

# Multiple Primary Malignancies in Gynecologic Cancer Patients in Thai Tertiary Care Center: a 10-Year Retrospective Study

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## ABSTRACT

**Objective:** To investigate the incidence, pathologic features, clinical characteristics, oncologic outcomes, and prognostic factors in gynecologic cancer patients with multiple primary malignant tumors (MPMT).

**Methods:** This single-center retrospective study included the medical records of gynecologic cancer patients diagnosed with MPMT according to Warren and Gates's criteria who were treated at the Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Siriraj Hospital during January 2006 and December 2016. Relevant demographic, clinical, and pathologic data were collected and analyzed.

**Results:** Of 8,076 cases of gynecologic cancer during the study period, 146 women with MPMT were included. Ninety-four women had multiple primary gynecologic cancers (MPGC), and 52 had gynecologic cancer coexisting with non-gynecologic cancer (GNC). The prevalence of MPGC was 1.2%. Synchronous cancer, nulliparous, premenopause, and early stage of endometrial and ovarian cancer were significantly more common among MPGC than GNC. Five-year recurrence-free survival (RFS) was significantly longer in the MPGC group (87.3% vs. 79.6%). Coexisting endometrial and ovarian cancer was the most frequently observed MPGC, with a 5-year overall survival (OS) and RFS of 98.1% and 86.0%, respectively. Specific to this cancer combination, residual tumor and depth of myometrial invasion were found to be independently associated with shorter RFS.

**Conclusion:** The prevalence of MPGC in this study was 1.2%. Five-year RFS was significantly longer among MPGC than among GNC. Three-quarters of MPGC patients had synchronous endometrial-ovarian cancer. Residual tumor and the depth of myometrial invasion were identified as prognostic factors that were independently associated with RFS in the patients with synchronous endometrial-ovarian cancer.

**Keywords:** Clinical characteristics; oncologic outcomes; gynecologic cancer patients; multiple primary malignancies (Siriraj Med J 2018;70: 310-319)

## INTRODUCTION

The condition referred to as multiple primary malignant tumors (MPMT) was first described by Warren and Gates in 1932.<sup>1</sup> The essential criteria for diagnosis of this condition according to Warren and Gates is histopathologic cancer diagnosis in different organs that is not caused by metastasis from the first tumor

to one or more subsequent tumors. There are a variety of other definitions of MPMT, but the Warren and Gates definition is the mostly widely accepted and used. Regarding duration between diagnosis date of distinct malignancies, MPMT is classified as either synchronous or metachronous. Diagnosis of both tumors within a 6-month period is termed synchronous, with duration of

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diagnosis between the two tumors longer than 6 months termed metachronous.

The reported prevalence of MPMT varied from 0.4%-21.0% depending on the type of publication and the ethnicity of the study participants.<sup>2-5</sup> Synchronous tumor and metachronous tumor accounted for 34%-38% and 62%-66% of all MPMT, respectively.<sup>2</sup> Specific to gynecologic malignancy, the reported overall prevalence was 1.9%-4.3%.<sup>6,7</sup> The most frequently observed combination of coexisting gynecologic tumors was endometrial and ovarian cancer (81.0%).<sup>8,9</sup> It is possible that the incidence of MPMT may increase as a result of lifespan extension, more effective screening, and the development of improved cancer treatments. Moreover, previous studies reported different characteristics of MPMT compared to those of single primary malignancy, including younger age<sup>9</sup>, significantly associated family history<sup>7</sup>, typical pathologic features, and better prognosis.<sup>10,11</sup>

Given the increasing trend in the occurrence of MPMT and reported variations in characteristics between MPMT and single primary malignancy, the aim of this study was to investigate the prevalence, pathologic features, clinical characteristics, oncologic outcomes, and prognostic factors in gynecologic cancer patients with MPMT. These results might be helpful in prognostication and surveillance plan regarding the risk of second malignancy.

## MATERIALS AND METHODS

This single-center retrospective study included the medical records of gynecologic cancer patients diagnosed with multiple primary malignancy tumors (MPMTs) according to Warren and Gates's criteria who were treated at the Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, Siriraj Hospital from 1<sup>st</sup> January 2006 to 31<sup>st</sup> December 2016 Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 807/2016). Written informed consent was waived due to the retrospective design of this study.

Patient data that were collected included multiple primary gynecologic cancers (MPGC) or gynecologic cancer coexisting with non-gynecologic cancer (GNC), synchronous or metachronous tumor, interval between first and second cancers, cancer site combinations, age at diagnosis of first malignancy, age at diagnosis of cancer at each location, pathologic findings, nulliparous, menopause, family history of malignancy, genetic testing, venous thromboembolism, stage of cancer at each location,

complete response, recurrence, death, 5-year overall response, and 5-year recurrence-free response.

Warren and Gates criteria for diagnosis of MPMT are, as follows: 1) Each tumor exhibits evidence of cancer; 2) Each tumor has distinct pathologic feature(s); and, 3) Metastasis or recurrent disease from prior cancer must be excluded.<sup>1</sup> All cases were diagnosed by expert pathologists at our center. Pathologic slides that were used to establish a diagnosis at another hospital were re-evaluated by our expert gynecologic pathologists to confirm diagnosis. The time of diagnosis was the time that histopathologic diagnosis was established. Response rate after receiving primary treatment and time to event (recurrence, death, and/or last follow-up) were calculated. Overall survival (OS) was defined as the interval from the date of initial diagnosis of the specified cancer to the date of death or last follow up. Recurrence-free survival (RFS) was calculated as the interval from the date of initial diagnosis of the specified cancer to the date of recurrence or last follow-up. Patients who were lost to follow-up before they completed primary treatment of either cancer were excluded from this study.

## Statistical analysis

All data analyses were performed using PASW Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize demographic and clinical characteristics. Qualitative data are presented as frequency and percentage, and quantitative data are presented as mean  $\pm$  standard deviation or median and range. Chi-square test (categorical data) and Student's t-test (continuous normally distributed data) were used to compare clinical and pathological data between groups. Kaplan-Meier survival analysis was performed, and the results were compared using log-rank test. Factors associated with survival were analyzed by Cox regression. A *p*-value less than 0.05 was regarded as being statistically significant.

## RESULTS

Of 8,076 cases of gynecologic cancer identified during the 2006 to 2016 study period 7,930 cases were excluded for the following reasons: pathologically proven single primary malignancy (7,730), and loss to follow-up before completion of primary treatment.<sup>11</sup> The remaining 146 women were enrolled in this study. Included subjects were divided into either the multiple primary gynecologic cancers (MPGC) group or the gynecologic cancer coexisting with non-gynecologic cancer (GNC) group.

### *Multiple primary gynecologic cancers (MPGC)*

The prevalence of MPGC in this center was 1.2%. Eighty-six of 94 MPGC cases (91.5%) were synchronous cancer. The most frequently observed coexisting gynecologic tumors were endometrial-ovarian cancer (76.6%), followed by cervical-ovarian cancer (10.6%) and cervical-endometrial cancer (5.3%). The remaining eight patients had metachronous tumors, with a median duration between diagnosis of the first and second cancers of 12.5 years (range: 0.7-24.2), and all of them presented with either cervical or vulvar cancer. The mean age at diagnosis was 53.4, 53.2, and 50.7 years for endometrial, ovarian, and cervical cancers, respectively. Fifty-three (56.3%) of the 94 MPGC women were nulliparous, and 46 (48.9%) were in menopause. Venous thromboembolism was identified in six patients (6.3%). The vast majority of endometrial cancers (92.4%) and ovarian cancers (80.5%) were early-stage. Complete response rate was achieved in 92.4% of cases. The 5-year overall survival (OS) and progression-free survival (PFS) rates were 96.1% (95% confidence interval [CI]: 91.8-100) and 87.3% (95% CI: 79.3-95.3), respectively. Patient characteristics and oncologic outcomes compared between MPGC and GNC are shown in [Table 1](#).

### *Synchronous endometrial and ovarian cancer*

The 72 cases of coexisting endometrial and ovarian cancer accounted for 0.9%, 4.4%, and 3.7% of gynecologic cancer, endometrial cancer, and ovarian cancer, respectively. All 72 cases were synchronous cancer. Mean age at diagnosis was 53.3±10.3 years. Early stage was observed in 69 (95%) and 57 (60%) endometrial and ovarian cancers, respectively. Of 72 cases, 37 had pretreatment measurement of CA125, with a median of 377.8 IU/ml (range: 15-5,135). CA125 values were all over 35 IU/ml, except for two. Regarding pathologic characteristics, endometrioid tumor type was found in 69 (95.8%) and 53 (73.6%) endometrial and ovarian carcinomas. Fifty-four cases (75%) of these two distinct cancers had exactly the same cell type. Forty well-differentiated endometrial tumors and 31 well-differentiated ovarian tumors were found in 66 specimens. Lymphovascular space invasion was detected in only one-tenth of cases. In 34 of 66 pair malignancies, precancerous lesions were found in at least one cancer, with precancerous lesions found in both cancers in 7 cases. Deep myometrial invasion was identified in 10 of 72 cases (13.9%) of endometrial cancer ([Table 2](#)).

Complete response after primary treatment was 97.2% in endometrial cancer and 97.3% in ovarian cancer. Accordingly, progression of disease was observed in 2.8%

of endometrial cancer and in 2.7% of ovarian cancer. Two patients succumbed to their disease. Recurrence was identified in 2 endometrial and 6 ovarian cancer patients. The 5-year OS was 98.1% (95% CI: 94.6-100), 98.1% (95% CI: 94.6-100), and 98.3% (95% CI: 95-100) for paired cancer, endometrial cancer, and ovarian cancer, respectively. The 5-year recurrence-free survival (RFS) was 86% (95% CI: 76.2-95.8), 96.8% (95% CI: 92.5-100), and 89% (95% CI: 79.8-98.2) for paired cancer, endometrial cancer, and ovarian cancer, respectively. In univariate and multivariate analysis for prognostic factors associated with OS, no significant association was found for menopausal status, presence of endometrioid tumor at both sites, residual tumor, depth of myometrial invasion, grade of endometrial cancer, or grade and stage of ovarian cancer. In contrast, residual tumor and depth of myometrial invasion were identified as independent prognostic factors related to RFS. More specifically, patients with residual tumor >0 to ≤1 cm and >1 cm had increased risk of recurrence (HR: 6.7 and 22.6, respectively) compared with those without residual tumor. Similarly, the recurrence rate was greater if deep myometrial invasion was present (HR: 11.6) ([Table 3](#)).

### *Gynecologic cancer coexisting with non-gynecologic cancer (GNC)*

In contrast to the very low proportion in the MPGC group, the majority of cases in the GNC group were metachronous cancers (90.4%). The most common type of coexisting non-gynecologic tumor was breast cancer (41/52). In a majority of those cases, breast cancer was found before the discovery of gynecologic cancer. The mean interval between diagnosis of the two distinct malignancies was 5.6 years for breast-endometrial cancer, and 8 years for breast-ovarian cancer. Mean age at diagnosis of breast cancer was 54.8 years. Ductal carcinoma accounted for 97.8% (40/41) of all histologies. Moderately differentiated carcinoma was found in three-fifths of cases, while 30% were poorly differentiated. Precancerous lesion was detected in approximately 25% of breast cancer patients. The most frequently observed ovarian histologic cell type associated with breast cancer was serous cell type (8/16), followed by clear cell (5/16) and endometrioid (3/16). In contrast, endometrioid was the most prevalent pathology found in endometrial cancer coexisting with breast cancer. Concerning 36 cases with available hormone profiles, 75.6% and 61.0% of breast cancer patients had positive estrogen receptor and positive progesterone receptor, respectively. Thirty-six percent of women were HER2-negative, and 14.0% were HER2-positive. The remaining proportion of patients had borderline result

**TABLE 1.** Patient characteristics and oncologic outcomes compared between MPGC and GNC

| Variables                                                                                | MPGC<br>(n=94)                                                                                            | GNC<br>(n=52)                                                                                               | P-value         |
|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------|
| Synchronous cancer, n (%)                                                                | 86 (91.5%)                                                                                                | 5 (9.6%)                                                                                                    | <b>&lt;0.05</b> |
| Interval between 1 <sup>st</sup> and 2 <sup>nd</sup><br>cancers (months), median (range) | 0 (0-290)                                                                                                 | 63 (1-147)                                                                                                  | <b>&lt;0.05</b> |
| Paired cancer sites, n (%)                                                               | Endometrium-ovary 72 (76.6%)<br>Cervix-ovary 10 (10.6%)<br>Cervix-endometrium 5 (5.3%)<br>Others 7 (7.4%) | Endometrium-breast 19 (36.5%)<br>Ovary-breast 19 (36.5%)<br>Endometrium-colon 4 (7.7%)<br>Others 14 (22.9%) | N/A             |
| Age at diagnosis of first<br>malignancy (years), mean±SD                                 | 52.7±10.5                                                                                                 | 54.5±10.51                                                                                                  | 0.371           |
| Age at diagnosis of EC (years), mean±SD                                                  | 53.4±10.4                                                                                                 | 62.5±8.5                                                                                                    | 0.454           |
| Age at diagnosis of OC (years), mean±SD                                                  | 53.2±10.0                                                                                                 | 55.9±11.1                                                                                                   | 0.251           |
| Age at diagnosis of CC (years), mean±SD                                                  | 50.7±9.3                                                                                                  | N/A                                                                                                         | N/A             |
| Age at diagnosis of BC (years), mean±SD                                                  | N/A                                                                                                       | 54.8±9.9                                                                                                    | N/A             |
| Nulliparous, n (%)                                                                       | 53 (56.3%)                                                                                                | 18 (34.6%)                                                                                                  | <b>0.038</b>    |
| Menopause, n (%)                                                                         | 46 (48.9%)                                                                                                | 40 (76.9%)                                                                                                  | <b>0.006</b>    |
| Obtained family history of malignancy, n (%)                                             |                                                                                                           |                                                                                                             |                 |
| Yes                                                                                      | 19 (20.2%)                                                                                                | 35 (67.3%)                                                                                                  | <b>&lt;0.05</b> |
| Positive                                                                                 | 8 (8.5%)                                                                                                  | 15 (28.8%)                                                                                                  |                 |
| Negative                                                                                 | 11 (11.7%)                                                                                                | 20 (38.5%)                                                                                                  |                 |
| No                                                                                       | 75 (79.8%)                                                                                                | 17 (32.7%)                                                                                                  |                 |
| Offered genetic testing, n (%)                                                           |                                                                                                           |                                                                                                             |                 |
| Performed                                                                                | 2 (2.1%)                                                                                                  | 15 (28.8%)                                                                                                  | N/A             |
| HNPPC                                                                                    | 2 (2.1%)                                                                                                  | 4 (7.7%)                                                                                                    |                 |
| BRCA1 mutation                                                                           | 0 (0.0%)                                                                                                  | 4 (7.7%)                                                                                                    |                 |
| BRCA2 mutation                                                                           | 0 (0.0%)                                                                                                  | 1 (1.9%)                                                                                                    |                 |
| Negative result                                                                          | 0 (0.0%)                                                                                                  | 4 (7.7%)                                                                                                    |                 |
| Deny testing                                                                             | 0 (0.0%)                                                                                                  | 2 (3.8%)                                                                                                    |                 |
| VTE, n (%)                                                                               | 6 (6.4%)                                                                                                  | 5 (13.2%)                                                                                                   | 0.296           |
| Stage of EC, n (%)                                                                       |                                                                                                           |                                                                                                             |                 |
| I-II                                                                                     | 73 (93.6%)                                                                                                | 15 (55.6%)                                                                                                  | <b>&lt;0.05</b> |
| III-IV                                                                                   | 5 (6.4%)                                                                                                  | 12 (45.4%)                                                                                                  |                 |
| Stage of OC, n (%)                                                                       |                                                                                                           |                                                                                                             |                 |
| I-II                                                                                     | 66 (80.5%)                                                                                                | 8 (38.0%)                                                                                                   | <b>&lt;0.05</b> |
| III-IV                                                                                   | 16 (19.5%)                                                                                                | 13 (62.0%)                                                                                                  |                 |
| Stage of BC, n (%)                                                                       |                                                                                                           |                                                                                                             |                 |
| I-II                                                                                     | N/A                                                                                                       | 27 (65.9%)                                                                                                  | N/A             |
| III-IV                                                                                   |                                                                                                           | 14 (34.1%)                                                                                                  |                 |
| CR, n (%)                                                                                | 85 (92.4%)                                                                                                | 37 (71.1%)                                                                                                  | <b>&lt;0.05</b> |
| Recurrence, n (%)                                                                        | 15 (16.0%)                                                                                                | 25 (48.1%)                                                                                                  | <b>&lt;0.05</b> |
| Death, n (%)                                                                             | 4 (4.2%)                                                                                                  | 5 (9.6%)                                                                                                    | <b>&lt;0.05</b> |
| 5-year OS, (%)                                                                           | 96.1%                                                                                                     | 97.6%                                                                                                       | 0.77            |
| 5-year RFS, (%)                                                                          | 87.3%                                                                                                     | 79.6%                                                                                                       | <b>0.036</b>    |

A *p*-value<0.05 indicates statistical significance

**Abbreviations:** MPGC, multiple primary gynecologic cancers; GNC, gynecologic cancer coexisting with non-gynecologic cancer; N/A, not applicable; SD, standard deviation; EC, endometrial cancer; OC ovarian cancer; CC, cervical cancer; BC, breast cancer; HNPPC, hereditary nonpolyposis colorectal cancer; BRCA, breast cancer gene; VTE, venous thromboembolism; CR, complete response; OS, overall survival; RFS, recurrence-free survival

**TABLE 2.** Pathologic characteristics of synchronous endometrial and ovarian cancers (n=72).

| Endometrial cancer, n | Ovarian cancer, n               |              |         |            |        |
|-----------------------|---------------------------------|--------------|---------|------------|--------|
|                       | FIGO staging                    | I            | II      | III        | IV     |
|                       | I                               | 37           | 15      | 13         | 2      |
|                       | II                              | 2            | 0       | 0          | 0      |
|                       | III                             | 2            | 0       | 0          | 0      |
|                       | IV                              | 1            | 0       | 0          | 0      |
|                       | Histology                       | Endometrioid | Serous  | Clear cell | Others |
|                       | Endometrioid                    | 52           | 2       | 4          | 11     |
|                       | Serous                          | 0            | 2       | 0          |        |
|                       | Clear cell                      | 1            | 0       | 0          |        |
|                       | Grading                         | Grade 1      | Grade 2 | Grade 3    |        |
|                       | Grade 1                         | 25           | 10      | 5          |        |
|                       | Grade 2                         | 4            | 10      | 6          |        |
|                       | Grade 3                         | 2            | 2       | 2          |        |
|                       | LVSI                            | Presence     | Absence |            |        |
|                       | Presence                        | 0            | 6       |            |        |
|                       | Absence                         | 1            | 54      |            |        |
|                       | Precancerous lesion             | Presence     | Absence |            |        |
|                       | Presence                        | 7            | 6       |            |        |
|                       | Absence                         | 21           | 32      |            |        |
|                       | Myometrial invasion             |              |         |            |        |
|                       | No myometrial invasion          | 30           |         |            |        |
|                       | Superficial myometrial invasion | 32           |         |            |        |
|                       | Deep myometrial invasion        | 10           |         |            |        |

**Abbreviations:** FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion

**TABLE 3.** Univariate and multivariate analysis for factors significantly associated with recurrence-free survival in patients diagnosed with synchronous endometrial and ovarian cancers (n=72).

| Variables            | Univariate |         |            | Multivariate |         |             |
|----------------------|------------|---------|------------|--------------|---------|-------------|
|                      | HR         | P-value | 95% CI     | HR           | P-value | 95% CI      |
| Menopausal status    |            |         |            |              |         |             |
| Premenopause         | 1          |         |            |              |         |             |
| Menopause            | 1.65       | .512    | .37-7.38   |              |         |             |
| Histologic cell type |            |         |            |              |         |             |
| Both endometrioid    | 1          |         |            |              |         |             |
| Others               | 2.11       | .308    | .5-8.86    |              |         |             |
| Residual tumor       |            |         |            |              |         |             |
| None                 | 1          |         |            | 1            |         |             |
| >0 - ≤1 cm           | 3.44       | .13     | .69-17.1   | 6.65         | .036    | 1.13-38.99  |
| >1 cm                | 8.28       | .021    | 1.38-49.59 | 22.58        | .005    | 2.55-199.73 |
| Grade of EC          |            |         |            |              |         |             |
| 1                    | 1          |         |            |              |         |             |
| 2-3                  | 2.32       | .249    | .56-9.72   |              |         |             |
| Grade of OC          |            |         |            |              |         |             |
| 1                    | 1          |         |            |              |         |             |
| 2-3                  | 1.004      | .996    | .25-4.03   |              |         |             |
| Stage of OC          |            |         |            |              |         |             |
| I-II                 | 1          |         |            |              |         |             |
| III-IV               | 1.92       | .43     | .39-9.52   |              |         |             |
| Myometrial invasion  |            |         |            |              |         |             |
| Inner half           | 1          |         |            | 1            |         |             |
| Outer half           | 4.24       | .048    | 1.01-17.76 | 11.58        | .007    | 1.94-69.19  |

A p-value<0.05 indicates statistical significance

**Abbreviations:** HR, hazard ratio; CI, confidence interval; EC, endometrial cancer; OC ovarian cancer

(a score of 2+). Of the 19 breast-endometrial cancer patients, 17 had taken tamoxifen. Mean duration of tamoxifen use was 4.5 years. Median duration between start of tamoxifen treatment and endometrial cancer diagnosis was 5.3 years (range: 1.9-13.3). Five-year OS and 5-year RFS were 97.3% (95% CI: 92-100) and 94.3% (95% CI: 86.5-100) for breast cancer (Table 1).

In the GNC group, the 5-year OS and 5-year RFS was 97.6% (95% CI: 92.9-100) and 79.6% (95% CI: 68.2-91), respectively (Table 1). There was no significant difference between MPGC and GNC for 5-year OS ( $p=0.77$ ). In contrast, the 5-year RFS was significantly longer among MPGC than among GNC ( $p=0.036$ ) (Fig 1). Among patients with endometrial cancer, in which advanced stage was presented in nearly half of all cases, the 5-year OS and 5-year RFS was 78.6% (95% CI: 59.2-98) and 71.1% (95% CI: 50.9-91.3), respectively. For patients with ovarian cancer, the 5-year OS and 5-year RFS were 92.3% (95% CI: 77.8-100) and 33.5% (95% CI: 9.4-57.6), respectively. Sixty-two percent of ovarian cancer patients presented at late stage.

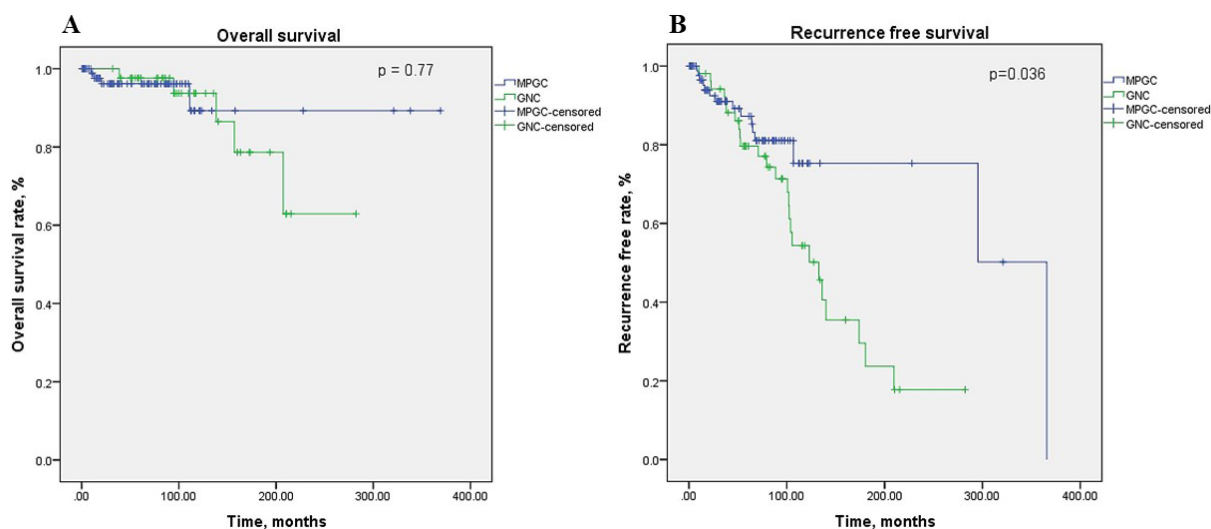
#### Family history of cancer and genetic testing

More GNC patients than MPGC patients were concerned about having hereditary cancer syndrome. Almost three times as many GNC patients as MPGC patients were assessed for family history of cancer. Subsequently, fewer MPGC patients (2.1%) than GNC patients (28.8%) were offered genetic testing. This study revealed 11 positive tests, as follows: 6 hereditary nonpolyposis colorectal cancer (HNPCC), 4 BRCA1 mutation, and 1 BRCA2 mutation. The detailed results of genetic testing in those 11 patients is shown in Table 4.

## DISCUSSION

This study focused on multiple primary malignancies in gynecologic cancer patients in two aspects: multiple primary gynecologic cancers (MPGC) and gynecologic cancer coexisting with non-gynecologic cancer (GNC). With regard to clinical characteristics, there was no significant difference in age at diagnosis in patients with paired cancer, endometrial cancer and ovarian cancer between the MPGC group and the GNC group, although endometrial cancer was detected at older age in the GNC group (62.5 vs. 53.4 years). This was concordant with our finding that significantly more GNC women than MPGC women were postmenopausal. Furthermore, less GNC patients than MPGC patients were identified at early stage of endometrial and ovarian cancers. This finding may be explained by accidental detection of asymptomatic second gynecologic malignancy during surgical staging of primary gynecologic cancer, which normally involves resection of the uterus and both adnexa, resulting in diagnosis of secondary tumor at an earlier stage. As a result, MPGC patients had better oncologic outcomes than GNC patients relative to complete response rate and recurrence-free survival.

Concerning synchronous endometrial and ovarian cancers, the prevalence rates observed in this study were comparable with those reported in prior studies, including 1-2% of gynecologic cancer, 3-5% of endometrial cancer, and 10% of ovarian cancer.<sup>12-14</sup> Several retrospective studies evaluated the clinical characteristics and oncologic outcomes of synchronous endometrial and ovarian cancers, as shown in Table 5. Mean age at diagnosis was lower in MPMT (mean age of 53 year) than in those with single primary cancer. This was consistent



**Fig 1.** Kaplan-Meier survival analysis with data comparisons by log-rank test. A) Comparison of overall survival between the MPGC and GNC groups (5-year overall survival: 96.1% vs. 97.6%, respectively;  $p=0.77$ ). B) Comparison of recurrence-free survival between the MPGC and GNC groups (5-year recurrence-free survival: 87.3% vs. 79.6%, respectively;  $p=0.036$ ).

**Abbreviations:** MPGC, multiple primary gynecologic cancers; GNC, gynecologic cancer coexisting with non-gynecologic cancer

**TABLE 4.** Multiple primary malignancies in gynecologic patients with positive genetic testing (n=11)

| Genetic test result | FHC | Group | First cancer, age at diagnosis (yr) | Stage                        | Recurrence, RFS (mo) | Status, Time to survival (mo) | Second cancer, age at diagnosis (yr) | Stage                        | Recurrence, RFS (mo) | Status, time to survival (mo) |
|---------------------|-----|-------|-------------------------------------|------------------------------|----------------------|-------------------------------|--------------------------------------|------------------------------|----------------------|-------------------------------|
| HNPCC               | Yes | MPGC  | Endometrium, 33                     | I                            | No                   | Remission, 38                 | Ovary, 38                            | II                           | No                   | Remission, 38                 |
| HNPCC               | Yes | MPGC  | Endometrium, 33                     | II                           | No                   | Remission, 18                 | Ovary, 38                            | I                            | No                   | Remission, 18                 |
| HNPCC               | Yes | GNC   | Colon, 63                           | II                           | No                   | Remission, 58                 | Endometrium, 64                      | I                            | No                   | Remission, 46                 |
| HNPCC               | Yes | GNC   | Colon, 70                           | I                            | No                   | Lost to FU, 52                | Endometrium, 74                      | IV                           | Yes, 47              | Loss FU, 11                   |
| HNPCC               | Yes | GNC   | Breast, 44                          | II, ER+, PR+, HER2-          | No                   | Remission, 51                 | Endometrium, 44                      | III                          | No                   | Remission, 46                 |
| HNPCC               | Yes | GNC   | Ovary, 45                           | II                           | Yes, 132             | Remission, 135                | Breast, 51                           | I, ER+, PR+, HER2-           | No                   | Remission, 64                 |
| BRCA1               | Yes | GNC   | Breast, 35                          | II, ER-, PR-, HER2 equivocal | No                   | Lost to FU, 193               | Ovary, 49                            | IV                           | Yes, 12              | Lost to FU, 31                |
| BRCA1               | Yes | GNC   | Breast, 43                          | III, ER+, PR+, HER2-         | Yes, 100             | Remission, 140                | Ovary, 50                            | I                            | No                   | Remission, 55                 |
| BRCA1               | Yes | GNC   | Ovary, 46                           | III                          | Yes, 22              | Remission, 60                 | Breast, 51                           | III, ER+, PR, HER2 equivocal | No                   | Remission, 5                  |
| BRCA1               | No  | GNC   | Ovary, 60                           | I                            | No                   | Remission, 50                 | Breast, 60                           | I, ER-, PR-, HER2 equivocal  | No                   | Remission, 49                 |
| BRCA2               | No  | GNC   | Breast, 60                          | I, ER+, PR+, HER2-           | No                   | Remission, 37                 | Ovary, 65                            | IV                           | Yes, 18              | Stable disease, 90            |

**Abbreviations:** FHC, family history of cancer; mo, months; RFS, recurrence-free survival; MPGC, multiple primary gynecologic cancers; GNC, gynecologic cancer coexisting with non-gynecologic cancer; HNPCC, hereditary nonpolyposis colorectal cancer; BRCA, breast cancer gene; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; FU, follow-up

with the findings of a German study that compared clinical characteristics of synchronous cancer to matched controls with either endometrial or ovarian cancer without other malignancies.<sup>15</sup> More than half of patients had premenopausal status, especially if endometrioid cell type was present in both organs. Although our study did not include information about body mass index (BMI), data from a previous study showed overweight in all non-

Asian populations and in the study of Chiang, *et al.*<sup>16</sup> Since younger age, premenopausal status, overweight, and endometrioid cell type were predominant in coexisting endometrial and ovarian cancers, hormonal effect is a possible causative factor in the development of MPMT. Concerning pathologic characteristics, our results were consistent with the pathologic criteria of synchronous cancer proposed by Scully, *et al.*<sup>17</sup>, including common

**TABLE 5.** Literature review of studies in synchronous endometrial and ovarian cancers

| Authors, country, year                      | N               | Age (yr)    | P0 (%) | Menopause (%) | BMI (kg/m <sup>2</sup> ) | EM in both sites (%) | Stage I-II (%) | G1 (%) | Deep MI (%) | EH (%) | Ovarian cancer Stage I-II (%) | G1 (%) | ES (%)      | 5-yr RFS (%) | 5-yr OS (%) | Prognostic factors                                       |
|---------------------------------------------|-----------------|-------------|--------|---------------|--------------------------|----------------------|----------------|--------|-------------|--------|-------------------------------|--------|-------------|--------------|-------------|----------------------------------------------------------|
| Eifel, USA, 1982 <sup>1</sup>               | 16              | 41          | 50     | 37            |                          | 55.1                 |                |        | 6           |        |                               |        |             |              | 100         | Both EM                                                  |
|                                             | EM-EM 11 others | 61          | 18     | 90            |                          |                      |                |        | 63          |        |                               |        |             |              | 45          |                                                          |
| Soliman, USA, 2005 <sup>2</sup>             | 84              | 50          | 33     | 49            | 28                       | 67.9                 | 92             | 42     | 18          |        |                               | 37     |             |              |             | Both EM                                                  |
|                                             | all             |             |        |               |                          |                      |                |        |             |        |                               |        |             |              |             |                                                          |
|                                             | 57 EM-EM        | <b>50</b>   | 33     | <b>43</b>     | 28                       |                      |                |        |             |        |                               |        |             |              |             | OS 119 mo                                                |
|                                             | 10              | <b>63</b>   | 40     | 75            | 27                       |                      |                |        |             |        |                               |        |             |              |             | OS 48 mo                                                 |
|                                             | EM-serous       |             |        |               |                          |                      |                |        |             |        |                               |        |             |              |             |                                                          |
|                                             | 7               | 54          | 50     | 67            | 27                       |                      |                |        |             |        |                               |        |             |              |             |                                                          |
|                                             | EM-clear cell   |             |        |               |                          |                      |                |        |             |        |                               |        |             |              |             |                                                          |
| Oranratanaphan, Thailand, 2008 <sup>3</sup> | 14              | 47          | 93     | 7.1           | 22.5                     |                      | 100            |        | 0           |        | 85.7                          |        |             | 64.2         | 92.8        |                                                          |
| Chiang, Taiwan, 2008 <sup>4</sup>           | 27              | 47          | 33     | 37            | 26.5                     |                      | 96             | 64     |             |        | 80                            | 62     |             |              | 85          | Early stage of EC and OC                                 |
| Caldarella, Italy, 2008 <sup>5</sup>        | 46              | 55          |        |               |                          | 45.6                 |                | 46     | 26          | 4.3    |                               | 35     |             |              | 67.5        | Age ≤50, grade 1 at both sites, but not EM at both sites |
| Williams, USA, 2009 <sup>6</sup>            | 1,355           | 54.7        |        |               |                          |                      | 72.5           | 43     |             |        | 47.9                          | 28     |             |              | 79          |                                                          |
| Gungor, Turkey, 2009 <sup>7</sup>           | 11              | 58.3        | 9      | 72.7          | 29.4                     | 0                    | 100            | 73     |             |        | 100                           | 45     |             |              |             |                                                          |
| Lim, Singapore, 2011 <sup>8</sup>           | 46              | 47.3        |        |               |                          |                      | 82.5           | 70     | 13          |        | 80.5                          | 48     |             |              | 84          | Age (borderline significance)                            |
| Rodolakis, Greece, 2012 <sup>9</sup>        | 30              | 51          | 37     | 47            |                          | 60                   | 93             | 43     | 17          | 47     | 76                            | 17     | 27          | 84.2         | 84.2        | Not histologic cell type                                 |
| Alhill, USA, 2012 <sup>10</sup>             | 15              | 55.1        | 33     |               | 31.2                     | 66                   | 100            | 73     |             |        | 100                           | 47     | 33.3        |              |             |                                                          |
| Broeders, Netherlands, 2012 <sup>11</sup>   | 21              | 56.2        | 47     | 70            |                          |                      | 76.2           |        |             |        | 76.2                          |        | 19          |              | 80          |                                                          |
| *Song, Korea, 2013 <sup>12</sup>            | 21              | 33          | 81     | 0             | 22.9                     | 42.8                 | 76             | 52     | 24          |        | 62                            | 38     |             |              |             |                                                          |
|                                             | (age <40 yr)    |             |        |               |                          |                      |                |        |             |        |                               |        |             |              |             |                                                          |
| Song, Korea, 2014 <sup>13</sup>             | 123             | 50.4        | 38     | 56.1          | 24.1                     | 45.5                 | 71.5           | 43     | 29.3        |        | 66.7                          | 29     |             | 66.9         | 80          | Pretreatment CA125, stage of OC                          |
| Heitz, Germany, 2014 <sup>14</sup>          | 77              | 55.8        | 26     |               |                          | 48.1                 | 94.8           |        |             |        | 68.8                          |        | 24.6        | 76.3         | 71.6        |                                                          |
| Kobayashi, Japan, 2015 <sup>15</sup>        | 32              | all         | 49.2   | 53.1          | 43.8                     | 22.8                 | 75             | 93.8   | 81          |        | 75                            | 62     |             |              |             |                                                          |
|                                             | 24              | <b>46.3</b> | 58.3   | <b>29.2</b>   | 22.2                     |                      |                |        |             |        |                               |        | <b>87.5</b> |              |             |                                                          |
|                                             | EM-EM           |             |        |               |                          |                      |                |        |             |        |                               |        |             |              |             |                                                          |
|                                             | 8               | <b>58.5</b> | 37.5   | <b>87.5</b>   | 24.6                     |                      |                |        |             |        |                               |        | <b>37.5</b> |              |             |                                                          |
|                                             | others          |             |        |               |                          |                      |                |        |             |        |                               |        |             |              |             |                                                          |
| Bese, Turkey, 2016 <sup>16</sup>            | 31              | <b>52.6</b> | 45.2   |               |                          | 93.6                 | 26             | 16.1   | 22.6        | 41.9   |                               |        |             |              | 67.7        | Residual tumor                                           |
| Present study, Thailand, 2018               | 72              | 53.3        | 70.8   | <b>48.4</b>   |                          | 72                   | 95             | 61     | 13.9        | 19.6   | 60                            | 47     | 42.4        | 86           | 98.1        | Residual tumor, myometrial invasion                      |

Statistically significant values are in bold, \*Includes only women aged less than 40 years

**Abbreviations:** P0, nulliparity; BMI, body mass index; EM, endometrioid; G, grade; MI, myometrial invasion; EH, endometrial hyperplasia; ES, endometriosis; RFS, recurrence free survival; OS, overall survival; EC, endometrial cancer; OC, ovarian cancer

well-differentiated grade, low frequency of vascular space invasion, and deep myometrial invasion. Broeders, *et al.* reported that deep myometrial invasion was detected in 28.6% of synchronous endometrial ovarian cancer, 100% of endometrial cancer with ovarian metastasis, and 76.5% of ovarian cancer with endometrial metastasis<sup>18</sup>. Several previous series and the present study all found histologic similarity in paired tumors. Accordingly, some suggest the potential value of immunohistochemistry and molecular studies, such as loss of heterozygosity on chromosome, DNA flow cytometry, beta-catenin, microsatellite instability, and PTEN.<sup>14,19</sup> That acknowledged, the efficacy of molecular study in this setting has not yet been established, and no consensus has yet been reached regarding diagnostic criteria. Regarding oncologic outcomes, the overall survival rate in this study was substantially higher than in other studies, but our rate was comparable to the rate reported by Oranratanaphan, *et al.*, who also reported from Thailand.<sup>20</sup> Many previous studies reported that synchronous cancer had better prognosis than single primary cancer. For example, our study reported 5-year survival rates of 98.1% and 98.3% for endometrial and ovarian cancer in paired malignancy, while another Thai study reported 5-year survival rates of 89% and 69.3% for endometrial and ovarian cancer in patients with single malignancy.<sup>21</sup> This may be due to more favorable characteristics found in synchronous cancer. In contrast, studies from Germany and the Netherlands showed similarity in overall survival rate between single and paired tumor, even after matching for potential factors, such as age, stage, and ECOG score.<sup>15,18</sup> Our study identified residual tumor and myometrial invasion as independent prognostic factors associated with shorter recurrence-free survival. A previous study from Turkey also found residual tumor to be a factor significantly associated with RFS.<sup>14</sup> Eifel, *et al.*, and Soliman, *et al.*, found presence of endometrioid cell type at both sites to be associated with better prognosis.<sup>22,23</sup> However, that finding was not consistent with the finding of two European studies.<sup>24,25</sup> Specifically, Caldarella, *et al.*, and Rodolakis, *et al.*, found age  $\leq 50$  years to be the only statistically significant predictor of RFS. Data from Taiwan and Korea revealed stage of ovarian cancer to be an important factor. It should be noted that relevant prognostic factors varied among articles.<sup>13,16</sup>

Regarding our analysis of GNC, breast cancer was found to be the most common coexisting non-gynecologic tumor. In most cases, breast cancer presented first, followed by the gynecologic malignancy. This finding was identical to that reported by Liou, *et al.*, and Martin-Dunlap, *et al.*,<sup>26,27</sup> but contrasted with the

reported finding of Grzankowski, *et al.*<sup>28</sup> In support of the causal relationship between tamoxifen use and the development of endometrial cancer, 14 of 17 cases in this study developed endometrial cancer after starting tamoxifen. The mean interval between diagnosis of the two distinct carcinomas was 5.6 years. Previous studies reported intervals that ranged from 3-10 years.<sup>21,27, 28</sup> For this reason, long-term surveillance should be encouraged since secondary cancer can develop as long as a decade after the initial cancer diagnosis. Regarding coexisting breast and ovarian cancer in this study, the most frequently observed ovarian histologic cell type was serous. Correspondingly, Liou, *et al.*, reported that serous ovarian carcinoma was associated with breast cancer, but that endometrioid cell type was not.<sup>26</sup>

The main limitation of the current study was its retrospective design, which made it vulnerable to potential biases due to missing data. In addition, the lack of pathologic review by the same set of reviewers could raise concerns about interobserver variability. The strength of this study is that 10 years of data from Thailand's largest national tertiary referral center were included and analyzed between MPGC and GNC. In addition, the authors performed and included a literature review of studies in synchronous endometrial and ovarian cancers – the most common paired cancer found in this study.

## CONCLUSION

Prevalence of MPGC in this study was 1.2%. Five-year recurrence-free survival was significantly longer among MPGC than among GNC. Three-quarters of MPGC patients had synchronous endometrial-ovarian cancer. Residual tumor and depth of myometrial invasion were identified as prognostic factors independently associated with recurrence-free survival in patients with synchronous endometrial-ovarian cancer.

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