Maternal survival of patients with pregnancy-associated cancers in Taiwan – A national population-based study

Sin-Syue Li¹,² | Ya-Ting Hsu¹ | Chih-Chieh Yen¹ | Ying-Wen Chen¹ | Pei-Ying Wu³ | Kung-Chao Chang⁴ | Chung-Yi Li⁵ | Tsai-Yun Chen¹

¹Division of Hematology / Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
²Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
³Department of Obstetrics & Gynecology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
⁴Department of Pathology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
⁵Department and Graduate Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Correspondence
Tsai-Yun Chen, Division of Hematology & Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, No. 138, Sheng-Li Rd. North District, Tainan City, Taiwan.
Email: teresa@mail.ncku.edu.tw

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Abstract
Pregnancy-associated cancer (PAC), defined as cancers diagnosed during pregnancy or the first year after delivery, affects one to two in every 1000 pregnancies. Although PAC is expected to be a growing issue, information about PAC in the Asian population is still scarce. Women with cancer diagnosed at the age of 16–49 years between 2001 and 2015 were selected from the Taiwan Cancer Registry and linked with the National Birth Reporting Database to identify PAC patients. We compared the overall survival of patients with PAC to patients without pregnancy. Among 126,646 female cancer patients of childbearing age, 512 were diagnosed during pregnancy, and 2151 during the first postpartum year. Breast cancer was the most common PAC (N = 755, 28%). Compared with patients without pregnancy in the control group, patients with cancers diagnosed during pregnancy and the first postpartum year generally had more advanced stages (odds ratio 1.35 and 1.36, 95% confidence interval [CI] 1.02–1.77 and 1.18–1.57, respectively). For all cancer types combined and controlled for the stage, age, and year of diagnosis, patients with PAC had similar overall survival with those in the control group, with a hazard ratio (HR) of 1.07 (95% CI 0.80–1.41) for the pregnancy group and HR 1.02 (95% CI 0.88–1.18) for the postpartum group. The diagnosis of breast cancer during the first postpartum year was linked with shorter survival (HR 1.34, 95% CI 1.05–1.72). In contrast, patients with postpartum lymphoma (HR 0.11, 95% CI 0.02–0.79) and cervical cancer (HR 0.40, 95% CI 0.20–0.82) had better prognosis. In general, the diagnosis of cancer during pregnancy or the first postpartum year does not affect the survival of patients with most cancer types. Exceptions include the worse prognosis of postpartum breast cancer and the better outcome of postpartum lymphoma and cervical cancer.

KEYWORDS
breast cancer, colorectal cancer, epidemiology and prevention, lymphoma, Survival, women's cancer
Pregnancy-associated cancers (PAC), usually defined as cancers diagnosed during pregnancy or the first year after delivery, had been reported to affect one to two in every 1000 pregnancies.1–5 Malignant melanoma, breast cancer, cervical cancer, lymphoma, and leukemia are among the most common PAC.1–3,5,7

While more women in the modern world prefer delaying childbearing, PAC is expected to be a growing issue.6 However, the diagnosis and treatment of PAC remain challenging, and it is a concern that the patients' outcome may also be affected by the status of gestation.9,10

The increased exposure to hormones during pregnancy and lactation may change the tumor's behavior, especially hormone-dependent tumors like breast cancer.11–13 During pregnancy, the suppressed immune system and increased vascularization may potentiate the tumor aggressiveness.14–17 Moreover physiological changes during pregnancy and lactation, such as increased plasma volume and glomerular filtration rate, may alter anticancer drugs' pharmacokinetics and affect the treatment outcome.18

Among all types of PAC, the outcome of pregnancy-associated breast cancer is the most widely studied. Patients with breast cancers diagnosed during pregnancy are usually in more advanced stages, have larger tumor sizes, have more lymph node involvement, have more undifferentiated histology, and with poorer prognosis.11–13,19–25 Furthermore, patients with postpartum breast cancer also have a poorer prognosis than patients without pregnancy, and the worser prognosis may persist longer than 5 years after childbirth.22,26 After controlling other prognostic factors, breast cancer diagnosed during pregnancy does not confer to an adverse outcome.12,13,25 In contrast, the diagnosis of postpartum breast cancer is an independent prognostic marker shown in some studies.3,27

Beyond breast cancer, studies regarding other PAC types are more scarce and are usually with limited case numbers. Some cancers commonly diagnosed in women of childbearing women have significant differences in epidemiologic and disease characteristics between the East and the West. For example, there is a higher proportion of younger and premenopausal breast cancer patients in Asia.28 Furthermore, malignant lymphoma has a lower incidence and a higher proportion of T and natural killer cell lymphomas in East Asia than in the West.29 Therefore, in the Asian population, a different PAC landscape is expected but was only reported in a few reports with limited case numbers.30–32

In this study, we report the incidence and cancer types of PAC from a national population-based cohort of patients in Taiwan and explore the links between pregnancy status with the survival of patients with PAC.

2 | MATERIAL AND METHODS

2.1 | Data sources

Taiwan Cancer Registry (TCR) was founded in 1979 to collect information about cancer cases diagnosed in hospitals with more than 50 beds. TCR had more than 98% overall coverage of potential cancer patients in Taiwan. The cancer diagnosis was verified by histological or cytological exams in 93% of patients (97.6% if liver excluded).33 All cases were registered in the short-form database with personal data and information about diagnosis and treatment. In addition to the essential information in the short-form database, the long-form database was established in 2002 to collect detailed information about staging, treatment, and recurrence of common malignancies, including cancers of the cervix, breast, oral cavity, lung, liver, colon, and rectum. Since 2008, the long-form database has started to cover the prostate, esophagus, and bladder cancers. It broadened further to include cancers of the nasopharynx, salivary gland, uterus, ovary, and hematologic system in 2009. In this study, we utilized both short- and long-form databases to extract the information on cancer diagnosis, staging, and treatment.

The National Birth Reporting Database (NBRD) of Taiwan was established in 1994. It includes information from all live- or still-births with a gestational age of 20 weeks or older delivered in hospitals or clinics in Taiwan, obligatorily reported by doctors. The NBRD provides gender, birth weight, gestational age, newborn's medical parameters, and complications during pregnancy and delivery.

The Cause-of-Death Database (CODD) of Taiwan collects the time, location, and underlying cause of each individual death, as reported in the death certificate. To protect the patient's privacy, information that can distinguish an individual's identity, such as name or address, was removed. An encrypted identification number can link the three datasets (TCR, NBRD, and CODD) to integrate information from the same individual. We performed the dataset linkage and data analysis in an access-restricted room after the approval from the Institute Review Board of National Cheng Kung University Hospital (NCKUH-A-ER-106-289), and the Center for Health and Welfare Data Analysis and Application, Ministry of Health and Welfare, Taiwan.

2.2 | Patient selection

We followed the eligibility criteria used in a previous study from Norway to identify the study cohort.3 First, we retrospectively identified women with cancer diagnosed at childbearing age (16–49 years) between 2001 and 2015 from TCR. Patients with non-invasive cancer, patients with cancer diagnosed by image or autopsy, and patients with a history of previous cancer
were excluded. After linkage with the NBRD, each patient in the study population was further categorized into three groups: (a) cancer diagnosed during pregnancy, (b) cancer diagnosed during the first postpartum year, and (c) cancer not associated with pregnancy. The duration of pregnancy was calculated by the date of delivery and the reported gestational week.

If a patient fulfilled the criteria for both group 1 and group 2 (ex. A woman diagnosed with cancer 11 months after the delivery of her first baby and was also pregnant at the time of cancer diagnosis), the patient would be categorized into the pregnancy group.

2.3 | Survival and statistics analysis

We categorized the extent of disease into localized (stage 1 or 2), regional (stage 3), and metastatic (stage 4), and compared the extents of disease in different groups with ordinal logistic regression. The Mann-Kendall method was used to test the time trend of incidence and average age during the study period. We compared each group’s age with the one-way analysis of variance (ANOVA) and categorical data with the chi-squared test.

The overall survival was calculated by the difference between the date of cancer diagnosis and the time of death. Patients without death records in CODD were considered alive at the latest database update (31st December 2016). We used the Kaplan-Meier method for survival analysis and compared the patients’ survival in the three groups with the log-rank test and the Cox proportional hazards model. Age, diagnostic year, and the initial extend of disease were adjusted in the multivariate analysis. The data manipulation and analysis were performed in software R version 3.5.1.

3 | RESULTS

3.1 | Incidence of PAC

We identified female patients with the first invasive cancer diagnosed during childbearing age (16–49 years) between 2001 and 2015 (Figure 1). Among the 126,646 eligible patients, the malignancy was diagnosed during pregnancy in 512, and during the first postpartum year in 2151. The remaining 123,983 patients whose diseases were not pregnancy-associated were regarded as the control group. Patients in the control group were older than patients in the pregnancy and postpartum group (Table 1) (p < 0.01, average 41.1 vs. 32.7 vs. 33.0 years, respectively). The number and proportion of different cancer types in each group are summarized in Figure 2A–D. Breast cancer was the most common cancer diagnosed during pregnancy and the first year postpartum (N = 156 and 599), followed by thyroid cancer (N = 60 and 483), colorectal cancer (CRC) (N = 27 and 163), cervical cancer (N = 38 and 141), and lymphoma (N = 19 and 101, respectively). During the study period, all three groups’ mean age increased (Figure 3, p < 0.01 in all groups). The incidence of cancer diagnosed during pregnancy also elevated from 10.1 cases per 100,000 pregnancies in 2001 to 27.3 in 2015 (Figure 4A, p < 0.01). Similarly, the increasing trend existed in the postpartum group, with the incidence elevated from 30.0 to 97.0 cases per 100,000 pregnancies during 2001–2015 (Figure 4A, p < 0.01). The percentage of the postpartum group among the entire study population was also increasing, while the proportion of the pregnancy group was not (Figure 4B, p = 0.04 and 0.28, respectively). On average, the incidence of PAC throughout the study period was 84.8 cases per 100,000 pregnancies. In other words, about one in every 1200 pregnancies was complicated with cancer.

3.2 | The extent of disease at diagnosis

For all cancer types combined, patients in both pregnancy and first postpartum year groups had higher extents of disease than patients of the control group (odds ratio [OR] 1.35, 95% confidence interval [CI] 1.02–1.77, p = 0.03; OR 1.36, 95% CI 1.18–1.57, p < 0.01, respectively) (Table 2). As for each cancer, breast cancers diagnosed during antenatal or postpartum periods were more likely to be in advanced stages. Compared with 23.2% in the control group, 37.2% in the pregnancy group and 33.8% in the postpartum group were more likely to be in advanced stages. Compared with 8.6% in the control group, 28.2% in the pregnancy group and 25.4% in the postpartum group were more likely to be in advanced stages at diagnosis (OR 2.11, 95% CI 1.37–3.18, p < 0.01; OR 1.63, 95% CI 1.32–2.00, p < 0.01, respectively). The majority of CRC patients diagnosed during pregnancy were in advanced stages (15.4% regional
### TABLE 1  Basic characteristics of patients in different groups

| Group                  | Pregnancy ($n = 512$) | First year postpartum ($n = 2151$) | Control ($n = 123,983$) |
|------------------------|------------------------|------------------------------------|--------------------------|
| Age (mean ± SD)
| 32.7 ± 4.62            | 33.0 ± 4.67              | 41.1 ± 6.97               |
| Age, median (range)    | 33 (18–46)             | 33 (17–49)              | 43 (16–49)               |
| Age group, $n$ (%)     |                        |                        |                          |
| <30 years              | 125 (24)               | 475 (22)               | 9739 (8)                 |
| 30–39 years            | 348 (68)               | 1517 (71)              | 31,047 (25)              |
| ≥40 years              | 39 (8)                 | 159 (7)                | 83,197 (67)              |
| Year of diagnosis, $n$ (%)     |                        |                        |                          |
| 2001–2005              | 141 (28)               | 563 (26)               | 36,493 (29)              |
| 2006–2010              | 150 (29)               | 693 (32)               | 41,482 (34)              |
| 2011–2016              | 221 (43)               | 895 (42)               | 46,008 (37)              |
| Trimester of diagnosis, $n$ (%) |                        |                        |                          |
| Trimester 1 ($<13$ weeks) | 76 (15)               | NA                    | NA                       |
| Trimester 2 ($13–26$ weeks) | 183 (36)              | NA                    | NA                       |
| Trimester 3 ($>26$ weeks) | 253 (49)              | NA                    | NA                       |

*p < 0.01.

**FIGURE 2** Distribution of cancer types in (A) pregnancy, (B) first year postpartum, and (C) control groups. (D) Summary of the number and percentage of each cancer type in each group

**FIGURE 3** Mean age and standard error of the pregnancy, first year postpartum, and control groups
and 76.9% metastatic), leads to an OR of 11.11 (95% CI 2.97–71.97, \( p < 0.01 \)) compared with patients in the control group. A trend toward localized stages could be observed in patients with ovarian cancer diagnosed during pregnancy (OR 0.30, 95% CI 0.09–0.79, \( p = 0.03 \)) and the postpartum period (OR 0.43, 95% CI 0.14–1.08, \( p = 0.10 \)). There was no significant difference between each group in lymphoma and cancers of cervix, nasopharynx, and lung. Due to the small numbers of patients with stage data in each group, we could not perform meaningful comparison in the skin and gastric cancer (GC) subgroups.

### Overall survival of PAC

With all cancer types combined and the control group as a reference, a worse overall survival can be observed in patients with cancer diagnosed during pregnancy (Hazard ratio [HR] 1.37, 95% CI 1.17–1.62, \( p < 0.01 \)), but not in patients of the postpartum group (HR 0.97, 95% CI 0.88–1.06, \( p = 0.45 \)). The hazard ratios turned insignificant after adjustment with age, stage, and the year of diagnosis (Table 3; Figure 5A).

As for each site of cancer diagnosed during pregnancy, we observed an elevated risk of death in patients of breast cancer (Figure 5B; HR 2.31, 95% CI 1.71–3.12, \( p < 0.01 \)), lung cancer (Figure 5J; HR 2.02, 95% CI 1.05–3.89, \( p = 0.04 \)), and gastric cancer (Figure 5L; HR 3.15, 95% CI 1.64–6.07, \( p < 0.01 \)). Similarly, an increased risk of death could also be seen in patients with breast cancer (Figure 5B; HR 1.88, 95% CI 1.60–2.21, \( p < 0.01 \)), CRC (Figure 5D; HR 1.44, 95% CI 1.14–1.80, \( p < 0.01 \)), and gastric cancer (Figure 5L; HR 1.59, 95% CI 1.15–2.21, \( p < 0.01 \)) diagnosed during the first postpartum year. After adjustment with age, stage, and diagnostic year, the inferior outcome remained significant in patients with skin cancer diagnosed during pregnancy (adjusted HR 3.77, 95% CI 1.18–12.02, \( p = 0.02 \)) and postpartum breast cancer (Table 3; adjusted HR 1.34, 95% CI 1.05–1.72, \( p = 0.02 \)).

In contrast, patients with postpartum cervical cancer (Figure 5E; HR 0.56, 95% CI 0.35–0.90, \( p = 0.02 \)) and lymphoma (Figure 5F; HR 0.19 95% CI 0.08–0.47, \( p < 0.01 \)) had better outcomes than patients without pregnancy. The differences were significant in the multivariate analysis, with adjusted HR 0.40 (95% CI 0.20–0.82, \( p = 0.01 \)) for cervical cancer, and HR 0.11 (95% CI 0.02–0.79, \( p = 0.03 \)) for lymphoma (Table 3).
| Table 2 | Initial extent of disease of patients in different groups |
|---------|--------------------------------------------------|
|         | N      | Localized (%) | Regional (%) | Metastatic (%) | No data (%) | OR     | 95% CI   | p-value |
| All     |        |               |              |               |             |        |          |         |
| Control | 63,263 | 49.5          | 15.8         | 11.7          | 23.0        | 1a     |          |         |
| Pregnancy | 286  | 39.5          | 15.7         | 13.6          | 31.1        | 1.35   | 1.02–1.77 | 0.03    |
| First year postpartum | 1199  | 35.9          | 14.7         | 12.4          | 36.9        | 1.36   | 1.18–1.57 | <0.01   |
| Breast  |        |               |              |               |             |        |          |         |
| Control | 25,582 | 71.5          | 17.6         | 5.6           | 5.3         | 1a     |          |         |
| Pregnancy | 92   | 57.4          | 23.4         | 13.8          | 5.3         | 2.11   | 1.37–3.18 | <0.01   |
| First year postpartum | 337  | 63.6          | 25.0         | 8.8           | 2.5         | 1.63   | 1.32–2.00 | <0.01   |
| Thyroid |        |               |              |               |             |        |          |         |
| Control | 7636   | 12.4          | 1.0          | 0.4           | 86.2        | 1a     |          |         |
| Pregnancy | 33   | 13.2          | 0.0          | 0.0           | 86.8        | NA     | NA       | NA      |
| First year postpartum | 289  | 11.8          | 0.0          | 0.0           | 88.2        | NA     | NA       | NA      |
| Colon & rectum |    |               |              |               |             |        |          |         |
| Control | 4609   | 23.8          | 38.7         | 29.1          | 8.4         | 1a     |          |         |
| Pregnancy | 16   | 0.0           | 15.4         | 76.9          | 7.7         | 11.11  | 2.97–71.97 | <0.01   |
| First year postpartum | 95   | 24.1          | 33.0         | 38.4          | 4.5         | 1.27   | 0.89–1.84 | 0.19    |
| Cervix  |        |               |              |               |             |        |          |         |
| Control | 3154   | 64.5          | 18.4         | 10.2          | 6.9         | 1a     |          |         |
| Pregnancy | 21   | 60.9          | 13.0         | 4.3           | 21.7        | 0.63   | 0.18–1.73 | 0.41    |
| First year postpartum | 79   | 66.7          | 11.5         | 12.6          | 9.2         | 0.87   | 0.52–1.41 | 0.59    |
| Lymphoma |       |               |              |               |             |        |          |         |
| Control | 1747   | 42.6          | 10.7         | 19.2          | 27.6        | 1a     |          |         |
| Pregnancy | 8    | 44.4          | 22.2         | 11.1          | 22.2        | 0.87   | 0.18–3.38 | 0.85    |
| First year postpartum | 53   | 42.2          | 14.1         | 17.2          | 26.6        | 0.99   | 0.55–1.72 | 0.97    |
| Ovary   |        |               |              |               |             |        |          |         |
| Control | 3220   | 45.6          | 22.2         | 7.1           | 25.1        | 1a     |          |         |
| Pregnancy | 35   | 60            | 8.6          | 2.9           | 28.6        | 0.30   | 0.09–0.79 | 0.03    |
| First year postpartum | 27   | 57.6          | 9.1          | 6.1           | 27.3        | 0.43   | 0.14–1.08 | 0.10    |
| Nasopharynx |    |               |              |               |             |        |          |         |
| Control | 1121   | 21.3          | 26.8         | 24.9          | 27.0        | 1a     |          |         |
| Pregnancy | 10   | 10.0          | 40.0         | 20.0          | 30.0        | 1.19   | 0.33–4.49 | 0.79    |
| First year postpartum | 38   | 8.0           | 32.0         | 26.0          | 34.0        | 1.60   | 0.87–3.00 | 0.13    |
| Lung    |        |               |              |               |             |        |          |         |
| Control | 2927   | 26.8          | 12.5         | 58.1          | 2.7         | 1a     |          |         |
| Pregnancy | 5    | 16.7          | 0.0          | 83.3          | 0.0         | 3.11   | 0.50–59.85 | 0.30    |
| First year postpartum | 36   | 35.9          | 5.1          | 48.7          | 10.3        | 0.7    | 0.36–1.37 | 0.28    |
| Skin    |        |               |              |               |             |        |          |         |
| Control | 994    | 6.3           | 0.4          | 0.4           | 93.0        | 1a     |          |         |
| Pregnancy | 5    | 0.0           | 0.0          | 0.0           | 100.0       | NA     | NA       | NA      |
| First year postpartum | 20   | 0.0           | 0.0          | 0.0           | 100.0       | NA     | NA       | NA      |
| Stomach |        |               |              |               |             |        |          |         |
| Control | 1227   | 25.4          | 16.8         | 36.8          | 20.9        | 1a     |          |         |
| Pregnancy | 3    | 0.0           | 0.0          | 60.0          | 40.0        | NA     | NA       | NA      |
| First year postpartum | 22   | 4.3           | 21.7         | 56.5          | 17.4        | NA     | NA       | NA      |

(Continues)
The trend toward better survival could be observed in patients aggressive B-cell lymphomas (Figure 6A; HR 0.23, 95% CI 0.07–0.72, p = 0.01) and T-cell lymphomas (Figure 6C; HR 0.17, 95% CI 0.02–1.20, p = 0.07), but not in Hodgkin lymphoma (Figure 6B; HR < 0.01, 95% CI 0–Infinity, p = 0.99) and indolent lymphomas (Figure 6D; HR < 0.01, 95% CI 0–infinity, p = 0.994). The survival of patients with leukemia, thyroid, ovarian, nasopharyngeal, primary brain, and other cancers is not affected by pregnancy or postpartum status (Figure 5C,G,H,I,M,N). Analysis performed in the subgroup of 2009–2015 showed comparable results as the study cohort (Table S1).

### DISCUSSION

In this study, we identified a total of 2663 patients with PAC, and the overall crude incidence was 84.8 cases per 100,000 pregnancies, which was lower than most previous studies that generally reported an incidence above 100.3,34,35 The difference might be primarily due to the ethnic difference in the incidence of malignant melanoma between Caucasian and Asian populations. In previous reports, malignant melanoma is common and is even the most common PAC in Scandinavian countries and Australia.3,7,34 In contrast, the most common cancer diagnosed during pregnancy in the Taiwan population was breast cancer, while pregnancy-associated melanoma was rare. Our result was different from the studies of other East Asian countries. The most common cancer diagnosed during pregnancy is breast cancer in a single-institute report from Korea,31 is leukemia in a multi-center study from China,32 and is cervical cancer in a multi-center survey from Japan.30 However, contrary to the nationwide population-based cohort used in our study, all these reports are limited with small case numbers.

During the study period, PAC’s overall incidence increased, from 40.1 cases per 100,000 pregnancies in 2001 to 124.3 in 2015. The increasing incidence of PAC was also observed in the reports from Norway, Australia, and the United States.3,5,34 We believe it is associated with the trend of delay childbearing and the elevating incidence of cancer.36,37 The average age of childbearing women in Taiwan has increased from 28.2 in 2001 to 32.0 years old in 2018, as well as the age at first pregnancy (elevated from 26.9 to 30.9).38 We showed an increasing average age of PAC patients in our study, and there’s also a rising proportion of postpartum cancer among all cancer in women of childbearing age. Therefore, the incidence of PAC is expected to increase in the future and warrant more attention.

Breast cancer is the most common PAC in Taiwan, and pregnancy-associated breast cancer is more likely to be in advanced stages and have poorer outcomes. During pregnancy and lactation, a breast lump or inflammation may be regarded as normal changes rather than malignancy, and patients with pregnancy-associated breast cancer may experience diagnostic delays.39 The initiation of breast cancer treatment in pregnant women is also likely to be delayed.40 Beyond delay in diagnosis and treatment, the higher risk of metastasis and death in young women’s breast cancer,41–43 and the higher proportion of hormone negative and HER2-positive subtypes also contribute to the worse outcome of pregnancy-associated breast cancer.13

In our study, patients with breast cancer diagnosed during pregnancy had similar survival with patients without pregnancy after controlling stage, age, and the year of diagnosis. Conversely, the diagnosis of breast cancer during the first postpartum year was an independent poor prognostic factor. The result was consistent with previous studies and highlighted the importance of judging these two groups differently.3,13,26,27 Patients diagnosed postpartum have a higher risk of recurrence and metastasis,26 with a distinct metastatic preference to the liver.44 At the end of milk production, the mammary gland undergoes a tissue remodeling process known as involution.45 Evidence from preclinical studies suggests that the microenvironment during involution promotes tumorigenesis and increases the risk of metastasis.44,46–48 The underlying molecular mechanism warrants further exploration to discover a way to prevent or treat postpartum breast cancer in the future.49

Consistent with previous reports, patients with pregnancy-associated GC and CRC in our cohort have poor survival.50,51 More than 70% of patients with pregnancy-associated CRC or GC were in an advanced stage at diagnosis.

### Table 2 (Continued)

| N | Localized (%) | Regional (%) | Metastatic (%) | No data (%) | OR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| Others | | | | | | | |
| Control | 9979 | 37.1 | 8.8 | 9.2 | 44.9 | 1a |   |
| Pregnancy | 41 | 19.0 | 11.9 | 9.5 | 59.5 | 2.02 | 0.82–4.78 | 0.11 |
| First year postpartum | 165 | 21.1 | 8.0 | 9.0 | 61.8 | 1.64 | 1.05–2.52 | 0.03 |

The table was generated with patients diagnosed between 2009 and 2015 because of data integrity. There were no data of stage in leukemia and brain cancers. NA was generated due to low case numbers.

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio.

aReference group.
|                  | N       | Crude HR | 95% CI   | p-value<sup>a</sup> | p-value<sup>b</sup> | Adjusted HR | 95% CI     | p-value<sup>a</sup> |
|------------------|---------|----------|----------|----------------------|----------------------|-------------|------------|---------------------|
| **All**          |         |          |          |                      |                      |             |            |                     |
| Control          | 123,983 | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 512     | 1.37     | 1.17–1.62 | <0.01               | 1.07                 | 0.80–1.41   | 0.65       |
| First year postpartum | 2151 | 0.97     | 0.88–1.06 | 0.45                 | <0.01               | 1.02        | 0.88–1.18   | 0.77                |
| **Breast**       |         |          |          |                      |                      |             |            |                     |
| Control          | 48,487  | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 156     | 2.31     | 1.71–3.12 | <0.01               | 1.02                 | 0.64–1.62   | 0.95       |
| First year postpartum | 599 | 1.88     | 1.60–2.21 | <0.01               | <0.01               | 1.34        | 1.05–1.72   | 0.02                |
| **Thyroid**      |         |          |          |                      |                      |             |            |                     |
| Control          | 13,009  | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 60      | 1.08     | 0.15–7.74 | 0.94                 | 1.81                | 0.25–13.09 | 0.56       |
| First year postpartum | 483 | 0.30     | 0.07–1.19 | 0.09                 | 0.19                | 0.46        | 0.11–1.86   | 0.27                |
| **CRC**          |         |          |          |                      |                      |             |            |                     |
| Control          | 8897    | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 27      | 1.67     | 0.97–2.88 | 0.07                 | 0.80                | 0.38–1.68   | 0.55       |
| First year postpartum | 163 | 1.44     | 1.14–1.80 | <0.01               | <0.01               | 1.08        | 0.80–1.46   | 0.60                |
| **Cervix**       |         |          |          |                      |                      |             |            |                     |
| Control          | 9010    | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 38      | 1.16     | 0.60–2.23 | 0.66                 | 2.09                | 0.86–5.07   | 0.10       |
| First year postpartum | 141 | 0.56     | 0.35–0.90 | 0.02                 | 0.05                | 0.40        | 0.20–0.82   | 0.01                |
| **Lymphoma**     |         |          |          |                      |                      |             |            |                     |
| Control          | 3528    | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 19      | 1.41     | 0.63–3.15 | 0.40                 | 1.51                | 0.21–10.88 | 0.68       |
| First year postpartum | 101 | 0.19     | 0.08–0.47 | <0.01               | <0.01               | 0.11        | 0.02–0.79   | 0.03                |
| **Ovary**        |         |          |          |                      |                      |             |            |                     |
| Control          | 6171    | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 52      | 0.48     | 0.23–1.01 | 0.05                 | 0.73                | 0.18–2.95   | 0.66       |
| First year postpartum | 51 | 0.75     | 0.40–1.40 | 0.37                 | 0.10                | 1.04        | 0.33–3.25   | 0.95                |
| **Nasopharynx**  |         |          |          |                      |                      |             |            |                     |
| Control          | 2622    | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 21      | 1.15     | 0.51–2.56 | 0.74                 | 0.97                | 0.13–7.00   | 0.97       |
| First year postpartum | 74 | 0.92     | 0.56–1.51 | 0.75                 | 0.90                | 1.05        | 0.42–2.60   | 0.92                |
| **Leukemia**     |         |          |          |                      |                      |             |            |                     |
| Control          | 2,191   | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 30      | 0.88     | 0.52–1.48 | 0.62                 | 0.99                | 0.58–1.68   | 0.96       |
| First year postpartum | 57 | 0.86     | 0.57–1.28 | 0.45                 | 0.49                | 0.91        | 0.60–1.36   | 0.64                |
| **Lung**         |         |          |          |                      |                      |             |            |                     |
| Control          | 5472    | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 12      | 2.02     | 1.05–3.89 | 0.04                 | 2.71                | 1.01–7.28   | 0.05       |
| First year postpartum | 58 | 1.01     | 0.73–1.41 | 0.93                 | 0.09                | 1.25        | 0.79–1.98   | 0.34                |
| **Skin**         |         |          |          |                      |                      |             |            |                     |
| Control          | 2157    | 1<sup>c</sup> |          | 1<sup>c</sup>       |                      |             |            |                     |
| Pregnancy        | 13      | 2.84     | 0.91–8.89 | 0.07                 | 3.77                | 1.18–12.02 | 0.02       |
| First year postpartum | 49 | 0.73     | 0.23–2.28 | 0.59                 | 0.15                | 0.93        | 0.29–2.97   | 0.91                |
in our cohort, suggesting a delay in diagnosis. During pregnancy, symptoms of gastrointestinal cancers, such as vomiting, constipation, and rectal bleeding, are easily overlooked and attributed to pregnancy. Early diagnosis of CRC or GC in pregnant women is challenging, while radiologic and endoscopic examinations may also be limited or delayed.

Although some early studies suggested a possible link between hormones and the aggressiveness of CRC, recent evidence indicates the protective role of estrogen against the CRC carcinogenesis through estrogen receptor β (ER β) signaling. Moreover, a recent study reported a negative impact on survival with estrogen receptor α (ER α) expression in CRC, but not with progesterone receptor. In GC, the expression of ER α is also an indicator of poor prognosis. These findings suggested a potential role of hormone exposure in pregnancy-associated gastrointestinal cancers and warrant further investigation.

Cervical cancer is the fourth most common PAC in Taiwan. Like previous studies, our patients with cervical cancer diagnosed during pregnancy had a similar distribution of stages and survival with patients without pregnancy. Interestingly, in our data, patients with postpartum cervical cancer had a significantly better outcome than the control group. The finding is contrary to two previous reports, one reported similar, and the other reported worse outcomes in the postpartum group. The difference in the Pap smear rate between groups may be a possible explanation. The overall Pap smear rate in Taiwan is only around 50%, which confers to a higher incidence of cervical cancer in Taiwan than in developed countries. In our data, there is also a higher proportion of patients in advanced stages of cervical cancer than the report from Norway. On the contrary, women at perinatal care may have more frequent Obstetrics clinic visits and a higher likelihood to receive Pap smear, which may confer to a better outcome in such a group.

In our cohort, lymphoma patients who were diagnosed during pregnancy had similar survival with the control group. The result was consistent with previous reports on maternal outcomes after Hodgkin and non-Hodgkin lymphomas (NHL). Surprisingly, our results showed that patients with postpartum lymphoma had significantly better survival than the control group. The superiority was observed across different lymphoma subtypes and remained true after controlled with age and the extent of disease. The hormone changes during pregnancy and postpartum lactating period provide a possible explanation to the survival superiority in these patients. We could find clues in epidemiology studies showing that women have a lower incidence and better survival in most subtypes of lymphoma. Women taking oral contraceptives have an even lower risk of developing NHL than those who did not. Moreover, multi-parity and early age at first birth are protective factors against NHL. In recent years, there is emerging evidence about the role of estrogen in B-cell lymphomas. The study from Yakimchuk et al. also provided in vitro evidence to suggest that targeting ER β with agonists may be a potential treatment for lymphoma.

Our data showed similar survival and a trend toward the early stage for women with ovarian cancer diagnosed during pregnancy. The high proportion of localized disease echos the findings from other reports. During pregnancy, routine physical and ultrasound examinations

| Table 3 (Continued) |
|---------------------|
| N | Crude HR | 95% CI | p-value<sup>a</sup> | p-value<sup>b</sup> | Adjusted HR | 95% CI | p-value<sup>a</sup> |
|---------------------|
| **Stomach**         |
| Control             | 2912 | 1<sup>c</sup> | 1<sup>c</sup> |
| Pregnancy           | 9    | 3.15 | 1.64–6.07 | <0.01 | 2.23 | 0.70–7.08 | 0.17 |
| First year postpartum | 49 | 1.59 | 1.15–2.21 | <0.01 | <0.01 | 1.48 | 0.91–2.43 | 0.12 |
| **Primary brain**   |
| Control             | 1464 | 1<sup>c</sup> | 1<sup>c</sup> |
| Pregnancy           | 9    | 1.76 | 0.79–3.93 | 0.17 | 1.93 | 0.86–4.32 | 0.11 |
| First year postpartum | 24 | 0.99 | 0.56–1.75 | 0.97 | 0.38 | 1.03 | 0.58–1.83 | 0.92 |
| **Others**          |
| Control             | 18,063 | 1<sup>c</sup> | 1<sup>c</sup> |
| Pregnancy           | 66   | 1.34 | 0.91–1.99 | 0.14 | 1.21 | 0.60–2.44 | 0.59 |
| First year postpartum | 302 | 0.94 | 0.76–1.17 | 0.57 | 0.29 | 1.24 | 0.82–1.88 | 0.31 |

Univariate analyses are presented as crude HR at the left column. Multivariate analyses are adjusted for age, diagnostic year, and extend of disease at diagnosis (presented at the right column).

Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup>Cox proportional hazards.

<sup>b</sup>Log-rank test.

<sup>c</sup>Reference group.
FIGURE 5 Kaplan-Meier survival curves of patients of each cancer type in the pregnancy, first year postpartum, and control groups. Log-rank test $p$ values are displayed.
provide a chance of early diagnosis of ovarian tumors. An ovarian tumor may also be noticed incidentally during the Caesarean section. In addition to early diagnosis, ovarian malignancies in young women have a predominance of germ cell and sex cord-stromal tumors, which have a good prognosis. We did not see the worse prognosis in postpartum ovarian cancer patients, as shown in the report from Stensheim et al. However, the number of postpartum subgroups in both studies have small numbers, and the results should be interpreted with caution.

Our study had some limitations. First, the NBRD only report deliveries with a gestational age of more than 20 weeks. Patients who terminated gestation early may not be registered and lead to an under-estimation of the PAC incidence, especially PAC diagnosed during the first trimester. However, the limit exists in most reports utilizing a similar approach, and the comparison between our data and other studies are reasonable. Second, the stage data is not available for all types of cancers, particularly in patients diagnosed before 2009. The limitation may affect the result of survival analysis after control with age, diagnosis period, and extent of the stage. Therefore, we performed a subgroup analysis in patients diagnosed between 2009 and 2015 (Table S1). The subgroup analysis did not change the trend and result obtained in most cancers.

Despite these limitations, our study provided the first population-based evaluation of PAC from an Asian country. In conclusion, the incidence of PAC in Taiwan was increasing, with breast cancer being the most common. In general, the cancer...
diagnosis during pregnancy or the first postpartum year does not affect patients’ survival with most cancer types. Exceptions include the worse prognosis of postpartum breast cancer and the better outcome of postpartum lymphoma and cervical cancer.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the Center for Health and Welfare Data Analysis and Application, Ministry of Health and Welfare, Taiwan, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

ORCID
Sin-Syue Li https://orcid.org/0000-0003-0112-8324
Ya-Ting Hsu https://orcid.org/0000-0001-7649-2812
Kung-Chao Chang https://orcid.org/0000-0001-9665-5236
Chung-Yi Li https://orcid.org/0000-0001-7099-8054
Tsai-Yun Chen https://orcid.org/0000-0001-9665-5236

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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