EJGO European Journal of Gynaecological Oncology

Original Articles

Examination of the time interval between diagnoses in women with metachronous primary endometrial and colorectal cancers supporting universal Lynch testing

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Summary

Purpose: The time interval between diagnoses of endometrial and colorectal cancers is not well established in women with metachronous primary tumors of both sites. The authors sought to examine the time interval between diagnoses, identify associations with clinicopathologic factors, and compare current genetic screening practices. *Materials and Methods:* The authors identified 53 patients who developed both cancers between 1966-2014. These patients were divided into two groups based on having colorectal (group 1) or endometrial (group 2) cancer first. Risks of MLH1, MSH2, MSH 6, or BRCA1/2 mutations, as well as the chance of developing a subsequent ovarian or breast cancer were estimated. *Results:* There were 18 and 35 patients in groups 1 and 2, respectively. The mean time interval was longer in group 2, 70 *vs*. 43 months. Median PFS and OS for endometrial cancer tended to be longer in group 2 (PFS: 66 *vs*. 58 and OS: 77 *vs*. 58 months). Median PFS and OS for colorectal cancer were significantly longer in group 1 (PFS: 22 *vs*.74 and OS: 22 *vs*. 86 months). The estimated risk of any MMR mutations was at least 25% in the majority of the patents, with 21 of those patients > 50%, and 13 > 75%. *Conclusions:* The mean estimated prevalence of MMR mutation in patients with metachronous endometrial and colorectal cancers is 100-fold greater than the general population. The time interval between the diagnosis of endometrial and colorectal carcinomas is 5.8 years if endometrial cancer develops first and 3.5 years if colorectal develops first. These results are useful in counseling women at risk.

Key words: Endometrial cancer; Colorectal cancer; Lynch syndrome.

Introduction

There are an estimated 13.4 million people living with cancer in the United States, of which 66.1% survive at least five years [1]. Since cancer survival is improving with advancement of therapeutic options, the number of patients who live long enough to develop a second or third cancer is also escalating. Compared with the general population, cancer patients have 31% increased risk of developing a successive malignancy [2]. Second cancers can be attributed to the late effects of treatment, lifestyle choices including tobacco, alcohol, and diet, host factors and genetics, environmental exposures, or any combination of these [3]. Those with hereditary cancer syndromes can develop dual primary or metachronous cancers at an even higher rate. Hereditary cancer syndromes account for 3-5% [4] of cases of endometrial cancer (EC) and 5-10% of colorectal cancer (CRC) [5]. The most common genes associated with both CRC and EC are MLH1, MSH2, MSH6, and PMS2 and can result in Lynch syndrome [4]. The women at risk comprise an important group in which every effort should be made to identify early as medical, surgical, and lifestyle interventions are available that can reduce their risk.

The American Cancer Society has estimated that there were 52,630 new cases of EC and 136,830 cases of CRC in the year 2014. [6]. The lifetime risk for a diagnosis of EC based on the 2007-2011 rates was reported at 2.7% and 4.7% for CRC [7, 8] The SEER database reported the median age of diagnosis of EC as 62-years-old and 68-years-old for CRC, while the median age of mortality was 71 -years-old for EC and 74-years-old for CRC [7, 8]. When adjusted by stage, the SEER reported a five-year relative survival of 95.1% for those with locally confined disease, 67.7% for those with regional lymph node disease, and 17.5% for those with metastatic EC [7]. Similarly, in CRC

Revised manuscript accepted for publication July 25, 2016

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVIII, n. 4, 2017
doi: 10.12892/ejgo3822.2017

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five-year relative survival was 89.8%, 70.5%, and 12.9%, respectively[8].

In the present study, the authors identified all individuals diagnosed with both CRC and EC in their institutional cancer registry. The primary objective of this study was to define the mean interval between diagnoses of the two metachronous cancers. In addition, the authors evaluated survival based on order of malignancy diagnosis. Finally, we estimated the risk of mismatch repair (MMR) gene mutations and subsequent gender-specific cancers in this group of women. The present results are important for counseling at risk women who may deliberate strategies to modify risk.

Materials and Methods

The Roswell Park Cancer Institute (RPCI) Tumor Registry (Buffalo, NY) was searched for all patients diagnosed with both EC and CRC between 1966 and 2013. After obtaining IRB approval, a retrospective review of the medical records was performed that included age, stage and grade of each cancer type at diagnosis, outpatient and in-patient treatment, including surgery, radiation, and chemotherapy. Study outcomes included overall survival (OS) and time to progression (PFS), measured from the time of diagnosis. Progression was defined as objective evidence of recurrence, either from examination or imaging studies. The duration of OS was the interval between diagnosis and date of last contact or death. Data were censored at the last follow-up for patients with no evidence of recurrence, progression, or death.

The patients were divided into two groups. In group 1 patients, the diagnosis of CRC predated the diagnosis of EC. In group 2 patients, the diagnosis of EC preluded diagnosis of CRC. The time interval between diagnoses of the first and second malignancy

Table 1. — *Patient characteristics.*

Table 1: Patient Characteristics		**Group 1:CRC first**	**Group 2:EC first**	**Total (N)**	**p-value**
Overall	N(%)	18 (34.0)	35 (66.0)	53 (100)	
Age at diagnosis of the first cancer in months	Mean	61.4(range 45-82)	58.9 (Range 24-86)	59.7	0.665
	Median	59.5	60		
Time interval between diagnosis	Mean	1284 days or 43 months	2111 days or 70 months	1830 days or 61 months	0.182
EC Grade	1	7 (38.9%)	16 (45.7)	23 (43.4%)	0.610
	2	4 (22.2%)	10 (28.6)	14 (26.4%)	
	3	7 (38.9%)	9 (25.7)	16 (30.2%)	
CRC Grade	1	2 (11.1%)	2 (5.7)	4 (7.5%)	0.3512
	2	15 (83.3%)	26 (74.3%)	41 (77.4%)	
	3	1 (5.6%)	7 (20%)	8 (15.1%)	
EC Stage	I	12 (66.7%)	25 (71.4%)	37 (69.8%)	0.280
	II	2 (11.1%)	7 (20.0%)	9 (17.0%)	
	III	4 (22.2%)	2 (5.7%)	6 (11.3%)	
	IV	0 (0%)	1 (2.9%)	1 (1.9%)	
CRC Stage	I	8 (44.4%)	8 (22.9%)	16 (30.2%)	0.077
	II	8 (44.4%)	13 (37.1%)	21 (39.6%)	
	III	1 (5.6%)	12 (34.3%)	13 (24.5%)	
	IV	1 (5.6%)	2 (5.7%)	3 (5.7%)	
EC status at last follow up	Unknown	2 (11.1%)	4 (11.4%)	6 (11.3%)	0.659
	NED	8 (44.4%)	20 (57.1%)	28 (52.8%)	
	AD	8 (44.4%)	11 (31.4%)	19 (35.8%)	
CRC status at last follow up	Unknown	2 (11.1%)	3 (8.6%)	5 (9.4%)	0.633
	NED	7 (38.9%)	18 (51.4%)	25 (47.2%)	
	AD	.9 (50 0%)	14 (40.0%)	23 (43.4%)	

EC=Endometrial cancer; CRC=Colorectal cancer; NED=no evidence of this disease; AD= with this disease

Table 2: Survival time in months		Group 1:CRC first	Group 2:EC first	p-value
EC PFS	Median	58	66	0.219
EC OS		58	77	0.089
CRC PFS	Median	74	22	0.008
CRC OS		86	22	0.003
Combined PFS	Median	26	45	0.117
Combined OS		86	77	0.518
Cause of Death	From Cancer	10 (56%)	15(43%)	0.331
	Other Cause	1(11%)	8(23%)	
	Alive	6(33%)	12(34%)	

EC=Endometrial cancer; CRC=Colorectal cancer

Table 2. — *Survival time.*

Table 3:Chance of mismatch repair (MMR) mutation, BRCA mutation, or risk of subsequent cancer		Group 1:CRC first	Group 2:EC first	p-value
MLH1	Mean % (Range)	15.9 (0.04-40.7)	12.1 (0.03-39.1)	0.357
MSH2		18.1 (0.05-46.1)	13.7(0.04-44.3)	0.357
MSH6		8.6 (0.35-43.0)	10.5(0.20-79.4)	0.671
MMR any [carrier prevalence~0.27%]		42.5 (0.45-92.89)	36.1(0.27-90.5)	0.534
BRCA any [carrier prevalence ~0.25%]	Mean % (Range)	0.1 (0.04-0.17)	0.1 (0.04-0.23)	1
Ovarian Cancer	Lifetime mean % (Range)	0.76 (0.3-1.30)	0.69 (0.3-1.20)	0.439
Breast Cancer	Lifetime mean % (Range)	6.22 (2.1-10.70)	5.67 (2.1-10.30)	0.498

EC=Endometrial cancer; CRC=Colorectal cancer

Table 3. — *Chance of mismatch repair mutation.*

was calculated for each group. No patients were diagnosed with both malignancies on the same date.

All statistical analyses were performed with SAS 9.3 software. Comparisons for categorical variables were obtained from Fischer exact test and for continuous variables via Wilcoxon rank sum test on medians. Chi squared test was used to compare data set for trend evaluation. Estimated survival distributions were calculated by use of Kaplan and Meier. Tests of significance with respect to survival distributions were based on the log-rank test.

The potential risk of BRCA1, BRCA2, or both mutations was calculated for each patient using the BRCAPRO software [9]. The potential risk of MMR mutations, including MLH1, MSH2, MSH6, or any, was calculated for each patient using the MMRPRO software [10]. CAGene software [11] was used to estimate the lifetime chance of developing a subsequent ovarian or breast cancer. These computer programs implement a statistical model for calculating an individual's probability of carrying a deleterious mutation of the aforementioned genes on the basis of the individual's cancer status. These models use the Mendelian characteristics of the genes, and incorporate prevalence and penetrance on the basis of published results [12].

Results

A total of 3,640 women were diagnosed with CRC and 3,654 women were diagnosed with EC during the study period. Fifty-three women (0.73%) had metachronous diagnoses of CRC and EC. This study was focused on these 53 women. There were 18 women in group 1 (CRC before EC) and 35 women in group 2 (EC before CRC).

The characteristics of the study population are presented

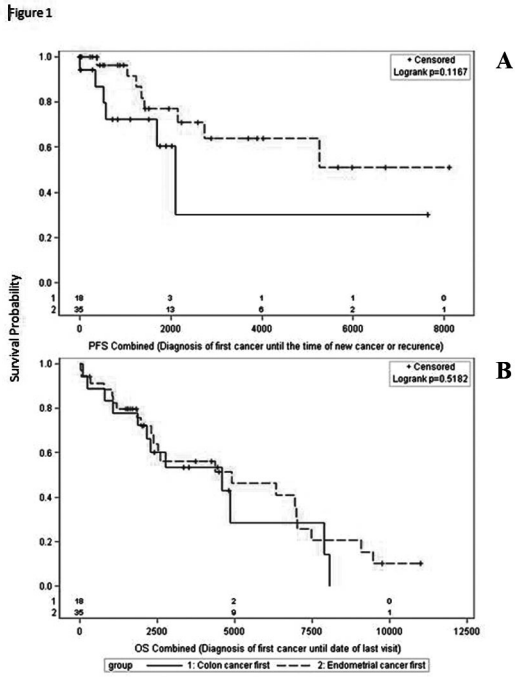

Figure 1. — Kaplan-Meier analysis of A: PFS and B: OS for CRC and EC combined. Group 1 patients trended to a shorter PFS than group 1 but had comparable OS (p = 0.117; p = 0.518, respectively).

in Table 1. The mean ages of the study population were 61 and 60 years for groups 1 and 2, respectively (range 24 to 86 years; p = 0.665). The majority of patients presented with Stage I EC (69.8%) with predominantly low grade histology (43.4%). Similarly, the majority of the patients diagnosed with CRC presented with Stage I (30.2%) or Stage II (39.6%) disease with moderately differentiated histology (77.4%). There were no statistically significant differences in stage or grade of either cancer in group 1 *vs.* group 2.

The mean time interval between diagnoses was shorter in group 1 at 43 months *vs*. 70 months in group 2 (p = 0.182; Table 1). Table 2 lists the median survival time in months. Median PFS and OS for EC were comparable in both groups [PFS: 58 *vs*. 66 months (p = 0.219) and OS: 58 *vs*. 77 months (p = 0.089)]. Median PFS and OS for CRC were statistically longer in group 1 for both PFS and OS [PFS: 74 *vs*. 22 months (p = 0.008) and OS: 86 *vs*. 22 months (p = 0.003)] however, it is important to note that the many of patients were still alive at the conclusion of this collection and this likely resulted in the significant difference. Median combined PFS, defined as date of diagnosis of first cancer to date of diagnosis of second cancer and combined OS, defined as date of diagnosis of first cancer to date of last contact, favored group 2 but failed to reach statistical significance [PFS: 26 *vs*. 45 months (p = 0.215) and OS: 86 *vs*. 77 months (p = 0.873); Figure 1A and B].

With comparable mean follow up, group 2 patients were more likely to be free of disease at the last follow-up, 44% *vs*. 57% for EC and 39% *vs*. 51% for CRC (Table 1). Cause of death was attributed to cancer in 56% and 43% of patients in groups 1 and 2, respectively (Table 2). One-third of each group was alive at time of data collection.

The study population MMR mutation risk ranged between 0.27% and 92.89% with known carrier prevalence of 0.27% in the general population of any MMR mutations (Table 3). The mean risk of MLH1 mutation was 15.9%, MSH2 18.1%, and MSH6 8.6% in group 1, and in group 2 risks were: 12.1%, 13.7%, and 10.5%, respectively. The BRCA mutation risk of the study population, ranged between 0.04% and 0.23%, with mean 0.14% in both groups 1 and 2. This was lower than the known carrier prevalence of 0.25% in the general population of any BRCA1 or BRCA2 mutation for all patients examined in this case series (Table 3). The calculated lifetime risk of ovarian cancer was 0.76% and 0.69% for groups 1 and 2, respectively, slightly decreased from the 1.3% lifetime risk for the general population. The lifetime risk for breast cancer was 6.22% and 5.67% for groups 1 and 2, respectively, nearly half of the reported lifetime risk of 12.3% among the general population [13].

Discussion

In 1913, Dr. Aldred Scott Warthin first described a family with hereditary associated uterine and gastrointestinal cancers [14]. This family, now widely known as family G, was explored thoroughly and knowledge was expanded on by Dr. Henry Lynch and colleagues starting in 1971 [15, 16]. Lynch syndrome, previously known as hereditary nonpolyposis colorectal cancer, an autosomal dominant cancer susceptibility syndrome, was characterized in seminal reports by Lynch *et al.* as early as 1966 [17]. Defects in MMR system, responsible for repairing single nucleotide base errors that occur during DNA replication result in not only CRC and EC, but many others including ovarian, gastric, small bowel, some types of breast, to name a few [18].

Lynch syndrome accounts for the most cases of both hereditary EC and CRC and in one reported study the incidence of Lynch syndrome was 2.3% and 2.2% in patients who presented with EC and CRC, respectively [19-21]. Based on published reports, the risk of both CRC and EC ranges from 18-61% and 16-61%, respectively, through the age of 70 [19, 22]. However before the age of 50, it is estimated that 5-13% of cases of EC and CRC and 3-5% between age 50 and 60 years are due to Lynch syndrome [23]. Although historically linked to CRC, Lynch syndrome in women often presents with EC as is sentinel malignancy, which was represented in the present findings as well with 66% of the present population having EC first [24]. As all

of the patients in this study were diagnosed with EC prior to the routine use of MMR testing via immunohistochemistry (IHC), and microsatellite instability (MSI), testing their Lynch status was not known. Many of the patients were diagnosed prior to routine clinical screening for Lynch syndrome as well, which is a weakness of the study resulting in absent genetic information on the 53 women.

In the present patients there are two main screening criteria used to help identify patients at risk for Lynch syndrome. Amsterdam criteria, developed in 1990 and revised in 1999 to include extracolonic cancers as a defining diagnosis, is one such list. However only 13-36% of families in population based studies with molecular confirmation of Lynch syndrome met the Amsterdam criteria that includes the requirement of three relatives with a Lynch associated cancer one that is a first degree relative of the other two, two successive affected generations, one of the cancers diagnosed before age 50, and the exclusion of familial adenomatous polyposis [25, 26]. The Bethesda guidelines, developed in 1997, and revised in 2004 incorporate age, personal and family history of cancer, and tumor histology and offer high sensitivity but lower specificity in diagnosis Lynch patients. These guidelines state that all patients with either endometrial or colorectal cancer diagnosed before age 50 should have genetic assessment, and the Society for Gynecology Oncology (SGO) even suggests molecular tumor testing on EC diagnosed less than age 60 regardless of personal or family history [26-28].

The median OS data of the 53 women who had metachronous primary diagnosis of both cancers was 86 and 77 months, for groups 1 and 2, respectively. Although there was not documentation of genetic evaluation on these patients in the present records as many patients were diagnosed prior to 1990 introduction of clinical criteria and 1998 standardization MSI testing, the authors indirectly evaluated each patient for possibility of MMR and BRCA mutations using BRCA PRO, MMR PRO, and CAGene software [30]. Strikingly, of the 53 women in this study had a calculated risk of BRCA mutation below the carrier rate, and all but one patient had a risk greater than the carrier prevalence for MMR mutations (one patients risk equaled the carrier prevalence). The calculated mutation likelihood that the present authors have reported depended mostly on patients' available data and basic family history. The authors believe that the mutation risk would probably have been higher, and the range narrower for most of the patients, had there been a complete family history available. MMR mutation risk was 42% in group 1 and 36% in group 2 patients. The suggested MMR mutation was greater than the carrier rate in 98% of the patients examined, with 51% having at least a 100-fold increased risk, and 19% with a 300-fold increased risk of having somatic mutations. This demonstrates the need for routine genetic screening in patients with Lynch syndrome associate cancers. Interestingly a change in National Comprehensive Cancer Network (NCCN) guidelines have even been updated recently to reflect the use of MMR in prediction and triaging of patients whom to test for Lynch syndrome [29].

Recognition of Lynch syndrome is important, not only for the patient that is diagnosed with the genetic mutation and malignancy in prevention of second cancers, but also those family members who are currently disease free and that intervention could prevent cancer or detect at a less advanced stage more amenable to cure. The NCCN guidelines for MMR mutation carries with Lynch syndrome include colonoscopy at age 20-25 years or two to five years prior to the earliest onset of colon cancer, repeated every one to two years. The NCCN and SGO also recommends prophylactic hysterectomy and risk-reducing bilateral salpingo-oophorectomy in women who have completed childbearing or by age 40-45 and annual endometrial sampling starting at age 30-35, especially in the setting of change in menstrual bleeding pattern is also suggested [26, 28, 29]. Patients who are not identified to have Lynch syndrome cannot take advantage of screening or prophylactic surgical interventions. The present authors were unable to identify based on chart review how many of the women in group 1 were offered prophylactic hysterectomy and risk-reducing bilateral salpingo-oophorectomy at the time of their colon cancer surgery or afterwards, although all patient in this group were age 45 or older and should have been encouraged to have this based on today's standards.

In summary, the present authors have identified information that could benefit women at risk for hereditary cancer syndromes, especially Lynch syndrome. This study included 53 women with both endometrial and colorectal cancer diagnosis, a relatively large number from a single institution. Although, MSI testing was not performed on the majority of patients, either due to age or the year of diagnosis, this paper shows the potential benefit of universal molecular tumor testing at all ages in women with EC. The efficacy and cost effectiveness of universal or reflex testing of CRC with IHC and MSI testing, has already been confirmed by a Centers for Disease Control (CDC) working group [30, 31]. In the era of personalized medicine, the need for patients and clinicians to understand the role of genetic testing, including when to screen, and how to manage ongoing surveillance for cost-effective improved health outcomes, is crucial. As the mean and median ages of diagnosis of the first cancer in the present study population was greater than 50 years, as in Bethesda criteria, none of these women would have been tested for Lynch until the diagnosis of their second cancer years later when the prime window of opportunity for screening, surgical intervention, and risk counseling in other family members may have already passed. Ultimately, a much larger multicenter study evaluating cost and effectiveness of reflex IHC and MSI testing in EC is required and may be crucial in proactively managing and reducing a woman's risk for subsequent cancers.

Acknowledgements

This work was supported by Roswell Park Cancer Institute grants NCI P30CA16056 and NIH 5T32CA108456. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Clinical data delivery and honest broker services for this study were provided by the Clinical Data Network which is funded by the National Cancer Institute and are Roswell Park Cancer Institute Cancer Center Support Grant shared resources.

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