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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

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.

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 disorder [9–12].

While inherited EC (including malignancies occurring in patients with LS) accounts for only 5% of all cases [13], no large-cohort studies in the Asian population have specifically investigated the risk of metachronous EC/CRC to inform surveillance guidelines. 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% [14]. 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 number: 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) [15]. 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 [16]. 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 association of the categorical variables between groups. Cumulative survival curves were plotted with the Kaplan-Meier method and compared with the log-rank test, and *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 into three groups (initial EC, initial CRC, and synchronous, Table 2), significant differences in age between groups were also observed ($p < 0.001$). Post-hoc pairwise comparisons indicated that the age at diagnosis in synchronous (mean: 61.3 years) was significantly different from EC group (mean: 54.3 years, $p = 0.045$). Similar to EC, 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 synchronous/metachronous EC/CRC or EC, no significant differences were found.

Table 1
Characteristics of the population-based cohort of 62,764 women in Taiwan between 2007 and 2015

Variable	EC		CRC		Metachronous EC/CRC		p value
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
≥ 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 (%)	10,955				114		0.116
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)	

Abbreviations: *EC*, endometrial cancer; *CRC*, colorectal cancer; *SD*, standard deviation

Table 2
Age of different patient groups

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, count (%)	4249	(30.6)	6286	(12.9)	23	(31.9)	17	(25.8)	5	(17.2)	< 0.001
≥ 50, count (%)	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				

Abbreviations: *EC*, endometrial cancer; *CRC*, colorectal cancer; *SD*, standard deviation

Epidemiological trends of endometrial and colorectal cancers

Throughout the study period (2007–2015), the incidence rates of EC and CRC in Taiwanese women both showed upward trends (Fig. 2). 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 the Kaplan-Meier estimates for time to developing 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 CRC (including synchronous malignancies) were 39.6% and 42.1%, respectively. The 5-year risk rates were 11.9% and 8.4%, respectively. There was no significant difference in time of developing a second metachronous tumor of CRC/EC for women who presented with initial EC *versus* initial CRC (log-rank, 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 three study groups were 72.8%, 24.0%, and 43.6%, respectively. Therefore, women with EC had 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 3). 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 3). 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 (adjusted p values = 0.004 and 0.012, respectively; Table 3).

Table 3
Survival comparison between different study groups

Comparison	Log-rank P value	Adjusted P value
EC, CRC, and metachronous EC/CRC	< 0.001	
EC *versus* CRC		< 0.001
EC *versus* metachronous EC/CRC		< 0.001
CRC *versus* metachronous EC/CRC		< 0.001
Initial EC followed by CRC, initial CRC followed by EC, and synchronous EC/CRC	< 0.001	
Initial EC followed by CRC *versus* initial CRC followed by EC		0.965
Initial EC followed by CRC *versus* synchronous EC/CRC		0.004
Initial CRC followed by EC *versus* synchronous EC/CRC		0.012
Abbreviations: *EC*, endometrial cancer; *CRC*, colorectal cancer		

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., 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%).

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 [17]. Notably, the age at diagnosis of first EC for patients who subsequently developed a second primary CRC was 54.7 years [17]. 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 due to the presence of mutations in the MMR genes [18, 19], although this hypothesis needs to be further investigated [10, 12, 20, 21].

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*. [22]. 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” [22]. 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 of the diagnosis of EC. 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 [23, 24]. This is particularly the case 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 evident in presence of synchronous EC/CRC. These data indicate that synchronous EC/CRC is a prognostically adverse phenotype compared to metachronous EC/CRC. Whether this is a result of specific molecular alterations needs to be addressed in genetic epidemiology studies.

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, it would have been interesting to include environmental and clinical risk factors in the survival analysis. Unfortunately, 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.

Abbreviations

CRC
colorectal cancer
EC
endometrial cancer
MMR
mismatch repair
LC
Lynch syndrome
NDR
National Death Registry
TCR
Taiwan Cancer Registry

Declarations

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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.

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 number: 201801202B0C502).

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Figures

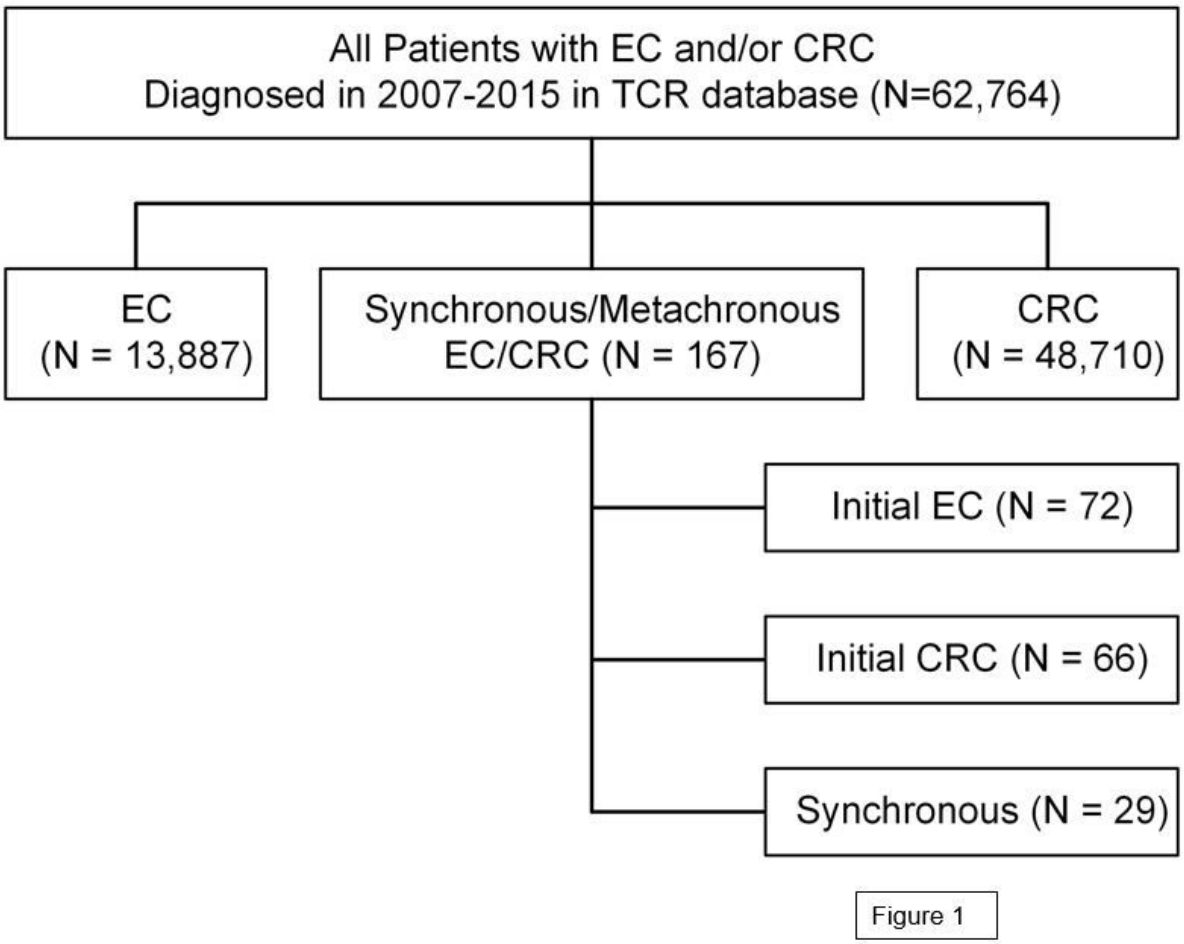

Figure 1

Flow diagram of the study. Abbreviations: EC, endometrial cancer; CRC, colorectal cancer.

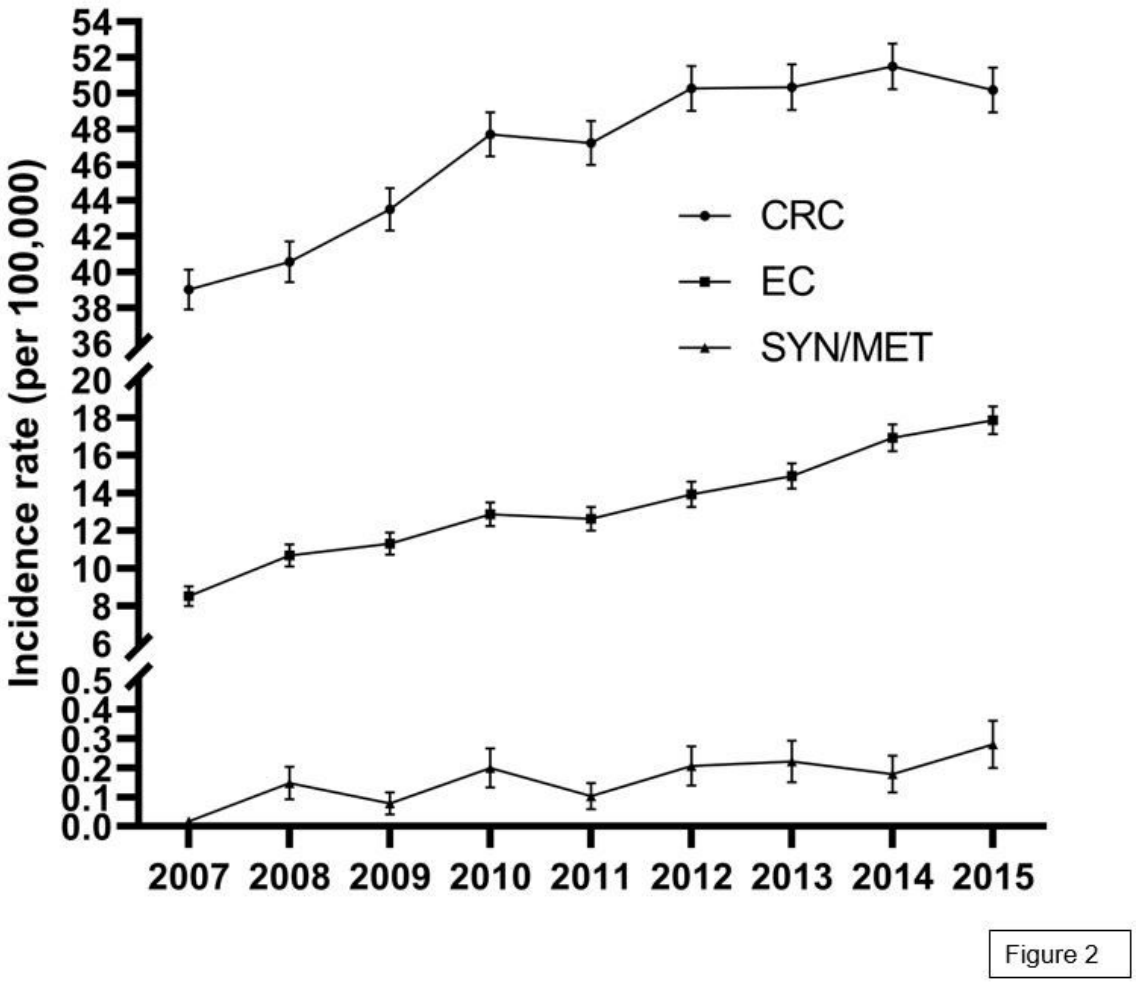

Figure 2

Trends for the incidence of EC, CRC, and synchronous/metachronous EC/CRC in Taiwanese women. Abbreviations: SYN/MET: synchronous/metachronous.

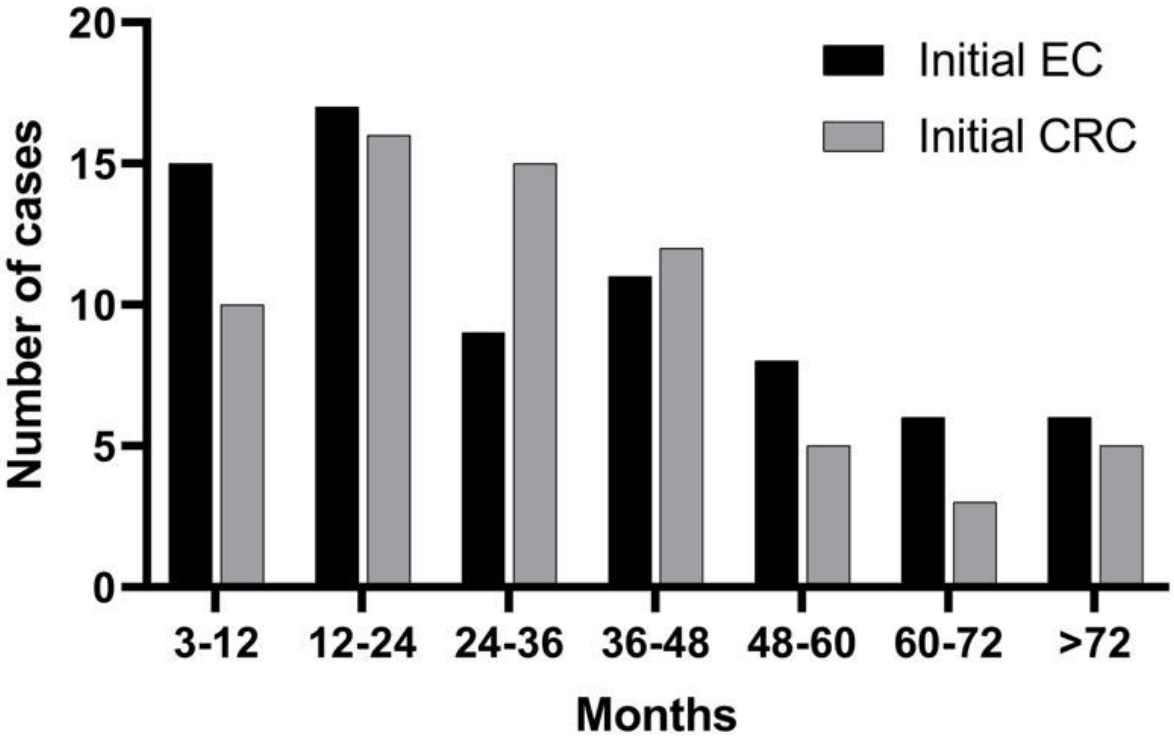

Figure 3

Figure 3

Number of cases with metachronous EC/CRC according to different time frames from the first cancer diagnosis.

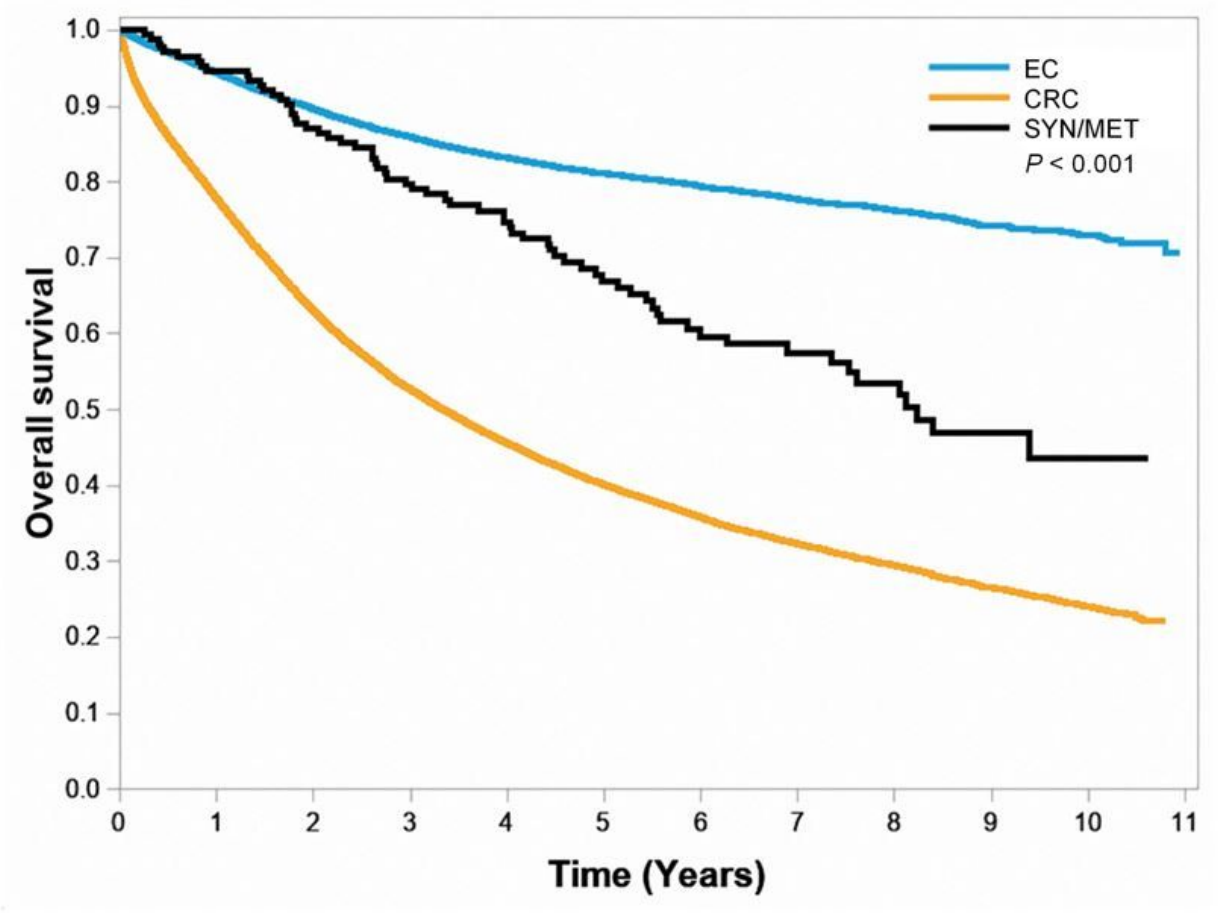

Figure 4

Overall survival figures of women with EC, CRC, and synchronous/metachronous EC/CRC. Abbreviations: EC, endometrial cancer; CRC, colorectal cancer. Abbreviations: SYN/MET: synchronous/metachronous.

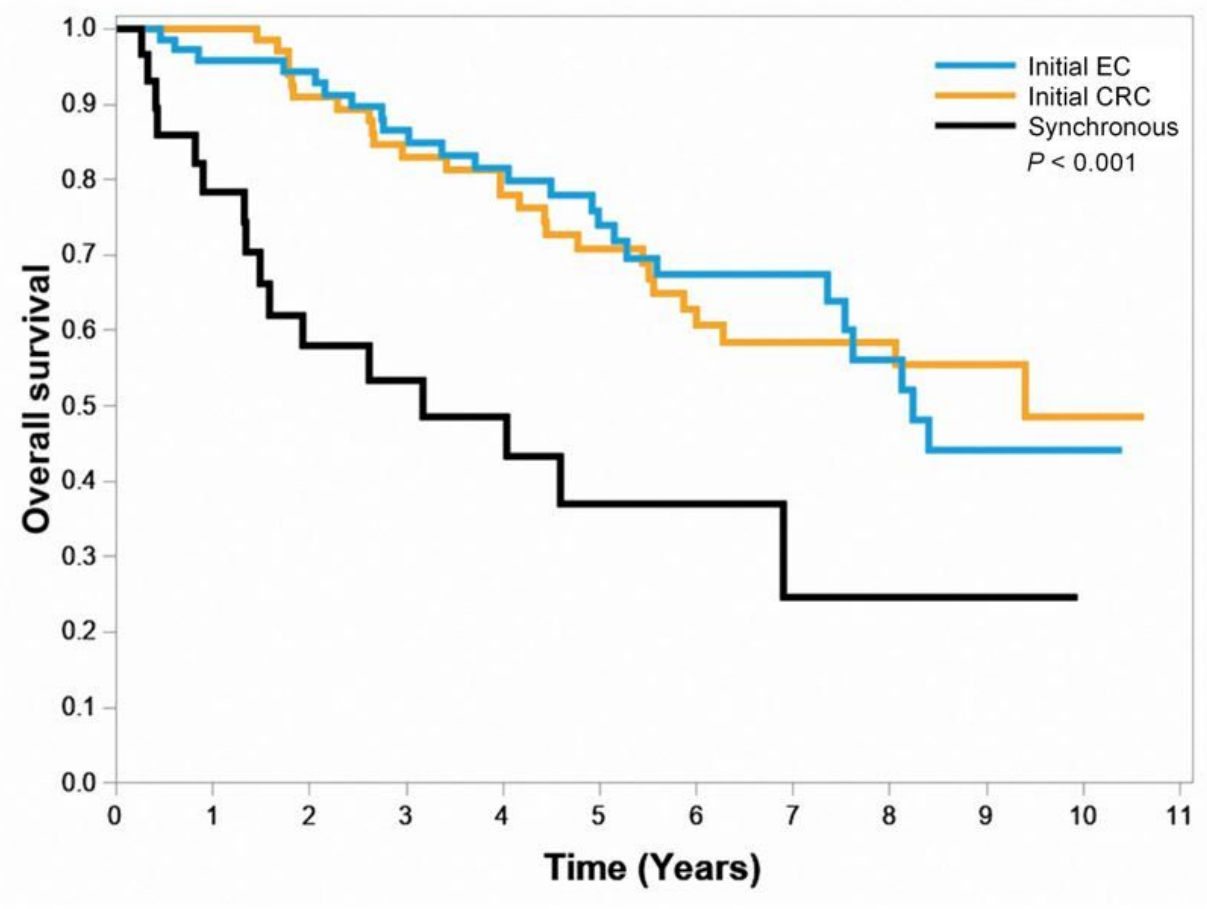

Figure 5

Figure 5

Overall survival figures of women with synchronous EC/CRC versus metachronous EC/CRC according to the chronological presentation of tumors.