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ORIGINAL ARTICLE

A 12-year experience at a tertiary hospital on patients with multiple primary malignant neoplasms

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Summary

Purpose: *The incidence of multiple primary malignant neoplasms (MPMN) has dramatically increased. The purpose of this retrospective study was to present the 12-year experience at a University Hospital in patients with MPMN and to investigate the role of genetic factors in their pathogenesis.*

Methods: *The medical records of 7516 cancer patients, treated in our Institution from 2000 to 2012, were reviewed. Diagnosis of MPMN was based on the Warren and Gates' criteria.*

Results: *Among 7516 patients, 39 (0.5%) (10 men, mean age 70.0±6.98 years, and 29 women, mean age 64.7±8.24 years) presented with MPMN. Eighty-two percent of them developed 2 primary malignant neoplasms (PMNs), whereas 3 PMNs were developed in 7 patients. Breast cancer was the most common cancer type diagnosed among female patients (59%); 14 and 3 had 2 and 3 PMNs, respectively. Eight had a family history of breast cancer while in 3 genetic testing revealed mutations in BRCA1 and BRCA2 genes. The second most common type of malignancy was colorectal cancer (24%); 5 developed 2 PMNs, whereas 2 developed 3 PMNs. Five patients had a family history of colorectal cancer. Colon cancer was the most frequent neoplasm among male patients (50%); 3 developed 2 and 2 3 PMNs. In 2 patients the family history was positive for colorectal cancer.*

Conclusions: *Although many factors may contribute to MPMN development, positive family history and inherent mutations significantly predispose to MPMN appearance. Thus, management of MPMN patients should be based on a detailed family history and genetic testing.*

Key words: *family history, multiple primary malignant neoplasms*

Introduction

The phenomenon of MPMNs has always been a field of scientific research. It was first described by Theodor Billroth in 1889 [1], but the first review on MPMNs was published in 1932 by Warren and Gates, who presented 1259 patients with MPMNs [2]. Since then, the incidence of MPMNs has increased dramatically, estimated between and 0.73 to 11.7% [3-5].

MPMNs have been defined as tumors that present *de novo* in patients with known malignancies, when the probability of metastasis or recurrence has been excluded. According to Moertel [6,7], synchronous malignant neoplasms are those occurring within 6 months of the diagnosis of a previous malignant tumor, while metachronous malignant neoplasms are those appearing after 6 months from the occurrence of a previous tumor. The diagnosis of a MPMN is based on the criteria first described by Warren and Gates [2] and they are still widely applied, while several modifications have been proposed [7-9].

The purpose of this retrospective study was to present the experience at a tertiary university hospital in patients with MPMNs in a 12-year period and to investigate the pathogenesis and the possible genetic substrate.

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Table 1. The criteria for the diagnosis of multiple primary malignant neoplasms as described by Warren and Gates and modified by other authors [7-9]

• Each tumor must have a clear picture and histological confirmation of malignancy
• Each tumor must be separate and distinct topographically and separated by healthy mucosa (at least 2 cm of normal mucosa between two tumors of the same region)
• The probability that a tumor is metastasis of another cancer must be excluded.

Methods

This retrospective study included 7516 patients with histologically confirmed malignancy, treated in our Department from January 2000 to December 2012. For the MPMN diagnosis, the Warren and Gates' criteria were applied (Table 1). The patient hard copy medical records as well as the registry of the Pathology laboratory were reviewed and the following data were registered: age, gender, type and location of primary tumor and MPMNs, and treatment options chosen. Patients with unclear histological findings of malignancy (e.g. borderline serous ovarian tumor) were excluded. Data from family history and genetic testing were used to investigate the involvement of genetic factors in the pathogenesis of MPMN.

Statistics

Standard descriptive statistics (reported as mean±standard deviation/SD) were used to summarise demographic data. Frequency analysis in the form of percentages was also used to present the results of this study.

Results

Out of 7516 patients, 39 (0.5%) with MPMN were identified: 10 male, mean age 70.0±6.98 years, and 29 female, mean age 64.7±8.24 years. Thirty-two of them (82%) developed 2 MPMNs, while the remaining 7 (18%) developed 3 MPMNs.

Female patients

The most common cancer among female patients was breast cancer (17 of 29 female patients, 59%), which appeared in combination with ovarian cancer in 5 patients, endometrial cancer in 4, kidney cancer in 2, whereas in a single patient breast cancer was combined with pancreatic cancer, carcinoid of the ileum and thoracic wall angiosarcoma. Detailed data are presented in Figure 1. The remaining 3 patients with breast cancer had 3 MPMNs; 2 had a second primary breast cancer in combination with ovarian and gastric cancer, and the last one developed skin melanoma and ovarian cancer.

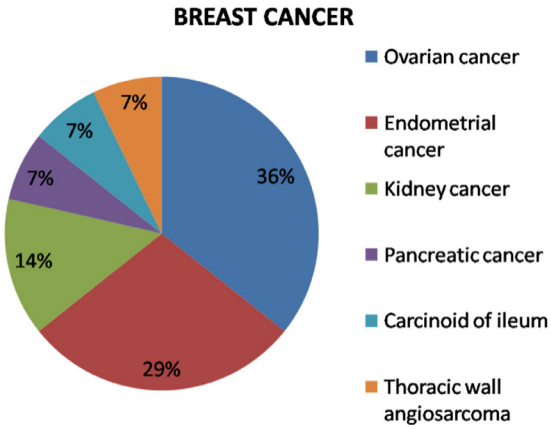

Figure 1. Analysis of female patients with breast cancer and a second primary neoplasm.

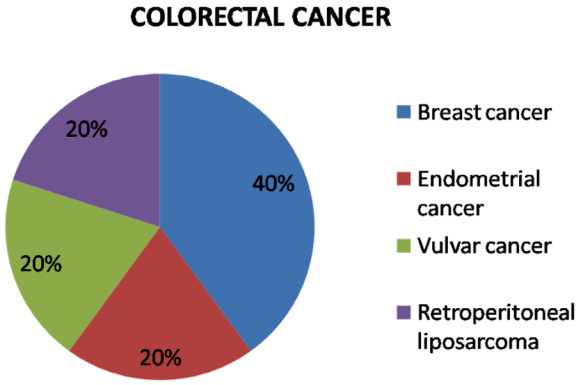

Figure 2. Analysis of female patients with colorectal cancer and a second primary neoplasm.

Eight out of 17 women (47%) had a family history of a first-degree relative with breast cancer. Three of them underwent genetic testing, which revealed mutations in the BRCA1 and BRCA2 genes. A single female patient who had undergone radiotherapy for breast cancer, developed angiosarcoma of the thoracic wall.

The second most common cancer type in female patients, which developed in 7 out of 29 female patients (24%) with MPMNs, was colorectal cancer. In particular, colorectal cancer occurred in conjunction with breast cancer in 2 patients, whereas it was combined with endometrial cancer, vulvar cancer and retroperitoneal liposarcoma in single patients. Detailed data are presented in Figure 2. Two female patients with colorectal

cancer developed 3 second primary malignant tumors; in one patient in conjunction with Hodgkin's lymphoma and ovarian cancer and in the second in conjunction with breast cancer and urinary bladder cancer. Positive family history was detected in 5 out of the 7 female patients with colorectal cancer.

Another cancer type that was frequently identified among female patients with MPMNs, was endometrial cancer; this developed in 3 out of 29 female patients (10%) with MPMN. Endometrial cancer was found in conjunction with hepatocellular cancer, kidney cancer and ovarian cancer in one patient each.

In a 63-year-old female patient who suffered from hepatocellular cancer a primary carcinoid of stomach developed. Moreover, in another 59-year-old female patient with primary liposarcoma, thyroid cancer developed.

Male patients

The most common cancer among male patients was colorectal cancer in 5 of 10 patients (50%). This appeared in association with large cell lymphoma, hepatocellular carcinoma and urinary bladder cancer in one patient each. The remaining 2 patients with colorectal cancer developed 3 second primary neoplasms: in one patient colorectal cancer was combined with urinary bladder cancer and prostate cancer, whereas in the other one with nasopharyngeal cancer and thyroid cancer. All cases of male and female patients with 3 primary neoplasms are listed in Table 2.

Two out of 5 male patients with colorectal cancer had positive family history in first-degree relatives.

Table 2. Cases of patients with three primary neoplasms

	Female patients	
1st neoplasm	*2nd neoplasm*	*3rd neoplasm*
Breast cancer	Breast cancer	Ovarian cancer
Breast cancer	Breast cancer	Gastric cancer
Breast cancer	Skin melanoma	Ovarian cancer
Colon cancer	Hodgkin's lymphoma	Ovarian cancer
Colon cancer	Breast cancer	Urinary bladder cancer
	Male patients	
1st neoplasm	*2nd neoplasm*	*3rd neoplasm*
Colon cancer	Urinary bladder cancer	Prostate cancer
Colon cancer	Nasopharynx cancer	Thyroid cancer

In 2 of 10 male patients (20%) gastric cancer was presented in combination with pancreatic adenocarcinoma in one patient and with gastrointestinal stromal tumor (GIST) in the other one.

In a 69-year old male patient who had developed hepatocellular carcinoma, second primary prostate cancer appeared, whereas a retroperitoneal sarcoma was followed by a larynx tumor in another 72-year-old patient. In addition, in a male patient who suffered from breast cancer, skin melanoma developed later.

The time interval between the appearance of the first primary malignancy and the development of the second and third cancer in all 39 patients is presented in Table 3.

Discussion

The frequency of MPMNs has increased over the recent years and this phenomenon is multifactorial, with no clear cause–effect relationship. Increase of life expectancy coupled with aging of the population have maximized the problem. In several studies, 75% of the patients with MPMNs are over 50 years [10], while Spratt and Hoag [11] concluded that people reaching extreme ages are expected to develop multiple tumors at a greater frequency. The findings of our study are consistent to this speculation, as the mean age of 39 patients included was 70.0±6.98 years for male and 64.7±8.24 years for female patients.

Furthermore, the development of new sophisticated diagnostic modalities and advances in cancer therapy have increased survival rates of patients with cancer, making the development of a new metachronous tumor more likely to occur. Analysis in the database of the Surveillance, Epidemiology, and End Results (SEER) of the National Cancer Institute of USA showed that 13.7% of cancer survivors developed one or more primary neoplasms [12]. Most current diagnostic modalities, such as PET/CT, provide the ability of accurate and prompt identification of synchronous cancers in earlier subclinical stages [13].

Environmental and lifestyle factors, such as smoking and various types of radiation involved in the pathogenesis of malignancy, could be implicated in the development of another primary cancer. In addition, the widespread application of chemotherapeutic agents or radiotherapy appears to be responsible for the development of several cancer types [9,14,15]. In our study, a female patient who had undergone radiation therapy for breast cancer developed later angiosarcoma of the thoracic wall.

Table 3. Time interval between the first, the second and the third neoplasm in male and female patients

Age (years)	*1st Cancer*	*Time interval (months)*	*2nd Cancer*	*Time interval (months)*	*3rd Cancer*
			Male patients		
73	Colon	32	Hepatocellular		
79	Colon	57	Large cell lymphoma		
70	Colon	25	Urinary bladder		
75	Colon	49	Urinary bladder	21	Prostate
77	Colon	18	Nasopharynx	10	Thyroid gland
58	Stomach	44	Pancreas		
59	Stomach	35	GIST		
69	Hepatocellular	36	Prostate		
72	Retroperitoneal sarcoma	28	Larynx		
68	Breast	30	Skin melanoma		
			Female patients		
63	Breast	25	Ovary		
59	Breast	0 (synchronous)	Ovary		
63	Breast	32	Ovary		
47	Breast	28	Ovary		
65	Breast	36	Ovary		
58	Breast	40	Endometrium		
60	Breast	45	Endometrium		
60	Breast	38	Endometrium		
78	Breast	43	Endometrium		
68	Breast	48	Kidney		
69	Breast	57	Kidney		
70	Breast	50	Pancreas		
60	Breast	13	Carcinoid of ileum		
63	Breast	59	Thoracic wall angiosarcoma		
55	Breast	25	Breast	19	Ovary
74	Breast	32	Breast	24	Stomach
76	Breast	30	Skin melanoma	33	Ovary
70	Colon	38	Breast		
69	Colon	54	Breast		
52	Colon	52	Endometrium		
77	Colon	78	Vulva		
53	Colon	42	Retroperitoneal liposarcoma		
78	Colon	63	Hodgkin's lymphoma	19	Ovary
75	Colon	30	Breast	64	Urinary bladder
59	Endometrium	33	Hepatocellular		
71	Endometrium	44	Kidney		
62	Endometrium	0 (synchronous)	Ovary		
63	Carcinoid of stomach	20	Hepatocellular		
59	Liposarcoma	52	Thyroid cancer		

Heredity, undoubtedly, lies behind many cases of MPMNs, especially in tumors that appear in functionally and anatomically unrelated locations [3]. Patients with positive family history for cancer may inherit a genetic predisposition to malignancy [4]. Several gene defects have been identified as predisposing factors for cancer development. For instance, mutations in BRCA1 or BRCA2 tumor suppressor genes have been implicated in familial breast and ovarian cancer development [16]. Mutations in tumor suppressor genes, such as p16 and p53, are involved in the occurrence of multiple tumors, such as breast and soft tissue tumors [17,18]. Moreover, the syndrome of Hereditary Non Polyposis Colorectal Cancer (HNPCC), which is caused by microsatellite instability, is associated with the development of multiple primary tumors, such as in the colon, endometrium, ovary and transitional epithelium [19]. In our study, the most frequent tumors in patients with MPMNs were breast cancer and colon cancer. Eight out of 17 (47%) female patients with breast cancer and other primary tumors had a first-degree relative with breast cancer, which may reinforce the hypothesis that heredity plays a major role in the pathogenesis of MPMNs. Three women had undergone genetic testing and were positive for mutations of BRCA1 and BRCA2. In cases of colon cancer, heredity obviously participated in 5 out of 7 (71%) female and in 2 out of 5 (40%) male patients with colon cancer and other PMNs who had a first-degree relative with colorectal cancer. Unfortunately, further genetic testing was not performed in any of the families.

In conclusion, the frequency of MPMNs has increased rapidly in recent years. This may be a result of increase in life expectancy and the aging of the population, environmental factors and great advances in diagnostic modalities. However, the role of inherent factors seems to be significant. The management, thus, of patients with MPMNs should include a detailed and accurate family history and genetic testing.

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