimate the incidence risk of main events between groups.

The hazard ratios (HRs) of main events with PID exposure estimated by Cox proportional hazard model in different statistical modeling, including univariate, multivariate modeling and inverse propensity score weighting. The inverse propensity score weighting Cox proportional hazard models was conducted to explore the hazard ratios, while the confounding bias may be exist in our study. KM plotter evaluation of main outcomes (ectopic pregnancy, colorectal cancer, breast cancer, gynecologic cancer, and urinary tract cancer) between the PID and control were also conducted.

Results

A total of 47,333 PID cases and 189,332 for control group were included in this study (Figure 1). The characteristics between the PID and control group were shown in Table 1. The significant variables existed between the PID and control group, including urbanization, low income, outpatient visits, length of hospital stay, comorbidities, old events (ectopic pregnancy, colorectal cancer, breast cancer, gynecologic cancers and urinary tract cancers) before baseline.

The incidence rates and rate ratios of main outcomes for the PID and control groups were shown in Table 2. The ectopic pregnancy incidence rate (per 10000 person months) was 1.912 and 0.595 in the PID and control group, respectively; the rate ratio was

3.211 (confidence interval, CI = 2.931-3.519). There were significantly different in gynecologic cancer and urinary tract cancer between the PID and control group (Table 2); the rate ratios (95% C.I.) were 1.903 (1.672-2.166) and 1.566 (1.211-2.025), respectively. However, there were no significant differences in colorectal cancer and breast cancer between the PID and control group; the rate ratios (95% C.I.) were 1.281 (0.989-1.659) and 1.030 (0.923-1.150), respectively.

Table 1. baseline characteristics of PID and control groups.

	Group		p value
	Control N=189,332	PID N=47,333	
Age at baseline			1.0000
<15	936 (0.49%)	234 (0.49%)	
15-24	41004 (21.66%)	10251 (21.66%)	
25-34	51968 (27.45%)	12992 (27.45%)	
35-44	48320 (25.52%)	12080 (25.52%)	
45-54	31448 (16.61%)	7862 (16.61%)	
55-64	9648 (5.1%)	2412 (5.1%)	
>=65	6008 (3.17%)	1502 (3.17%)	
Urbanization			<0.0001
Urban	120550 (63.67%)	28975 (61.22%)	
Sub-urban	53242 (28.12%)	14062 (29.71%)	
Rural	15540 (8.21%)	4296 (9.08%)	
Low income	1098 (0.58%)	353 (0.75%)	<0.0001
Outpatient visits			<0.0001
0	11526 (6.09%)	184 (0.39%)	
1-13	58988 (31.16%)	7229 (15.27%)	
14-27	55537 (29.33%)	13854 (29.27%)	
28-55	46680 (24.66%)	17638 (37.26%)	
>=56	16601 (8.77%)	8428 (17.81%)	
Length of hospital stay			<0.0001
0	167806 (88.63%)	38465 (81.26%)	
1-6	15674 (8.28%)	6667 (14.09%)	
7-13	3426 (1.81%)	1437 (3.04%)	
>=14	2426 (1.28%)	764 (1.61%)	
Old event before baseline			
Ectopic pregnancy	758 (0.40%)	656 (1.39%)	<0.0001
Colorectal cancer	115 (0.06%)	36 (0.08%)	0.2379
Breast cancer	809 (0.43%)	214 (0.45%)	0.4615
Gynecologic cancer	532 (0.28%)	317 (0.67%)	<0.0001
Urinary tract cancer	100 (0.05%)	47 (0.10%)	0.0003
Co-morbidities			
Asthma	5925 (3.13%)	2003 (4.23%)	<0.0001
Atopic dermatitis	269 (0.14%)	121 (0.26%)	<0.0001
Chronic liver disease	10093 (5.33%)	3503 (7.40%)	<0.0001
Peptic ulcer	16336 (8.63%)	6599 (13.94%)	<0.0001
Zoster	5487 (2.90%)	1816 (3.84%)	<0.0001
Hepatitis B virus infection	2559 (1.35%)	854 (1.80%)	<0.0001
Hepatitis C virus infection	701 (0.37%)	241 (0.51%)	<0.0001
Gout	3228 (1.70%)	1109 (2.34%)	<0.0001
Chronic lung diseases	9921 (5.24%)	3402 (7.19%)	<0.0001
Cerebrovascular diseases	2431 (1.28%)	757 (1.60%)	<0.0001
Ischemic heart diseases	4649 (2.46%)	1764 (3.73%)	<0.0001
Congestive heart failure	1323 (0.70%)	469 (0.99%)	<0.0001
Renal failure	909 (0.48%)	267 (0.56%)	0.0201
Urinary tract infection	23788 (12.56%)	12860 (27.17%)	<0.0001

PID, pelvic inflammatory disease

The hazard ratios (HRs) of main events with PID exposure were shown in Table 3. There were no significant difference between the PID and control group in the hazard ratio of breast and colorectal

cancer by univariate, multivariate modeling and inverse propensity score weighting analyses. Hazard ratio of gynecologic cancer in PID group was significantly different from the control group by using varied modeling analyses (Table 3). In analyzing the hazard ratio of urinary tract cancer, there was no statistically significance between the PID and control group by multivariate modeling analysis; there were statistically significance between the PID and control group by univariate modeling and inverse propensity score weighting analyses. By using inverse propensity score weighting model, the main outcomes, including ectopic pregnancy, gynecologic cancer and urinary tract cancer, showed significant differences between the PID and control group.

KM plotter evaluations of main outcomes (ectopic pregnancy, colorectal cancer, breast cancer, gynecologic cancer, urinary tract cancer) between the PID and control group were shown in Figure 2.

Discussion

Our study found that PID was associated with increasing risks of ectopic pregnancy, gynecologic cancer and urinary tract cancer but not colorectal cancer or breast cancer. Most cases of gynecologic cancer were diagnosed within one year after episode of PID.

The result involving the association of PID with ectopic pregnancy of our study is consistent with previous studies [17, 18]. Tubal damage caused by PID increases the risk of ectopic pregnancy and infertility. The association of tubal factor infertility after PID with number and severity of PID episodes was reported by a cohort study using diagnostic laparoscopy (index laparoscopy) to verify disease for clinical suspicious of acute PID patients [17]. The authors also demonstrated that the incidences of ectopic pregnancy in the first pregnancy patients after laparoscopically-confirmed PID and those without PID at laparoscopy were 9.1% and 1.4%, respectively [17]. The increased expression of uteroglobin in damaged fallopian tubes by PID was proposed by Quintar et al [19]. The authors claimed that situation may play an important role in ectopic pregnancy.

The association between PID and colorectal

cancer was shown by a matched cohort study through 5-year follow-up period by using the data from the Longitudinal Health Insurance Database 2005 (LHID2005) in Taiwan [20]. The adjusted hazard ratio of colorectal cancer risk for women with PID compared to the comparison cohort was 1.71 (95% CI 1.10–2.65) [20]. The researchers constructed the PID patient group by at least two consensus diagnosis of PID and excluded women younger 13 years or older than 45 years of age. Some important information of the study subjects was not contained in the Database, and this led to a limitation of uniform diagnosis of PID [21, 22]. Re-analyzing biological gradient was performed by the researchers and the colorectal cancer probabilities were related to frequencies of PID visit [22]. The odds ratio of colorectal cancer during visits 1–12 and >12 visits for PID patients compared with the control group were 1.72 ($p = 0.019$) and 2.84 ($p = 0.043$), respectively [22]. In our study, we defined the PID patients with at least two outpatient visits and one admission. Rate ratio of colorectal cancer in PID and control groups were 1.281 (Table 2). Adjusted hazard ratio of colorectal cancer with PID exposure, estimated by Cox proportional hazard model in inverse propensity score weighting model, revealed 1.185. There was no significant association between PID and colorectal cancer also shown by KM plotter evaluation (Figure 2).

The association between PID and ovarian cancer was firstly reported by Risch and Howe. A case-control study, including 450 cases of epithelial ovarian cancer and 565 population controls during 1989–1992, was conducted [23]. The authors showed that PID increased the risk of developing epithelial ovarian cancer and inflammatory changes of the ovarian epithelium played a crucial role for the association [23]. However, Parazzini et al. analyzed the association between history of PID and the risk of subsequent epithelial ovarian cancer by conducting a case-control study during 1983–1991 in Italy [24]. The cases studied were 971 females with epithelial ovarian cancer and control subjects were 2758 women. The authors demonstrated absence of association between history of PID and risk of ovarian cancer [24].

Table 2. Incidence rates of main outcomes in PID and control groups.

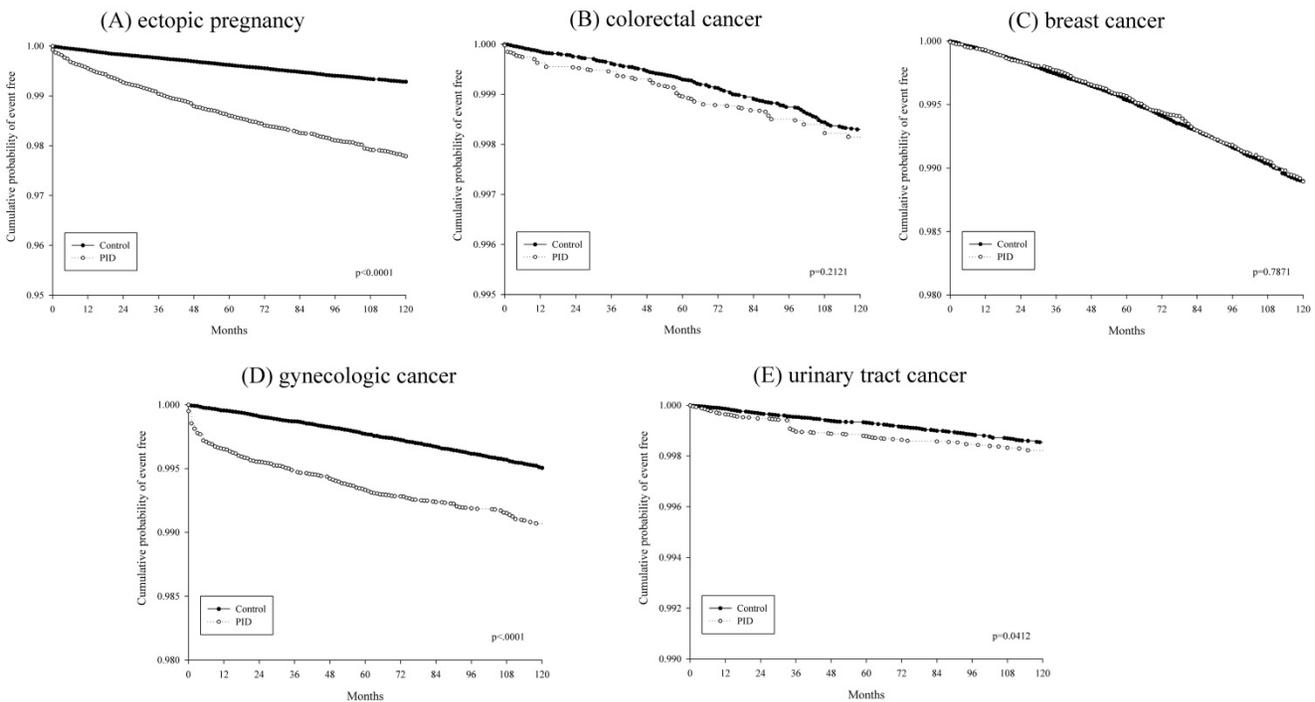
	Control N=189,332				PID N=47,333				Rate ratio (95% C.I.)
	At risk n at baseline	Follow up person months	Event	Incidence rate*	At risk n at baseline	Follow up person months	Event	Incidence rate*	
Main outcome									
Ectopic pregnancy	188409	17366854	1034	0.595	46739	4314786	825	1.912	3.211(2.931-3.519)
Colorectal cancer	189202	17483616	235	0.134	47290	4412875	76	0.172	1.281(0.989-1.659)
Breast cancer	188453	17366531	1539	0.886	47110	4380708	400	0.913	1.030(0.923-1.150)
Gynecologic cancer	188712	17419788	709	0.407	47013	4377291	339	0.774	1.903(1.672-2.166)
Urinary tract cancer	189204	17482875	205	0.117	47295	4411713	81	0.184	1.566(1.211-2.025)

* Incidence rate, per 10000 person months. PID, pelvic inflammatory disease. 95% C.I., 95% confidence interval

Table 3. Hazard ratio of main events with PID exposure, estimated by Cox proportional hazard model in different statistical modeling.

Main outcome	Hazard ratio (95 % C.I.) for main events with PID exposure in different model					
	Univariate modeling		Multivariate modeling†		Inverse propensity score weighting	
	HR (95 % C.I.)	p value	aHR (95 % C.I.)	p value	HR (95 % C.I.)	p value
Ectopic pregnancy	3.210(2.929-3.518)	<0.0001	2.976(2.702-3.278)	<0.0001	3.208(2.930-3.512)	<0.0001
Colorectal cancer	1.281(0.989-1.659)	0.0606	1.237(0.946-1.617)	0.1205	1.185(0.908-1.547)	0.2121
Breast cancer	1.030(0.922-1.149)	0.6042	1.020(0.910-1.142)	0.7343	0.985(0.881-1.101)	0.7871
Gynecologic cancer	1.904(1.673-2.167)	<0.0001	2.018(1.763-2.310)	<0.0001	2.107(1.859-2.389)	<0.0001
Urinary tract cancer	1.567(1.212-2.027)	0.0006	1.233(0.945-1.61)	0.1233	1.322(1.011-1.728)	0.0412

† The covariates included age group, urbanization, income, medical utilization (like outpatient visit or hospitalization within 2 years before baseline), co-morbidities at baseline. aHR: Adjusted hazard ratios; HR: hazard ratios; PID, pelvic inflammatory disease; 95% C.I., 95% confidence interval

**Figure 2.** KM plotter evaluations of main outcomes (A) ectopic pregnancy, (B) colorectal cancer, (C) breast cancer, (D) gynecologic cancer and (E) urinary tract cancer between the PID and control.

Lin et al. showed an increased incidence of ovarian cancer in those patients with a history of PID (HR 1.92, 95% CI 1.27-2.92) during a follow-up period of three years [15]. The study cohort included ICD-9-CM code 614, 615 PID patients; nevertheless, ICD-9-CM code 616 refers to the inflammatory disease of lower genital tract, i.e. cervix, vagina, and vulva. Wrong classification of study population could exist in this survey [25]. Previous study also shown that the prevalence of PID with endometriosis is higher than the general population [26]. Some studies demonstrated the risks of breast, ovarian and uterine cancers following pelvic inflammatory disease [14, 27]. The authors selected the patients by at least two consensus PID for the study group. The adjusted hazard ratio of ovarian, breast or uterine cancer in PID group were: HR 1.326, HR: 1.39, and HR: 1.439 respectively in comparison with controls. The

researchers concluded that there were no increased risks for ovarian, breast or uterine cancer among women with PID compared to the control group [14].

The role of inflammatory change in ovarian cancer has been surveyed on the point of molecular biology [9]. The authors focused on activated B cells to explain pathophysiology of inflammation and cancer. Chronic inflammation is a crucial role in the pathogenesis of ovarian cancer. Immune cells, fibroblasts, the extracellular matrix and other various components all constitute the tumor stroma [28]. Cancer-associated fibroblasts (CAFs) are one of the components of the tumor microenvironment [28]. The biochemical interactions of cancer cells with their microenvironment may play a critical role in spreading aggressive cancer cells from the primary tumor [29]. Inflammatory cells influence tumor microenvironment which is essential for cancer progression, growth, invasion and

metastasis [28] Cancer-associated fibroblasts play a key role in tumor initiation, progression, and metastasis by modifying the components of the inflammatory microenvironment and mediating tumor-promoting inflammation [7].

The cause of ovarian cancer is still unclear [30]. The cellular microenvironment on the development of the ovarian cancer has been emphasized [31]. The oncogenic RAS-transformed ovarian epithelial cells generate pro-inflammatory secretome which diffuse into the stromal and cause fibroblasts senescence. Senescence of ovarian stromal fibroblasts create a secondary pro-inflammatory phenotype and convert the ovarian epithelial microenvironment into a field filled with inflammatory mediators that advance tumor progressing. The inflammatory network contribute the communication between the ovarian tumor epithelium and underlying stromal [31].

The role of inflammation in cancer progression on the ovarian cancer was emphasized [9]. The potential role of infection agents as well as PID in ovarian carcinogenesis has been examined by seven epidemiological studies [32]. Potential carcinogenic bacteria were detected; however, inconsistent results of the association between bacterial infection and ovarian cancer were found. Further researches were warranted [32].

Patients suffering from PID have a higher risk of cervical cancer was reported [33]. PID may be a risk factor for cervical cancer by examining the relationship PID and human papillomavirus (HPV). The potential of chronic PID as a risk factor to cervical dysplasia was examined the cervical smear pattern in patients with chronic PID [34]. The results showed there were higher cases of dysplasia in the chronic PID group than in the control. The authors claimed that cervical cancer screening programs should be intensified in chronic PID patients [34].

Our study provides epidemiologic evidence that PID associates with increased risks of gynecologic and urinary tract cancer but not colorectal or breast cancer. The useful information may lead to a strategy for cancer prevention and a reasonable healthcare usage through understanding PID epidemiology and controlling the inflammatory responses.

The major limitations of this study are our inability to include taking medicine information which may reduce the risk of developing cancers, including oral contraceptives and raloxifene. Use of oral contraceptives reduces the incidence rate of endometrial, ovarian, and colorectal cancer [35-37]. Raloxifene treatment reduces the incidence of breast cancer in postmenopausal women with osteoporosis and the outcome relevant to raloxifene continues beyond 4 years of treatment [38]. Another limitation

of our study was unable to evaluate the effect of different determination of PID. The clinical presentations of PID range from subclinical infection to severe situation which requires hospital admission for procedural intervention or intravenous antibiotics [39]. In this study, the cases with at least two outpatient visits and one admission were evaluated. Those cases with subclinical infection could be misclassified.

In conclusion, this study revealed PID associated with increased risks of gynecologic cancer and urinary tract cancer but not colorectal cancer or breast cancer. Most cases of gynecologic cancer were diagnosed within one year after episode of PID. This could be due to the procedure of PID diagnosis involving the notification of gynecologic cancer. Further investigations involving large studies using time interval analyses and separate analyses for different types of cancers are required to verify the association of PID with gynecologic cancer.

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Competing Interests

The authors have declared that no competing interest exists.

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