Synchronous/metachronous endometrial and colorectal malignancies in Taiwanese women: a population-based nationwide study

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Abstract

Introduction Endometrial cancer (EC) and colorectal cancer (CRC) may share a common genetic background. In a subset of patients, the two malignancies can coexist either at the time of diagnosis (synchronous) or develop consequently (metachronous). The purpose of this nationwide, population-based study was to investigate the occurrence and clinical outcomes of synchronous/metachronous EC/CRC in Taiwanese women.

Materials and methods Data for women diagnosed with EC and/or CRC between 2007 and 2015 were retrospectively retrieved from the nationwide Taiwan Cancer Registry. Mortality data were obtained from the National Death Registry. Women with synchronous/metachronous EC/CRC versus EC or CRC were compared in terms of clinical characteristics and outcomes.

Results Of the 62,764 Taiwanese women diagnosed with EC and/or CRC during the study period, 167 (0.3%) had synchronous/metachronous EC/CRC. Among them, 72 cases (43.1%) presented with EC followed by CRC, 66 (39.5%) with CRC followed by EC, and 29 (17.4%) with synchronous EC/CRC. Kaplan–Meier estimates for time-to-event data revealed that the 2-year risk rates of developing a metachronous tumor of interest (CRC or EC) in women diagnosed with an initial EC and CRC were 39.6% and 42.1%, respectively. The 5-year overall survival rates of women with metachronous EC/CRC who had an initial diagnosis of EC, CRC, and synchronous EC/CRC were 73.9%, 70.9%, and 37.0%, respectively.

Conclusions Endometrial cancer is the most common first tumor in Taiwanese women with metachronous EC/CRC. The 2-year risk rates of developing a metachronous tumor of interest (CRC or EC) in women diagnosed with an initial EC and CRC are not negligible. Surveillance for CRC is recommended for all women diagnosed with EC. The clinical outcomes of synchronous EC/CRC are markedly less favorable.

Keywords Endometrial cancer · Colorectal cancer · Metachronous tumors · Synchronous tumors · Taiwan

Abbreviations

CRC Colorectal cancer
EC Endometrial cancer
MMR Mismatch repair
LC Lynch syndrome

NDR National Death Registry
TCR Taiwan Cancer Registry

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Introduction

Epidemiological data have shown that the incidence rates of endometrial cancer (EC)—which is the sixth most common gynecologic malignancy worldwide—have been rising in countries characterized by rapid socioeconomic transitions [1, 2]. On analyzing the burden of EC in Taiwanese women, the incidence has been reported to increase from 11.96 cases per 100,000 person in 2012 to 15.11 cases per 100,000 person in 2018 [3, 4]. The most common histological type of EC is endometrioid carcinoma—which comprises approximately 85% of all cases, with the remaining types being serous carcinomas (3–10%) and clear cell carcinomas (< 5%) [5]. A molecular classification of EC has also been proposed [6].

Recent years have witnessed a growing interest in the biological links between EC and colorectal cancer (CRC) [7, 8]. Specifically, evidence has emerged that the two malignancies may share a common genetic background—which appears mainly related to germline mutations in the mismatch repair (MMR) genes [7]. In a subset of patients, the two malignancies can also coexist either at the time of diagnosis (synchronous) or develop consequently (metachronous). The coexistence of EC and CRC is also typical of the Lynch syndrome (LS), which is one of the most common autosomal dominant cancer susceptibility disorders [9–12].

While inherited EC (including malignancies occurring in patients with LS) accounts for only 5% of all cases in different ethnicities [13–15], no large-cohort study in the Asian population has specifically investigated the risk of metachronous EC/CRC to inform surveillance protocols. In addition, the survival figures of women who develop metachronous EC/CRC remain poorly investigated. The purpose of this nationwide, population-based study was to examine the occurrence and clinical outcomes of metachronous EC/CRC in Taiwanese women, and to assess whether any difference exists compared with those presenting with EC or CRC.

Materials and methods

Data source

The present retrospective study, using data obtained from the nationwide Taiwan Cancer Registry (TCR) database (Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan), complied with the principles set forth in the Declaration of Helsinki. The TCR was first established in 1979 and has prospectively recorded information on all patients with malignancies in Taiwan, along with site-specific variables and other clinical parameters related to patient care. As of 2005, the reported completeness of data registration in the TCR ranged between 97 and 98.4% [16]. Variables for this study were retrospectively retrieved for all of the Taiwanese women who were diagnosed with EC and/or CRC between January 1, 2007 and December 31, 2015. Once fully anonymized, the dataset was processed under current data protection laws and regulations. Ethics approval was received from the Institutional Review Board of the Chang Gung Medical Foundation (Approval No: 201801202B0C502). The requirement for written informed consent was waived due to the study design.

Diagnostic classification and survival analysis

Eligibility criteria comprised women with a diagnosis of EC and/or CRC who were included in the TCR. Diagnoses in this registry are coded according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). Specifically, women were deemed eligible in presence of the following disease codes: C540–C543 and C548–C549 (EC); C180, C182–C189, C199, and C209 (CRC) [17]. EC included the following histological types: endometrioid carcinoma, serous carcinoma, and clear cell carcinoma (histology codes: 8010, 8013, 8020, 8041, 8140, 8263, 8310, 8323, 8380, 8382, 8441, 8480, and 8570). Patients with EC were staged using the TNM criteria. The histology codes for colorectal adenocarcinoma were as follows: 8000, 8010, 8020, 8140, 8210, 8246, 8260, 8261, 8262, 8263, 8480, 8481, 8490, and 8570. Once women diagnosed with both EC and CRC were identified, the chronological order of the malignancies was assessed based on the date of diagnosis. Tumors that occurred within three months of the diagnosis of the previous neoplasm were considered as synchronous, whereas those that occurred more than three months apart were considered as metachronous. All-cause mortality data were retrieved from the Taiwanese National Death Registry (NDR) of the Department of Health [18]. Overall survival (OS) was defined as the time interval from the initial-cancer diagnosis to death from any cause, or censored at the last follow-up. Follow-up was terminated on December 31, 2017.

Statistical analysis

Differences between multiple groups on continuous variables were analyzed using one-way analysis of variance followed by the Tukey’s post hoc multiple comparison test. The Chi-square test was used to examine the distribution of categorical variables between groups. Cumulative survival curves were plotted with the Kaplan–Meier method and compared with the log-rank test. Post-hoc adjustments
were applied for pairwise comparisons. All analyses were performed with SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was determined by a two-tailed p value < 0.05.

Results

Prevalence and temporal sequence of synchronous/metachronous endometrial and colorectal cancers

A total of 62,764 Taiwanese women were diagnosed with EC and/or CRC between 2007 and 2015. Of them, 13,887 (22.1%), 48,710 (77.6%), and 167 (0.3%) had EC, CRC, and synchronous/metachronous EC/CRC, respectively. In the synchronous/metachronous group, 72 cases (43.1%) presented with EC followed by CRC, 66 (39.5%) with CRC followed by EC, and 29 (17.4%) with synchronous EC/CRC (Fig. 1).

Characteristics of women with synchronous/metachronous endometrial and colorectal cancers

The characteristics of women diagnosed with EC, CRC, and synchronous/metachronous EC/CRC are shown in Table 1. There were significant intergroup differences in terms of mean age at diagnosis, which was significantly higher in women with CRC (p < 0.001). When dividing the metachronous EC/CRC category into three groups (initial EC, initial CRC, and synchronous, Table 2), significant intergroup differences in terms of age were observed (p < 0.001). Post-hoc pairwise comparisons revealed that the age at diagnosis in patients with synchronous tumors (mean: 61.3 years) was significantly different from that observed in the initial EC group (mean: 54.3 years, p = 0.045). Similar to the initial EC group, early-stage disease was commonly observed in women with synchronous/metachronous EC/CRC. In contrast, early-stage CRC occurred more frequently in women with synchronous/metachronous EC/CRC compared to those diagnosed with CRC (Table 1). On analyzing the histology distribution of EC in patients with either synchronous/metachronous EC/CRC or EC, no significant differences were identified.

Epidemiological trends of endometrial and colorectal cancers

Throughout the study period (2007–2015), the incidence rates of both EC and CRC in Taiwanese women showed upward trends (Fig. 2 and Table 3). A similar—albeit less striking—pattern was observed for synchronous/metachronous EC/CRC, whose incidence reached 0.28 cases (95% confidence interval: 0.20–0.39) per 100,000 persons in 2015. The number of women with an initial diagnosis of EC who subsequently developed CRC, as well as of those who were initially diagnosed with CRC who subsequently developed EC, is depicted in Fig. 3. Based on Kaplan–Meier estimates for the time to a second metachronous tumor of interest (i.e., CRC or EC), the 2-year risk rates of women initially diagnosed with EC (including synchronous malignancies) and

![Flow of patients through the study. EC endometrial cancer, CRC colorectal cancer](image)
CRC (including synchronous malignancies) were 39.6% and 42.1%, respectively. The 5-year risk rates were 11.9% and 8.4%, respectively. There were no significant differences with respect to the time of developing a second metachronous CRC/EC for women who presented with initial EC versus initial CRC (log-rank test, \( p = 0.677 \)).

### Survival analysis

The median follow-up time was 1.4 years (range: 0–10.8 years). The 5-year OS rates of women with EC, CRC, and synchronous/metachronous EC/CRC were 81.1%, 40.0%, and 66.9%, respectively. The 10-year OS rates in the

**Table 1** Characteristics of the 62,764 Taiwanese women included in the study

| Variable | EC | CRC | Metachronous EC/ CRC |
|----------|----|-----|---------------------|
| Number of cases | 13,887 (22.1) | 48,710 (77.6) | 167 (0.3) |
| Age (years) at first cancer diagnosis | | | |
| Mean (SD) | 54.3 (11.0) | 66.2 (14.1) | 56.8 (11.6) | <0.001 |
| \(<50 \%\) | 4249 (30.6) | 6286 (12.9) | 45 (26.9) | <0.001 |
| \(\geq 50 \%\) | 9638 (69.4) | 42,424 (87.1) | 122 (73.1) | |
| EC histology, count (%) | | | 0.298 |
| Endometrioid carcinoma | 13,248 (95.4) | 156 (93.4) | |
| Serous carcinoma | 627 (4.5) | 11 (6.6) | |
| Clear cell carcinoma | 12 (0.1) | 0 (0) | |
| EC stage, count (%) | | | |
| I | 8173 (74.6) | 79 (69.3) | |
| II | 698 (6.4) | 13 (11.4) | |
| III | 1440 (13.1) | 13 (11.4) | |
| IV | 644 (5.9) | 9 (7.9) | |
| CRC stage, count (%) | 42,163 | 147 | 0.002 |
| I | 8460 (20.1) | 35 (23.8) | |
| II | 10,202 (24.2) | 50 (34.0) | |
| III | 13,482 (32.0) | 44 (29.9) | |
| IV | 10,019 (23.8) | 18 (12.2) | |
| Temporal sequence of metachronous tumors, count (%) | | | |
| EC followed by CRC | 72 | (43.1) | |
| CRC followed by EC | 66 | (39.5) | |
| Synchronous EC/CRC | 29 | (17.4) | |

**Table 2** Patient age according to the diagnostic group

| Variable | EC | CRC | Initial EC followed by CRC | Initial CRC followed by EC | Synchronous EC/CRC | \( p \) value |
|----------|----|-----|----------------------------|---------------------------|-------------------|-------------|
| Age (years) at diagnosis of first cancer | | | | | | |
| Mean (SD) | 54.3 (11.0) | 66.2 (14.1) | 56.1 (11.6) | 55.5 (10.8) | 61.3 (12.4) | <0.001 |
| Median (range) | 54 (19–94) | 67 (13–109) | 56.5 (35–87) | 54.5 (27–76) | 59 (38–91) | |
| \(<50\), \( n \) (%) | 4249 (30.6) | 6286 (12.9) | 23 (31.9) | 17 (25.8) | 5 (17.2) | <0.001 |
| \(\geq 50\), \( n \) (%) | 9638 (69.4) | 42,424 (87.1) | 49 (68.1) | 49 (74.2) | 24 (82.8) | |
| Adjusted pairwise \( p \) value | | | | | | |
| EC | <0.001 | 0.795 | 0.958 | 0.045 |
| CRC | <0.001 | <0.001 | <0.001 | 0.293 |
| Initial EC followed by CRC | 0.795 | <0.001 | 0.999 | 0.414 |
| Initial CRC followed by EC | 0.958 | <0.001 | 0.999 | 0.306 |
| Synchronous EC/CRC | 0.045 | 0.293 | 0.414 | 0.306 |

\( EC \), endometrial cancer; \( CRC \), colorectal cancer; \( SD \), standard deviation
three study groups were 72.8%, 24.0%, and 43.6%, respectively. Therefore, women with EC showed a more favorable OS than those with synchronous/metachronous EC/CRC \( (p < 0.001) \). The poorest survival outcomes were observed for women with CRC \( (p < 0.001 \) versus both EC and synchronous/metachronous EC/CRC; Fig. 4 and Table 4). The 5-year OS rates of women with synchronous/metachronous EC/CRC \( (n = 167) \) who received an initial diagnosis of EC, CRC, and synchronous EC/CRC were 73.9%, 70.9%, and 37.0%, respectively (Fig. 5 and Table 4). Collectively, these results indicate that the OS patterns of women with metachronous EC/CRC who had an initial diagnosis of EC and CRC were similar and significantly more favorable compared with that observed in synchronous EC/CRC \( (p \text{ values } = 0.004 \) and 0.012, respectively; Table 4).

### Table 3

| Calendar year | Total population | Incidence per 100,000 persons (95% CI) |
|---------------|-----------------|---------------------------------------|
|               |                 | EC (9.0–9.1)                           | CRC (39.9–40.2)                           | Metachronous EC/CRC (0.00–0.07) |
| 2007          | 11,349,593      | 8.5                                   | 39.0                                   | 0.02                                  |
| 2008          | 11,410,680      | 10.7 (10.1–11.3)                       | 40.6 (39.4–41.7)                       | 0.15 (0.09–0.24)                     |
| 2009          | 11,483,038      | 11.3 (10.7–12.0)                       | 43.5 (42.3–44.7)                       | 0.08 (0.04–0.15)                     |
| 2010          | 11,526,898      | 12.9 (12.2–13.5)                       | 47.7 (46.5–49.0)                       | 0.20 (0.13–0.30)                     |
| 2011          | 11,579,238      | 12.6 (12.0–13.3)                       | 47.2 (46.0–48.5)                       | 0.10 (0.06–0.18)                     |
| 2012          | 11,642,503      | 13.9 (13.3–14.6)                       | 50.3 (49.0–51.6)                       | 0.21 (0.14–0.31)                     |
| 2013          | 11,688,843      | 14.9 (14.2–15.6)                       | 50.3 (49.1–51.6)                       | 0.22 (0.15–0.33)                     |
| 2014          | 11,735,782      | 16.9 (16.2–17.7)                       | 51.5 (50.2–52.8)                       | 0.18 (0.12–0.27)                     |
| 2015          | 11,780,027      | 17.9 (17.1–18.7)                       | 50.2 (48.9–51.5)                       | 0.28 (0.20–0.39)                     |

EC endometrial cancer, CRC colorectal cancer, CI confidence interval

### Discussion

The main results of this nationwide population-based study conducted in Taiwan are as follows: (1) metachronous EC/CRC is more commonly characterized by the onset of EC as the first tumor; (2) women with synchronous EC/CRC tend to be older than those with EC; (3) early-stage CRC was observed more frequently in women with synchronous/metachronous EC/CRC compared with those showing CRC; (4) the 2-year risk rates of developing a second metachronous tumor of interest \( (i.e., \text{EC or CRC}) \) in women initially diagnosed with EC (including synchronous malignancies) and CRC (including synchronous malignancies) were 39.6% and 42.1%, respectively, (5) the 5-year OS rates of women with EC, CRC, and synchronous/metachronous EC/CRC were 81.1%, 40.0%, and 66.9%, respectively, and (6) women with synchronous EC/CRC had the less favorable 5-year OS rate (37.0%).

![Fig. 2 Temporal trends with 95% confidence intervals for the incidence of EC, CRC, and synchronous/metachronous EC/CRC in Taiwanese women. SYN/MET synchronous/metachronous](image1)

![Fig. 3 Number of cases with metachronous EC/CRC according to different time frames from the first cancer diagnosis. The numbers and percentages of patients with initial EC or initial CRC are presented for each time period](image2)
Growing evidence from molecular studies indicates that the presence of germline mutations affecting at least one of the MMR genes (i.e., MLH1, MSH2, MSH6, PMS2, and EPCAM) is associated with the LS in patients diagnosed with EC and CRC [7]. Mechanistically, an impaired function of MMR genes is related to microsatellite stability (MSI). The Amsterdam II criteria [9] and the Revised Bethesda Guidelines [10] maintain that patients with synchronous or metachronous CRC or LS-associated malignancies (including EC) should undergo MSI testing. A thorough examination of the family history plays an important role for risk prediction. In this scenario, a universal screening for MMR protein loss is generally undertaken [11, 12, 19]. Germline testing should be considered after the exclusion of MLH1 methylation [20].

In a previous study conducted in Taiwanese women with EC, the cumulative incidence of a second primary cancer was significantly higher in those aged ≥ 50 years than in younger patients [21]. Notably, the age at diagnosis of first EC for patients who subsequently developed a second primary CRC was 54.7 years [21]. The mean age of synchronous/metachronous EC/CRC in our study was 56.8 years. On analyzing the subset of women with synchronous EC/CRC, we found that they were older than those who presented with EC or CRC. This age effect may be related to mutations affecting MMR genes [22, 23], although this hypothesis needs to be further investigated [10, 12, 24, 25].

Our observation that women with synchronous/metachronous EC/CRC were more commonly characterized by the onset of EC is in line with the findings from Lu et al. [26].

**Fig. 4** Overall survival figures of women with EC, CRC, and synchronous/metachronous EC/CRC. The dotted line indicates the 5-year overall survival, with the percentages of surviving patients observed in the three groups at this time point. Abbreviations: EC, endometrial cancer; CRC, colorectal cancer

**Table 4** Survival comparison between different diagnostic groups

| Comparison | Log-rank p value | Adjusted p value |
|------------|------------------|------------------|
| EC, CRC, and metachronous EC/CRC | <0.001 | |
| EC (n=13,887) versus CRC (n=48,710) | | <0.001 |
| EC (n=13,887) versus metachronous EC/CRC (n=167) | | <0.001 |
| CRC (n=48,710) versus metachronous EC/CRC (n=167) | | <0.001 |
| Initial EC followed by CRC, initial CRC followed by EC, and synchronous EC/CRC | <0.001 | |
| Initial EC followed by CRC (n=72) versus initial CRC followed by EC (n=66) | 0.965 | |
| Initial EC followed by CRC (n=72) versus synchronous EC/CRC (n=29) | 0.004 | |
| Initial CRC followed by EC (n=66) versus synchronous EC/CRC (n=29) | 0.012 | |

EC endometrial cancer, CRC colorectal cancer
On analyzing 117 women with dual primary colorectal/gynecologic malignancies, the authors found that half of the gynecologic malignancies preceded the development of CRC—thereby acting as a “sentinel cancer” [26]. They also reported that the time interval between the diagnosis of EC and that of subsequent CRC was 11 years. In the present study, the cumulative rate for the development of CRC was within the first three years from EC diagnosis. In addition, the 5-year risk of developing a metachronous CRC in women diagnosed with EC was 11.9%. Collectively, our data indicate that women diagnosed with EC should undergo CRC surveillance for at least five years [27, 28]. This is particularly recommended for women who present with early-stage EC.

In our study, the 5-year OS rates of women with synchronous/metachronous EC/CRC were less favorable than those observed in EC. Furthermore, a 5-year OS rate as low as 37.0% was found for patients with synchronous EC/CRC. While reliable survival prediction models are not yet available, our data indicate that women diagnosed with EC should undergo CRC surveillance for at least five years [27, 28]. This is particularly recommended for women who present with early-stage EC.

There are limitations to this study. First, the TCR has no data concerning the family history of malignancies. In addition, no genetic testing was conducted on the study participants. Hence, we are unable to determine the frequency of the LS. Second, the question as to whether our results are generalizable outside Taiwan remains unanswered. Finally, we had no data concerning these parameters; therefore, they could not be included in the survival model.

**Conclusions**

EC is the most common first tumor in Taiwanese women with metachronous EC/CRC. The 2-year risk rates of developing a metachronous tumor of interest (CRC or EC) in women diagnosed with an initial EC and CRC are not negligible. Surveillance for CRC is recommended for all women diagnosed with EC. The clinical outcomes of synchronous EC/CRC are markedly less favorable.

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**Author contributions** AC and LYY: study concept and design. AC, RCW, and ASC: literature review; WYC and LYY: data analysis. AC, RCW, CHW, and LYY: manuscript writing. AC and CHL: critical revision of the manuscript for important intellectual content. All authors approved the final version.
Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval Ethics approval was received from the Institutional Review Board of the Chang Gung Medical Foundation (Approval No: 201801202B0CS02).

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