# Age-Specific Trend and Birth Cohort Effect on Different Histologic Types of Uterine Corpus Cancers

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# Abstract

To evaluate the uterine corpus cancer incidence rates, age-specific trends and birth cohort patterns by different histologic types. From the Taiwan Cancer Registry, we identified women with a primary diagnosis of uterine corpus cancer (*n*=28 769) from1998 to 2017. We analyzed the incidences, stages of disease at diagnosis and prognostic factors in endometrioid and non-endometrioid carcinoma. During the study period, uterine corpus cancer incidence rates increased over time from 5.3 to 15.21 per 100 000 woman-years. Incidence trends for endometrioid carcinoma increased in all age groups and the rise was steeper in women age 40 years and younger. For non-endometrioid carcinomas, incidence rates increased in women over 50 years. Women diagnosed after 2013 had significantly better cancer-specific survival (CSS) (hazard ratio [HR] =0.81, 95% confidence interval [CI] 0.73-0.89) compared with those at the period of 2009-2012. CSS also improved in stage I (HR=0.81, 95% CI 0.49-0.63) and stage III (HR 0.90, 95% CI 0.58-0.72) endometrioid carcinomas after 2013. Whereas CSS remained unchanged for non-endometrioid carcinomas. We found the incidences of both endometrioid and non-endometrioid carcinomas continued to increase among contemporary birth cohorts. Etiologic research is mandatory to explain the causes for these trends.


# Introduction

Uterine corpus (hereinafter referred to as uterine) cancer is the most common gynecologic malignancy in the U.S. and other Western countries [1]. The incidence of uterine cancer has increased in both consecutive generations and over time. The largest increases were observed in South Africa and in several Asian countries [2]. In Taiwan, in 2010, uterine cancer surpassed cervical cancer as the most common gynecologic malignancy, and in 2017, 2695 new cases were diagnosed [3]. In addition, the incidence of uterine cancer doubled in the last decade, and it increased by approximately 4-fold over a 20-year period with a continuously rising trend [4, 5]. The rise in the incidence of uterine cancer was attributable to the rise in obesity, based on the association between excess body weight and uterine cancer shown in epidemiological cohort studies [6, 7]. The prevalence of obesity has increased substantially across all population groups, globally [8-10]. However, the prevalence of overweight and obesity were modest in Taiwan, and the increasing trend of obesity rates has apparently leveled off in recent years [11-13]. Consequently, it was necessary to investigate the current incidences and trends of uterine cancer.

Beyond the conventional diagnosis, there are two distinct types of endometrial cancer, based on histology and the molecular features. Type I endometrial cancer comprises 80–90% of all sporadic endometrial cancers. This type includes well to moderate differentiated endometrioid carcinomas and the prognosis is good. Type II endometrial cancer accounts for 10 to 20% of all endometrial cancers. They are poorly differentiated and include non-endometrioid differentiation, such as serous and clear cell carcinomas. Common risk factors of type I endometrial cancers include nulliparity, obesity, delayed menopause, endometrial hyperplasia, polycystic ovarian syndrome, and chronic anovulation [14]. In contrast, the epidemiology and biology of type II endometrial cancers are not well characterized. Like type I

endometrial cancer, the incidence of non-endometrioid carcinoma has also increased, based on data from the Surveillance, Epidemiology, and End Results (SEER) database in the US. However, the cause of the increase remains unclear [15]. Moreover, little is known about the risk factors for type II endometrial cancer. The rising prevalence of obesity and changes in hormonal risk factors cannot explain this increasing trend. Age-specific and birth cohort patterns are important etiologic clues, but have not been recently examined in type II endometrial cancer. Therefore, it is necessary to identify the epidemiology of type II endometrial cancer (or non endometrioid uterine cancer).

In the present retrospective population-based study, we investigated the incidences associated with different histologic types of uterine cancer and estimated the annual percent change in trend analysis. In addition, we assessed the effect of different factors on survival.

## Methods

# Study design and data source

Information on uterine cancer cases was retrieved from the National Cancer Registry of Taiwan [16, 17]. The population data was obtained from National Household Registration Profiles. All cases were followed up through data linkage to the Death Registration Database until December 31, 2018. The diagnosis of primary cancer of the uterus was based on the International Classification of Diseases for Oncology, third edition (ICD-O-3: C54.0–C54.3, C54.8–C54.9) and classified by histological codes. The histologic subtypes of uterine carcinomas included endometrioid adenocarcinoma (codes 81403, 82603, 8262, 82633, 83233, 83803, 83823, 83833, 83843, and 85703), non-endometrioid adenocarcinoma (codes 83103, 84413, 84603, 84613, 84803, 84813, 85603, 89503, 89513, and 89803), uterine sarcoma (codes 87143, 88003, 88023, 88053, 88513,88903, 88913, 88963, 89203, 89303, 89313, 89333, 89353, and 90403), and other carcinomas, defined by histological codes other than those mentioned above [18]. After 2009, information was collected about the cancer stage at the time uterine cancer was diagnosed. The stages were assigned according to the TNM staging system determined by the American Joint Committee on Cancer [19]. The final stage assignment was based on the best available information on the stage of the disease. Thus, when preoperative therapy was not performed, we used the pathologic stage, and when neoadjuvant therapy was performed first, we used the clinical stage.

# Statistical analyses

The age-adjusted annual incidences of uterine cancers from 1998 to 2017 were calculated for the different histological subtypes with the direct standardization method; the world population in 2000 was taken as the standard population. Trends in age-specific incidences of uterine cancer were estimated in 5-year age groups for the calendar year, histological subtypes, and birth cohorts. The incidences are presented as rate per 100 000 person-years. To quantify the incidence trends, we first evaluated the annual percent change (APC) with a joinpoint regression analysis (Joinpoint Regression Program, version 4.7, February 2019; National Cancer Institute, Bethesda, MD). Then, we calculated the average APC (AAPC) and confidence intervals (CIs). We calculated AAPCs for all ages, each age group, and the two

major subtypes (endometrioid and non-endometrioid carcinomas). The best fitting trend lines where the rate changed significantly were used by Monte Carlo permutation tests. The 95% CI of AAPC excluding zero was considered as statistically significant ($P < 0.05$). According to AJCC cancer stage and two time periods of diagnosis (2009-2012 and 2013-2017), the Kaplan-Meier analysis was used to evaluate the cancer-specific survival rate (CSS) of women with uterine endometrioid and non-endometrioid carcinomas. Multivariate Cox proportional-hazards regression model was used to identify covariates that were significantly associated with CSS. Hazard ratios (HRs) and the associated 95% confidence intervals (CIs) were calculated in the multivariate models. Two-sided statistical significance was defined as $P < 0.05$. All analyses were performed with SAS software version 9.4 (SAS Inc, Cary, NC).

# Ethics approval

The Research Ethics Committee of the National Taiwan University Hospital approved the study (202007069RINA). The informed consent was waived by the committee. This study was conducted in accordance with the Declaration of Helsinki and its later amendments.

## Results

# Age-adjusted uterine cancer incidences over time for various histologic types

We identified 28 769 women diagnosed with uterine cancer over a 20-year period in Taiwan from 1998 to 2017. We divided the 20-year period into 5-year quartiles (Table 1).Among all uterine cancers, endometrioid carcinoma comprised 72.8–79.7%, non-endometrioid carcinoma comprised 9.4–11.3%, and uterine sarcoma comprised 6.8–10.5%. The median age at diagnosis was older among patients with non-endometrioid carcinoma than among those with endometrioid carcinoma and those with sarcoma. The age-adjusted incidence of all uterine cancers increased by 3 folds from 1998 to 2017 (5.3/100 000 in 1998 and 15.2/100 000 in 2017) (Figure 1A). A parallel increase in the incidence of endometrioid carcinoma (3.97/100 000 in 1998, 12.3/100 000 in 2017) accounted for the overall rising trend in all uterine cancers. Notably, the age-adjusted incidence of non-endometrioid carcinoma showed a 4-fold increase (0.42/100 000 in 1998 to 1.63/100 000 in 2017). In contrast, although the incidence of uterine sarcoma also increased, it remained relatively low (0.58/100 000 in 1998 and 0.99/100 000 in 2017).

Table 1
Distribution of histological subtypes and age at diagnosis for 28 769 women with uterine corpus cancer from 1998 to 2017 in Taiwan

| | Year of Diagnosis | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Histological subtype** | **1998-2002** (n=3229) | | **2003-2007** (n=5154) | | **2008-2012** (n=8434) | | **2013-2017** (n=11952) | |
| **Cases, %** | | | | | | | | |
| Endometrioid | 2350 | (72.8) | 3859 | (74.9) | 6733 | (79.8) | 9521 | (79.7) |
| Non-endometrioid | 305 | ( 9.4) | 552 | (10.7) | 831 | ( 9.9) | 1356 | (11.3) |
| Sarcoma | 339 | (10.5) | 526 | (10.2) | 635 | ( 7.5) | 816 | ( 6.8) |
| Others | 235 | ( 7.3) | 217 | ( 4.2) | 235 | ( 2.8) | 259 | ( 2.2) |
| **Age at diagnosis, median (years)** | | | | | | | | |
| Endometrioid | 52 | | 52 | | 54 | | 55 | |
| Non-endometrioid | 57 | | 59 | | 58 | | 61 | |
| Sarcoma | 46 | | 46 | | 49 | | 51 | |
| Others | 52 | | 52 | | 55 | | 60 | |

We compared the age-specific incidence of uterine cancers during the four different time periods. The peak incidences of endometrioid carcinoma consistently occurred in the 55-59-year age group but the slopes became steeper from the 1998-2002 period to the 2013-2017 period (Figure 1B). The age-specific incidence of non-endometrioid carcinoma also increased in all time periods (Figure 1C). In contrast to the narrow, bell-shaped pattern observed for the incidences of endometrioid carcinoma, the peak incidences of non-endometrioid carcinoma varied between the sixties and the eighties age group in the different time periods. The incidence of non-endometrioid carcinomas increased and the steepest slope also occurred in the most recent period (2013-2017). The age-specific incidence of uterine sarcoma increased significantly and the peaks occurred in ages 45 to 54 in all four time periods (Figure 1D). Again, the steepest slope was observed in the 2013-2017 time period.

We further analyzed the age-specific incidences of endometrioid and non-endometrioid carcinomas for patients of different age groups (5-year age groups) from 1998 to 2017 (Figure 2). The age-specific incidences of both endometrioid and non-endometrioid carcinomas increased over time, with AAPCs of 6.7% (95% CI 6.1-7.3%, Figure 2A) and 6.5% (95% CI 5.4-7.6%, Figure 2B), respectively. The incidence of endometrioid carcinoma increased over time across all age groups (Supplementary Figure 1). A similar pattern was observed for non-endometrioid carcinoma (Supplementary Figure 2).We used AAPC to quantify temporal trends inn endometrioid and non-endometrioid carcinomas during 1998-2017. The

incidence of endometrioid carcinoma always showed positive AAPCs >5%, regardless of the age group (Figure 2C). Positive AAPCs were particularly pronounced in the age groups of 25-29, 30-34, and 35-39 years, where the AAPCs were 7.8%, 8.5% and 7.9%, respectively. The incidence of non-endometrioid carcinoma always showed increases in AAPCs, except in the 30-34-year age group (Figure 2D). Moreover, the AAPCs significantly increased after age 55 years, with AAPCs >5%. The highest AAPC was 10.6%, in the 75-79-year age group.

# Age-specific incidences of endometrioid and non-endometrioid carcinomas were steepest in young birth cohorts

The trends of age-specific incidences of uterine endometrioid carcinoma, grouped by birth cohort, are shown in Figure 3A. The age-specific rates began to rise among women born after 1950. The age-specific rates increased rapidly for cohorts born in the 1960s, and the later birth cohorts showed parallel slopes over time. The age-specific incidences of non-endometrioid carcinoma showed trends similar to those observed for endometrioid carcinoma. The age-specific incidences of non-endometrioid carcinoma rose in women born after 1940. The slopes of the incidence curves were similar in the later birth cohorts (Figure 3B).

# Different stage distributions for endometrioid and non-endometrioid carcinoma

The stage distributions were similar among groups with different years of diagnosis, regardless of the histologic type. Early-stage disease (stages I/II) accounted for 80-85% of endometrioid carcinomas in all years of diagnosis (Figure 4A). In contrast, early-stage disease (stages I/II) only accounted for 50% of non-endometrioid carcinomas. Approximately 30% and 20% of patients presented with stages III and IV disease, respectively (Figure 4B).

# Advanced stages at diagnosis indicated a poor prognostic factor

Significant difference in 5 –year CSS rates for endometrioid carcinoma was observed between the two periods (Figure 4C). The CSS rates of stage I patients improved from 96.7–97.9% (HR 0.63, 95% CI 0.49-0.81, *P*=0.0004). And the CSS rates of stage III patients also improved from 76.3–83.1% (HR 0.72, 95% CI 0.58-0.90, *P*=0.0039). The 5-year CSS rates of non-endometrioid carcinomas in each stage were lower than those of endometrioid carcinoma (Figure 4D). We did not observe any significant difference of the CSS rates of all stages for non-endometrioid carcinoma patients in the two periods (60.7% vs. 63.8%, HR 0.92, 95% CI 0.78-1.08, *P*=0.31). We analyzed the influences of clinical factors on the 5-year CSS rates in a multivariate analysis (Table 2). Older ages at diagnosis were associated with a shorter CSS (HR 1.32, 95% CI 1.01-1.74 for ages 50-59; HR 1.79, 95% CI 1.37-2.38 for ages 60-69; and HR 2.92, 95% CI 2.22-3.91 for ages 70 and older). Women diagnosed in the period of 2013-2017 had significantly higher CSS rates, compared to those diagnosed in the period of 2009-2012 (HR 0.81, 95% CI 0.73-0.89). The CSS rates were

lower in patients with advanced stages (III/IV) (HR 10.8, 95% CI 9.68-12.1) and non-endometrioid carcinoma (HR 2.69, 95% CI 2.41-3.00) compared to those in early stages (I/II) and with endometrioid carcinoma, respectively. The risk of non-endometrioid carcinoma reduced (univariate: HR 6.18, multivariate: HR 2.69) after adjusting the covariates. Stage was the main determinant of survival with the worst CSS.

Table 2
Univariate and multivariate analysis of 5-year cancer-specific survival (CSS) for uterine corpus cancer patients in Taiwan, 2009-2017

| Characteristics | *n* | 5-year CSS | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | 95% CI | *P* | HR | 95% CI | *P* |
| **Age (years)** | | | | | | | | |
| <40 | 1304 | 95.3% | 1.00 | Ref | | 1.00 | Ref | |
| 40-49 | 3145 | 94.8% | 1.10 | 0.82-1.50 | 0.537 | 0.87 | 0.65-1.18 | 0.358 |
| 50-59 | 6475 | 90.2% | 2.12 | 1.63-2.80 | <.0001 | 1.32 | 1.01-1.74 | 0.046 |
| 60-69 | 3423 | 85.3% | 3.21 | 2.47-4.26 | <.0001 | 1.79 | 1.37-2.38 | <.0001 |
| ≥70 | 1524 | 75.6% | 5.77 | 4.40-7.70 | <.0001 | 2.92 | 2.22-3.91 | <.0001 |
| **Diagnostic period** | | | | | | | | |
| 2009-2012 | 5672 | 88.0% | 1.00 | Ref | | 1.00 | Ref | |
| 2013-2017 | 10199 | 90.1% | 0.83 | 0.75-0.92 | 0.0004 | 0.81 | 0.73-0.89 | <.0001 |
| **Stage** | | | | | | | | |
| Early (stage I, II) | 12641 | 96.1% | 1.00 | Ref | | 1.00 | Ref | |
| Advanced (stage III, IV) | 3230 | 60.9% | 13.7 | 12.3-15.3 | <.0001 | 10.8 | 9.68-12.1 | <.0001 |
| **Histological subtype** | | | | | | | | |
| Endometrioid | 14063 | 92.5% | 1.00 | Ref | | 1.00 | Ref | |
| Non-endometrioid | 1808 | 62.4% | 6.18 | 5.58-6.84 | <.0001 | 2.69 | 2.41-3.00 | <.0001 |

HR: hazard ratio, CI: confidence interval

# Discussion

The present survey showed that the age-adjusted incidence rates of uterine cancer increased swiftly from 5.3 to 15.2 per 100 000 woman-years between 1998 and 2017. Endometrioid carcinoma accounted for the majority of uterine cancers, and thus, its incidence rates reflected those of all uterine cancers. However, the incidence rates of non-endometrioid carcinoma and uterine sarcoma also increased during the 20-year period. The age-specific incidence of endometrioid carcinoma peaked at 55-60 years of age. In contrast, the incidence rates of non-endometrioid carcinoma continued to increase with age and then plateaued after 60 years of age. Meanwhile, the percentage changes in the incidence of non-endometrioid carcinoma continued to rise with age, particularly among women over 60 years old.

We found that the incidence of endometrioid carcinoma increased rapidly over the past 20 years and the trend has continued without reaching a plateau to date. This fast-rising trend was not observed in other Western or Asian countries [20, 21]. Trends in the incidence of uterine cancer have also varied with the histologic type in other populations [15, 22]. Endometrioid carcinoma (type I) is estrogen-dependent, and obesity is a key driver of temporal trends in its incidence. The prevalence of overweight status and obesity are increasing globally, but the rates vary by country [23, 24]. This variation suggested that different risk profiles and protection factors might be found in different countries [25]. The Nutrition and Health survey conducted in Taiwan (NAHSIT) showed that the location of residence, educational level, and physical activity were correlated with obesity [11]. Three waves of NAHSIT data analyses showed that the percentages of individuals classified as overweight increased from 1993-1996 to 2005-2008, but stabilized between 2005-2018 and 2013. In contrast, over the same time periods, sharp increases were observed in the prevalence of both obesity (11.8%, 17.9%, to 22.1%, respectively) and morbid obesity (0.4%, 0.6%, to 1.4%) in our country [26]. Rubeis et al. and Song et al. found that overweight status in early adulthood was associated with an increased lifetime risk of cancers, including uterine cancer [27, 28]. The prevalence of overweight and obesity also increased among children and adolescents in Taiwan [12]. Moreover, the increasing trends in the prevalence of uterine cancer over the study period were more noticeable among younger women than among older women. Previous studies also reported that the most recent birth cohorts showed the greatest increases in the incidences of uterine cancer, particularly endometrioid carcinoma [29, 30], similar to our findings.

The measurement methods and classifications of obesity have varied widely. The prevalence of obesity among women was 19.3% in our country during 2013-2016, when obesity was defined as a body mass index (BMI) ≥27 kg/$m^2$ [14]. However, when obesity was defined in terms of the percentage of body fat (≥30% body fat for women), the prevalence of obesity largely increased from 40.2–80.8% over the past decade (NAHSIT 1993-1996 to NAHSIT 2005-2008) [31, 32]. Based on the BMI, the prevalence of obesity was only modest in Taiwan, so there was a large discrepancy between the prevalence based on BMI and the prevalence based on body-fat percentage. Regional differences in the prevalence of obesity were also observed in different studies. Some studies suggested that the risk of obesity was higher in Asian populations than in Caucasian populations, when using the same BMI cutoff point [33, 34]. It has been suggested that the percentage and distribution of body fat could be more closely related to obesity-related disorders than the BMI.

We observed that the most rapid increase of AAPCs in the incidence rates of endometrioid carcinoma among women aged 30 to 34 years (1.6% in 1998 and 5.66% in 2017) and among women aged 35 to 39 years (4.12% in 1998 and 11.2% in 2017). The obesity epidemic was partly reflected in the pronounced increases in risk observed in recent birth cohorts. Other potential explanations for the increasing incidence of uterine cancer might be the declining birth rates and a change in parity among Taiwanese women over time. In Taiwan, the average age of women at first delivery increased from 28.8 years in 2008 to 30.9 years in 2018 [33]. The risk of uterine cancer decreased with increasing parity. However, the association between the timing of delivery (mother's age at first and last births) and the risk of uterine cancer was inconclusive [36-38].

We found that the incidence of non-endometrioid carcinoma also increased significantly. Similarly, in the US, the rates of non-endometrioid cancers rose over time, and the most profound increases were observed among African American women [15, 39, 40]. Serous carcinoma comprised the majority of non-endometrioid carcinoma which mainly arose from the loss of p53 function during its molecular pathogenesis [14]. Although obesity was the most common causative factor addressed in studies on the increasing incidence of uterine cancer, it remains unknown whether obesity contributed to the increasing incidence of histologic types other than endometrioid carcinoma. Early diagnosis of non-endometrioid carcinoma had a minimal impact on the incidence, because the distribution of disease stages in women diagnosed with non-endometrioid carcinoma remained constant in this survey. The distributions of disease stages, grouped according to age at diagnosis, were similar between endometrioid and non-endometrioid carcinomas in this study (data not shown). Other factors that might influence the increasing incidence of uterine cancer should be further explored, rather than focusing solely on obesity.

Younger women and women with early-stage uterine endometrioid carcinoma had better survival rates than their counterparts. The hazard rates for non-endometrioid carcinoma decreased after adjusting age, diagnostic period and stage. This implied that advanced stage with increasing age at diagnosis, not non-endometrioid histology per se, adversely affected prognosis. Stage was still the strongest predictor of survival. The diagnostic period was also identified as a prognostic factor in this survey. Survival improvements could be attributed to more effective and tailored treatments. For example, a potential benefit might have been conferred by the incorporation of adjuvant chemotherapy over the past decade, in patients in advanced stages and women in early stages with high-risk features. Survival might have also been improved by changes in the management of uterine cancer by specialists, like gynecologic oncologists, in Taiwan and other countries [41].

The main strengths of our study were the national, population-based, cross-sectional design, and the 20-year study period. Moreover, we included all uterine cancers registered in the National Cancer Registry of Taiwan, and we assessed the incidence trends of different histologic types of uterine cancers. Another advantage of this study was that we characterized variations in the incidences of uterine cancer in groups stratified by age, histological type, calendar period of the diagnosis, and particularly, birth cohort. This study also had some limitations. First, it was retrospective in nature, because it was based on registry data. Consequently, we did not have information on factors that could contribute to the

development of uterine cancer, like BMI, hormonal therapy use, and reproductive history, including parity, pregnancy duration, and the timing and number of births. Another limitation was the absence of central pathology review, we could only categorize uterine cancers into four groups (endometrioid, non-endometrioid, sarcoma, and others), rather than the more common classifications of types I and II. In addition, we did not assess the prevalence of overweight/obesity or its association with uterine cancer in this study. Finally, the impact of the risk of obesity might have been limited by other confounders, such as the use of oral contraceptives.

# Conclusion

The incidences of uterine cancers increased significantly, irrespective of the histological type. Age-specific incidences continuously increased over time, in cohorts born after 1950. The incidences of endometrioid carcinoma consistently increased in successively younger birth cohorts, and substantial changes in trend were observed among women under age 40 years. These findings underscored the need for etiologic research to clarify the causes of these trends

# Declarations


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### Conflict of interest

The authors declare no competing interests

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon request.

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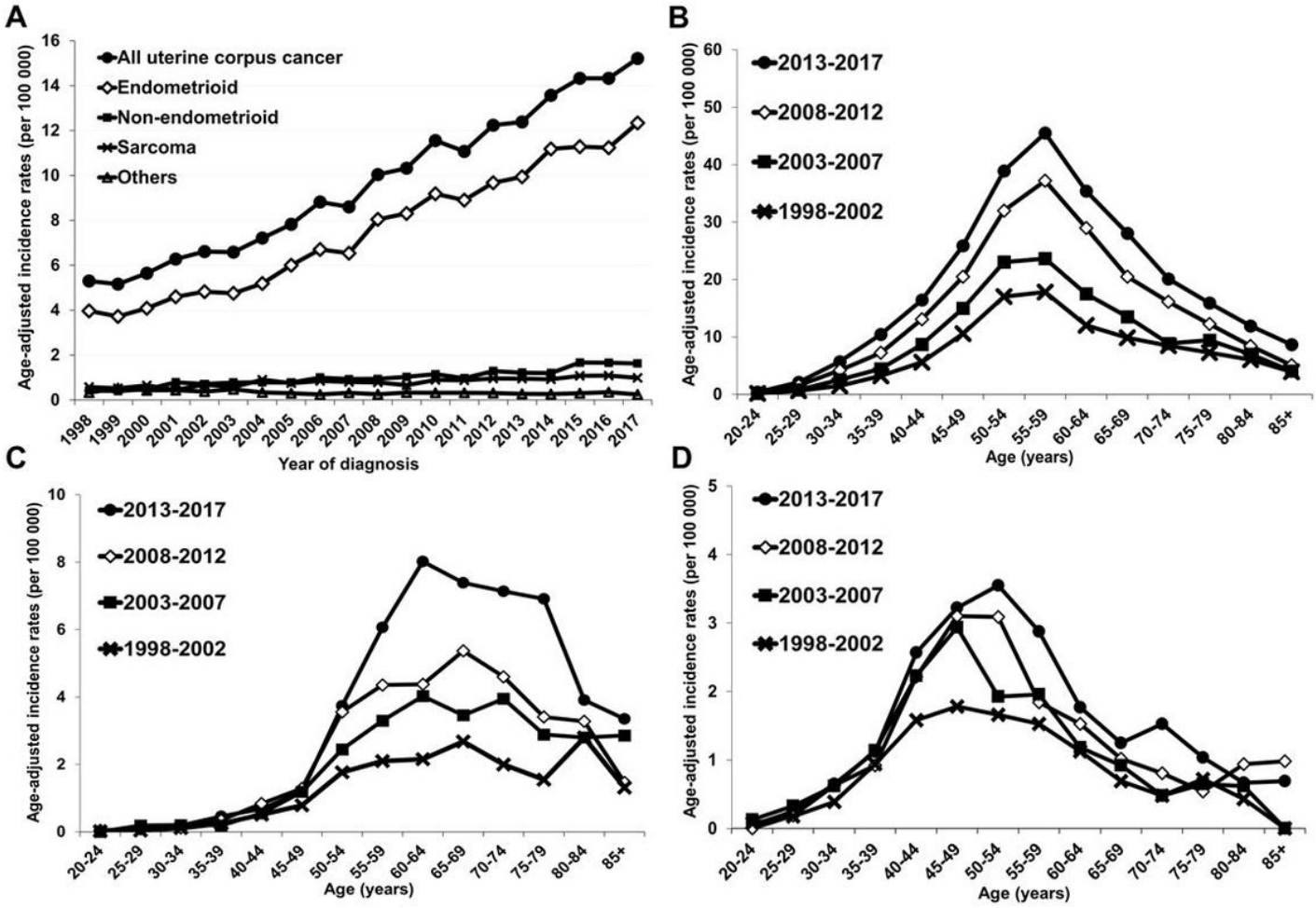
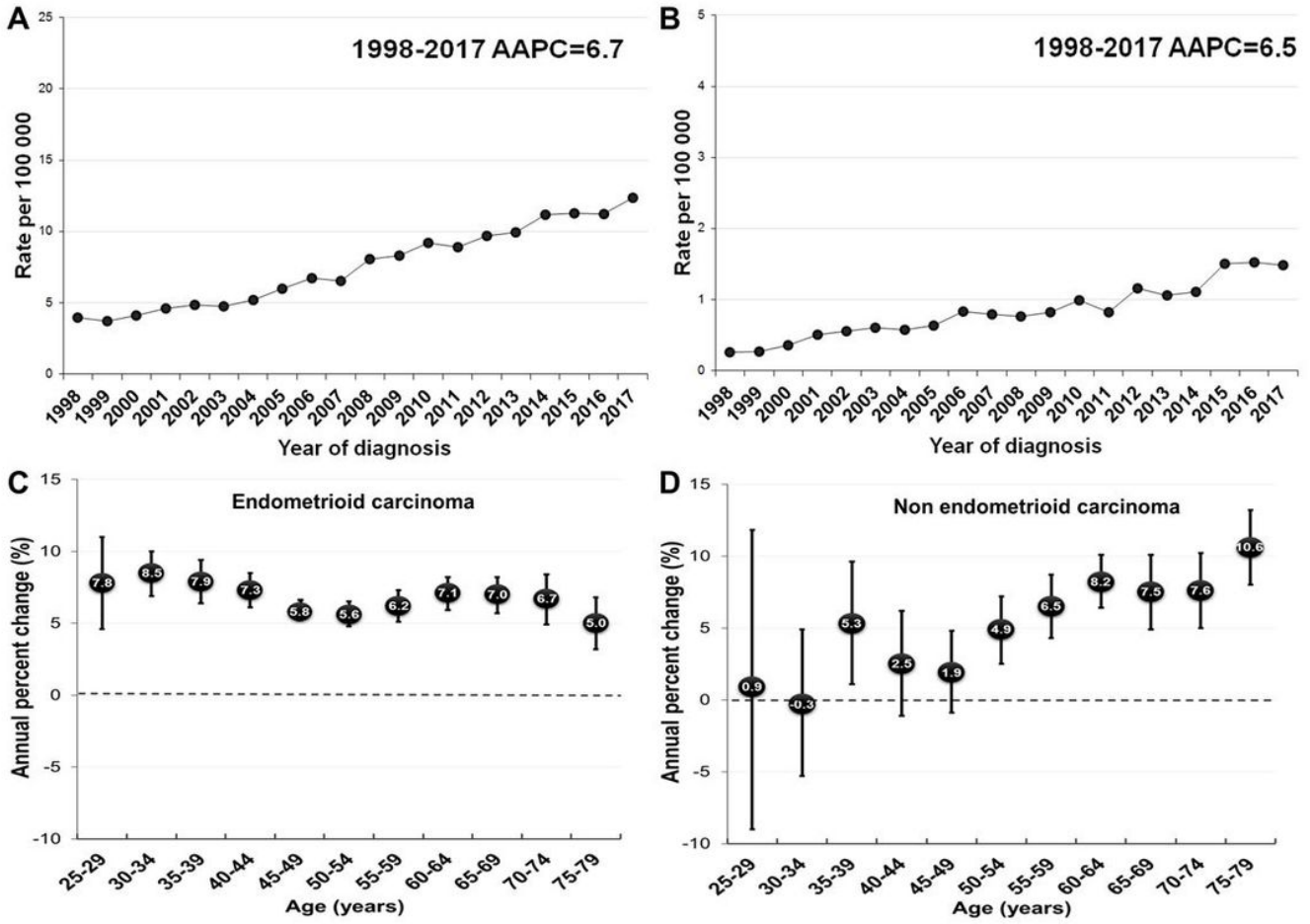
# Figures



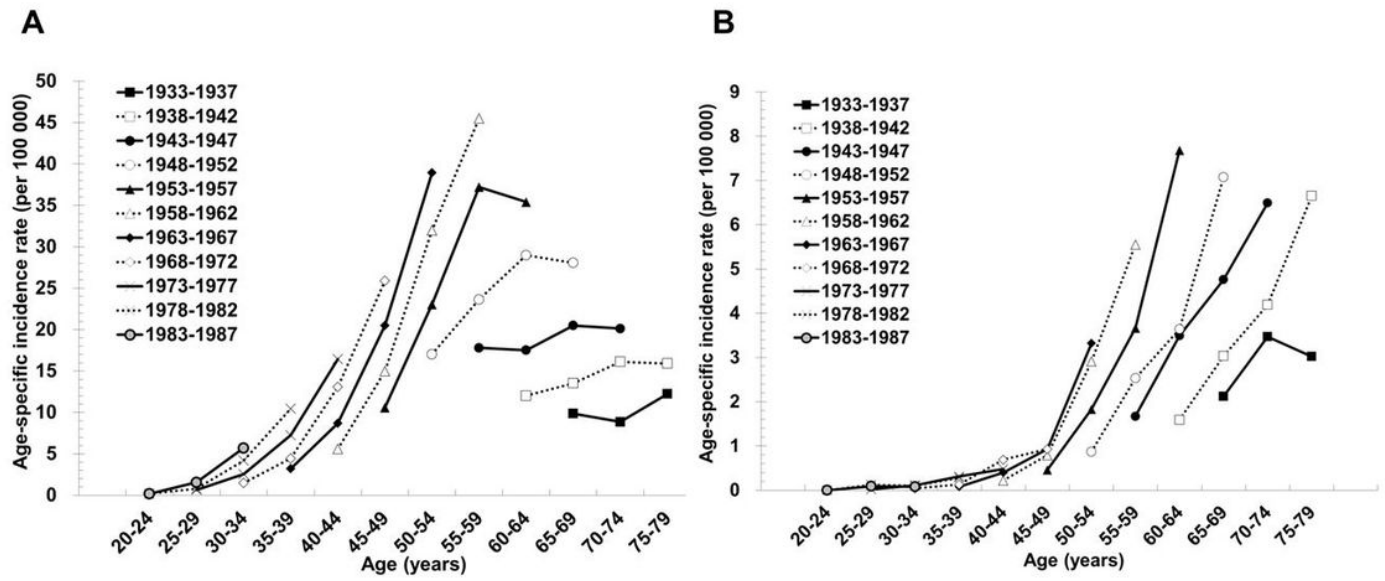

## Figure 1

Trends in the incidences of uterine corpus cancer in Taiwan during 1998–2017. (A) Age-adjusted incidence of uterine corpus cancers, stratified by histological type. Age-specific incidence of (B) endometrioid carcinoma, (C) non-endometrioid carcinoma, (D) uterine sarcoma, grouped by calendar year.




## Figure 2

Incidence of uterine corpus cancer in Taiwan between 1998 and 2017. Age-adjusted incidences of (A) endometrioid and (B) non-endometrioid carcinoma, characterized by the average annual percent change (AAPC). Summary of the AAPCs in the incidences of (C) endometrioid carcinoma and (D) non-endometrioid carcinomas in 5-year age groups. The error bars indicate 95% confidence intervals.




## Figure 3

Birth cohort effects on incidence trends of uterine corpus cancer and stage distribution over time. Age-specific incidence of (A) endometrioid carcinoma and (B) non-endometrioid carcinoma, grouped by birth cohort.

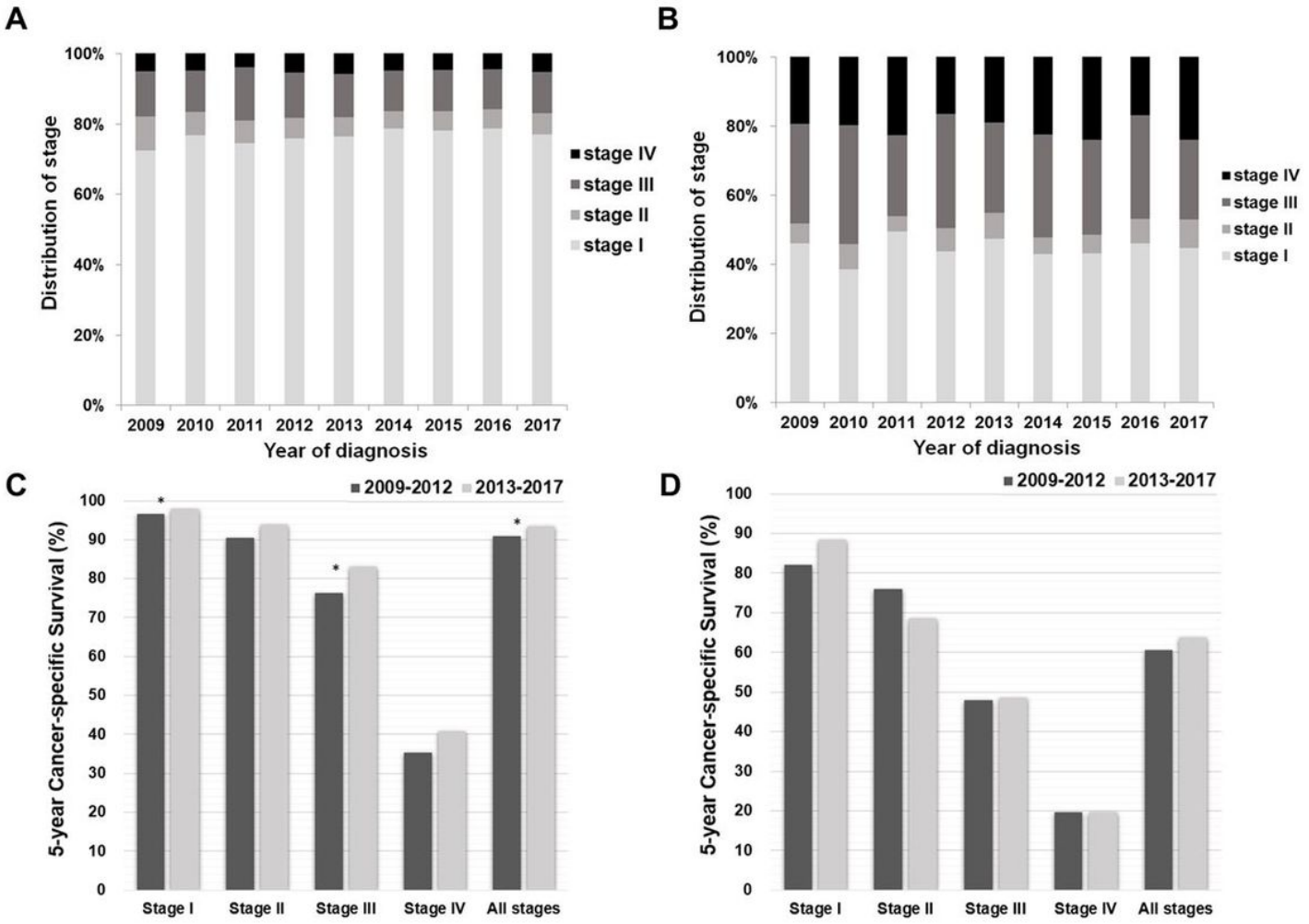



**Figure 4**

Survival and stage at diagnosis of patients with uterine cancer in Taiwan. The stages at diagnosis of (A) endometrioid and (B) non-endometrioid carcinoma between 2009 and 2017. Comparison of five-year cancer-specific survival for the two periods in (C) endometrioid and (D) non-endometrioid carcinomas, by stage. * P <0.05 by log-rank test.

# Supplementary Files

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- supplementaryFigure1.tif
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