JBUON 2020; 25(2): 1230-1236
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Trends in the incidence and overall survival of multiple primary cancers in Turkey

Fatma Sert[1], Ayse Caner[2], Ayfer Haydaroglu[1,2]

[1]Ege University Faculty of Medicine, Department of Radiation Oncology, Izmir; [2]Ege University Faculty of Medicine, Cancer Registration, Application and Research Center, Izmir, Turkey.

Summary

Purpose: *Multiple primary malignant tumors (MPCs) are defined as at least two histologically distinct malignancies in one individual. We aimed to present the risk of developing multiple primary cancers and to give information about the periods and prediction data regarding survival outcome for MPCs.*

Methods: *All patients with MPCs between 1992-2017 were included in this study. Patients were compared in terms of the primary cancer number, age at diagnosis of first primary cancer, gender, time interval after first cancer detected, cancer types seen mostly together, and the rate of MPCs during the years.*

Results: *The total number of included patients was 117,139. The proportion of patients with MPCs during the follow-up period was 4.95% (n=5,796). Eighteen percent of the cases were synchronous and 82% metachronous. MPCs were most commonly detected in the gastrointestinal tract and were detected more commonly in men than in women (p<0.001). Patients receiving radiotherapy (RT) (p<0.001) and chemotherapy (CT) (p <0.001) had more MPCs than those who never received RT or CT. Survival in MPCs was worse than in single primary cancers. The 5- and 10-year survival rates were 28.1%, and 12.4%, respectively.*

Conclusion: *We identified approximately 5% MPCs among 117,139 patients in our database. MPCs are more common at 60-69 years in males and at 50-59 years in females. In terms of the risk of MPCs, we should be aware of the cancers that have risk factors, habits, and genetic features commonly affecting primary cancers.*

Key words: *multiple cancers, incidence, survival, Turkey*

Introduction

Cancer is accepted as a serious disease with a high incidence, ranking second in terms of mortality in Turkey and the world. The survival rates of patients in many cancers have been gradually increasing due to the improved understanding of the causes and the availability of new treatment options [1,2]. However, the prolonged survival of cancer patients also led to an increase in the incidence of multiple primary tumors [3].

Multiple primary cancers (MPCs) are defined as two or more unrelated primary cancers that originate from different organs and occur in the body at the same time or one after another. According to the cancer diagnosis time interval, MPCs can be divided into two different categories: synchronous MPCs and metachronous MPCs [3]. Synchronous MPCs are defined if the tumors occur simultaneously or within 6 months of one another. On the other hand, metachronous MPCs term is used if the interval time is more than 6 months. The incidence of metachronous MPCs is lower than synchronous MPCs.

It is a very common condition that MPCs could be confused with metastasis or recurrence of a

Corresponding author: Fatma Sert, MD, PhD. Ege University Faculty of Medicine, Department of Radiation Oncology, Kazim Dirik Cod. University Sok no.1.
Tel: +90 5057947536, Email: gracilis81@yahoo.com
Received: 18/09/2019; Accepted: 14/10/2019

cancer known as primary since both are characterized by new lesions [4]. Therefore, MPCs are often misdiagnosed as recurrence or metastasis of the original primary malignancy, which may result in inappropriate treatments and adverse effects on the patient's prognosis.

The term of MPCs is used for defining the development of a new malignant lesion *de novo*. The features of the new lesions and clinical characteristics are completely different from those of the original tumor lesions in MPCs [5]. As a result, the prognosis, metastasis, and recurrence are also completely different between MPCs and the metastasis or recurrence of primary malignant diseases.

MPCs are an important medical problem, and the purpose of the present study was to determine the risk of developing MPCs and to give information about the periods and prediction data regarding survival outcome for MPCs.

Methods

All patients diagnosed with first primary cancer and registered in Ege University Faculty of Medicine Cancer Registry (Izmir, Turkey) between 1992 and 2017 were enrolled in this study. The incidence of other primary cancers as a second cancer diagnosis was assessed until the end of 2017. Cancer primary location sites were categorized into 16 groups according to the International Classification of Diseases (ICD) 10th Revision as described in a previous study [6] These categories are mouth/pharynx (C00–14), esophagus (C15), stomach (C16), colorectum (C18–20), liver (C22), gallbladder (C23, 24), pancreas (C25), larynx (C32), lung (C33, 34), breast for females (C50), uterus for females (C53–55), ovary for females (C56), prostate for males (C61), kidney/urinary tract/bladder (C64–68), thyroid (C73), and blood (C81–85, 88, 90, 91–96). All patient data were recorded to a specific computer program, called CANREG, according to World Health Organization (WHO) and The Surveillance, Epidemiology, and End Results (SEER) Program guidelines [7].

The diagnostic principles of Warren and Gates [8] and their combination with Liu Fusheng's [9] were used for determining MPCs. The defined criteria were 1) each tumor is malignant, 2) each tumor has its own pathological features, 3) tumors occur in different parts or organs and are not continuous with each other, and 4) each tumor has its own metastatic pathway. The exclusion criterion was the diagnosis of metastatic or recurrent tumors.

The included patients were compared in terms of the primary cancer number, age at diagnosis of first primary cancer, sex, time interval after the first cancer was detected, the cancer types seen mostly together, and the increased rate of MPCs during the years.

The standardized incidence ratio, which is the ratio of the observed to the expected number of second primary cancers, was calculated. In order to obtain the expected number of second primary cancers, each sex, age group, and year of diagnosis specific incidence rates in the general cancer population in Ege University Faculty of Medicine were calculated by using Ege University Faculty of Medicine Cancer Registry data. Ninety-five percent confidence intervals (CIs) of standardized incidence ratio were calculated assuming a Poisson distribution [10]. The standardized incidence ratios were calculated according to sites of first and second primary cancers and intervals between the first and second primary cancers.

Statistics

All data were statistically analyzed using the SPSS 23.0 software. Chi-square, General Linear Model (GLM) and Kaplan Meier survival analyzes were performed. Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon) and Tarone-Ware statistics were used for survival analysis and $p<0.05$ was considered statistically significant. Overall survival and median survival were used as indicators to assess survival time. Overall survival (OS) was calculated from the date of tumor diagnosis to the death or last follow-up date; if the patient was lost, the last follow-up date was defined as the study endpoint. For patients with synchronous MPCs, the survival time was calculated according to the confirmed date of the first tumor, whereas for patients with metachronous MPCs, the survival time was calculated from the confirmed date of the last diagnosis of the tumor.

Results

The total number of included patients was 117,139. The proportion of patients with MPCs during the follow-up period was 4.95% (n=5796). Forty-nine percent of registered patients with MPCs had 2 primary malignancies. Interestingly, we recorded 10 (0.01% of 117,139) patients who have even 5 primary cancers (Table 1). When patients with 4 or 5 primary cancers were evaluated, it was seen that they all had genetic predispositions to developing cancer. MPCs were evaluated

Table 1. Distribution of the multiple primary cancers according to the number of primary cancers

Primary cancer number	*n (%)*
Single primary cancer	111343 (95.05)
2 Primary cancer	5413 (4.62)
3 Primary cancer	357 (0.30)
4 Primary cancer	16 (0.01)
5 Primary cancer	10 (0.01)
Total registered patient number	117139 (100.0)
Total registered patients with multiple primary cancer	5796 (4.95)

in terms of the definition of both synchronous and metachronous MPCs. It was seen that 18% of the cases were synchronous and 82% metachronous MPCs in this current cohort.

MPCs were most commonly detected in the gastrointestinal tract. A total of 894 (15.4%) of the 5793 tumor lesions were located in the gastrointestinal tract. Skin (855/5796;14.8%), head and neck (733/5796;12.6%), female genital system (688/5796;11.9%), and respiratory system (570/5796;9.8%) were the other regions where MPCs were commonly seen (Table 2).

MPCs were significantly more common in men than women (p<0.001). There were some differences between males and females in terms of topographic distribution of detected primary tumor region of MPCs. In male patients with MPCs, the urinary tract tumors had nearly the same rate of the gastrointestinal tract tumors in female patients (13.7 vs 13.9%, respectively). The gastrointestinal tract tumors with MPCs were higher in male patients than in female patients. Table 2 summarizes the gender differences in terms of topographic distribution of MPCs.

We found a significant relation between the first primary region and the other malignancies which were diagnosed as second malignancy. This was clear for the patients with primary breast, uterus, and ovary cancers (p<0.001). Endocrine and genetic factors were important in this clear relation. MPCs with primary diagnosed lung cancer, which is the most common cancer for men, were detected as new primary in the respiratory tract and bladder cancer was the second most commonly detected malignancy for this group of patients and this was probably related to persistent smoking. Additionally, this relation was shown for esophagus, stomach, and colorectum (p<0.001). However, we identified low relation for first liver, gallbladder, pancreas, or lung cancers. In both genders, MPCs, which were detected in primary gastrointestinal tract, mostly developed malignancies from the gastrointestinal tract as a second and third similar with their primary cancer, and they were followed by urogenital system tumors.

Applied treatments were shown to have an important role in developing MPCs after the patients' first diagnosis. We compared the registered patients according to used treatments whether radiotherapy (RT) or chemotherapy (CT) were used. Patients receiving RT (p<0.001) and CT (p <0.001) had more cancers than those who had never received RT or CT (Tables 3 and 4).

Survival in MPCs was worse than in single primary cancers, and as multiple cancers increased, survival was decreased as expected (p<0.001). Five and 10-year OS rates for synchronous MPCs were 51.0% and 38.0%, respectively. Additionally, 5- and 10-year OS rates for metachronous MPCs were 49.0% and 38.4%, respectively. The difference between the OS rates was not statistically significant (p=0.506).

Table 2. Distribution of the multiple primary cancers according to both gender and the primary cancer topography

Primary cancer topographic region	*Males* *n (%)*	*Females* *n (%)*	*Total* *n (%)*
Gastrointestinal tract	555 (16.5)	339 (13.9)	894 (15.4)
Non-melanoma skin	528 (15.7)	327 (13.4)	855 (14.8)
Head & Neck	471 (14.0)	262 (10.8)	733 (12.6)
Female genital tract	0 (0.0)	688 (28.2)	688 (11.9)
Respiratory tract	494 (14.7)	76 (3.1)	570 (9.8)
Urinary tract	459 (13.7)	73 (3.0)	532 (9.2)
Male genital tract	487 (14.5)	0 (0.0)	487 (8.4)
Breast	12 (0.4)	389 (16.0)	401 (6.9)
Blood & Bone marrow	119 (3.5)	55 (2.3)	174 (3.0)
Lymphatic system	80 (2.4)	52 (2.1)	132 (2.3)
Central nervous system	61 (1.8)	71 (2.9)	132 (2.3)
Soft tissue	30 (0.9)	32 (1.3)	62 (1.1)
Endocrine organs	20 (0.6)	24 (1.0)	44 (0.8)
Other rare and undefined regions	43 (1.2)	46 (1.0)	89 (2.2)
Total	3359 (100.0)	2437 (100.0)	5796 (100.0)

Table 3. Comparison of the patients with multiple primary cancers according to the use radiotherapy in any part of primary cancer treatment

Primary cancer region	*Not used* *n (%)*	*Used* *n (%)*	*MPC in 'not used'* *n (%)*	*MPC in 'used'* *n (%)*	*Total* *n (%)*
Head & Neck	230 (10)	129 (20)	263 (12)	111 (16)	733 (13)
Gastrointestinal tract	342 (16)	43 (7)	417 (18)	90 (13)	892 (15)
Respiratory tract	133 (6)	40 (6)	292 (13)	104 (15)	569 (10)
Female genital tract	202 (9)	139 (22)	224 (10)	123 (18)	688 (12)
Breast	167 (8)	87 (13)	113 (5)	32 (5)	399 (7)
Male genital tract	207 (9)	40 (6)	208 (9)	31 (5)	486 (8)
Non-melanoma skin	334 (15)	93 (14)	350 (15)	78 (12)	855 (15)
Urinary tract	308 (14)	23 (4)	159 (7	39 (6)	529 (9)
Endocrine organs	29 (1)	0 (0)	13 (1)	2 (0)	44 (1)
Lymphatic system	74 (3)	10 (2)	40 (2)	8 (1)	132 (2)
Bone & Joint	5 (0)	4 (1)	13 (1)	5 (1)	27 (0)
Blood & Bone marrow	86 (4)	5 (1)	71 (3)	11 (2)	173 (3)
Eye & Structures	3 (0)	3 (0)	2 (0)	0 (0)	8 (0)
Central nervous system	43 (2)	15 (2)	50 (2)	23 (3)	131 (2)
Soft tissue	11 (1)	10 (2)	27 (1)	14 (2)	62 (1)
Rare tumors	5 (0	2 (0)	9 (0)	0 (0)	16 (0)
Other unspecified	3 (0)	0 (0)	0 (0)	0 (0)	3 (0)
Unknown primary	12 (1)	3 (0)	20 (1)	3 (0)	38 (1)
Total	2194 (100)	646 (100)	2271 (100)	674 (100)	5785 (100)

MPC: multiple primary cancers

Table 4. Comparison of the patients with multiple primary cancers according to the use chemotherapy in any part of primary cancer treatment

Primary cancer region	*Not used* *n (%)*	*Used* *n (%)*	*MPCs in 'not used'* *n (%)*	*MPCs in 'used'* *n (%)*	*Total* *n (%)*
Gastrointestinal tract	269 (13)	116 (16)	384 (18)	123 (16)	892 (15)
Non-melanoma skin	409 (19)	18 (2)	374 (17)	54 (7)	855 (15)
Head & Neck	306 (15)	53 (7)	255 (12)	119 (16)	733 (13)
Female genital tract	187 (9)	154 (21)	185 (8)	162 (21)	688 (12)
Respiratory tract	94 (4)	79 (11)	302 (14)	94 (12)	569 (10)
Urinary tract	277 (13)	54 (7)	158 (7)	40 (5)	529 (9)
Male genital tract	212 (10)	35 (5)	187 (9)	52 (7)	486 (8)
Breast	155 (7)	99 (14)	110 (5)	35 (5)	399 (7)
Blood & Bone marrow	50 (2)	41 (6)	66 (3)	16 (2)	173 (3)
Lymphatic system	30 (1)	54 (7)	37 (2)	11 (1)	132 (2)
Central nervous system	50 (2)	8 (1)	57 (3)	16 (2)	131 (2)
Soft tissue	14 (1)	7 (1)	29 (1)	12 (2)	62 (1)
Endocrine organs	27 (1)	2 (0)	10 (0)	5 (1)	44 (1)
Unknown primary	11 (1)	4 (1)	13 (1)	10 (1)	38 (1)
Bone & Joint	8 (0)	1 (0)	14 (1)	4 (1)	27 (0)
Rare tumors	3 (0)	4 (1)	4 (0)	5 (1)	16 (0)
Eye & Structures	4 (0)	2 (0)	1 (0)	1 (0)	8 (0)
Other unspecified	2 (0)	1 (0)	0 (0)	0 (0)	3 (0)
Total	2108 (100)	732 (100)	2186 (100)	759 (100)	5785 (100)

Discussion

In all global statistics, there was an increase in cancer incidence compared to years. In parallel to the global cancer burden, there was also an increase in cancer records at Ege University Hospital. Cancer registrations in the database of Ege University Hospital started in 1992, and during 25 years, 117139 cancer cases were recorded. This is the most comprehensive single center cancer database in Turkey. In these data, the MPCs were found to be a remarkable number and we decided to present our results.

More than one primary cancer, called MPCs, was detected in 5796 (4.95%) of our 117139 cancer cases in our cancer registry database. In the retrospective study of Xu et al, the MPCs incidence rate was 2.25% [11]. Mao et al evaluated the lung cancers in terms of the incidence of MPCs and they reported 5.18% MPCs rate in their lung cancer patient cohort [12]. Shibahara et al conducted an important trial regarding MPCs by using autopsy series [13]. They showed that there was a high incidence of MPCs with a rate of 10.8% for autopsy evaluations [13]. A previous study from data of European Cancer Registries done by Rosso et al, reported an overall incidence of MPCs of 6.3% (range, 0.4-12.9); Cancer Registries with registration periods of 10 years or less are reporting smaller percentages of MPCs, depending on the length of the registration [14]. Another study formed by Filali et al reported changes of the rates in MPCs between 6.1% and 10.5%, the percentage apparently stabilizing approximately 10 years after registration [15]. Our results were similar with current literature data.

An important issue in the evaluation of the incidence of MPCs was to determine the synchronous MPCs and the metachronous MPCs. According to the definition of Xu and Gu [11], synchronous MPCs were defined if the tumors occur simultaneously or within 6 months of one another. Metachronous MPCs term was used if the interval time was more than 6 months [11]. In their series of 167 cases with MPCs, 46 (27.5%) of them were synchronous and 124 (72.5%) were metachronous. Their results did not show any statistically different OS rates between metachronous and synchronous MPCs [11]. Baba et al evaluated 538 consecutive patients who had undergone resection of esophageal cancer [16]. At the time of surgery, they reported that 163 patients (30%) had MPCs. In the MPC series of Baba et al, 77 of 163 patients were metachronous MPCs and 86 of 163 were synchronous [16]. They showed that patients with synchronous MPCs had significantly shorter OS than those without MPCs (univariate p=0.032; multivariate p=0.040). Moreover, they saw that patients with metachronous MPCs had similar prognoses to those without MPCs [16]. In this current study cohort, 18% of the patients with MPCs were synchronous and 82% were metachronous. We could not show any difference in terms of OS rates between the patients with metachronous and synchronous MPCs (p=0.506).

Xu and Gu [11] evaluated their patients according to the number of primary cancers. Based on this evaluation, they saw that 167 of 170 patients with MPCs had 2 primary cancers, 2 of 170 patients had 3 primary cancers, and 1 of 170 patients had 4 primary cancers [11]. In our large patient cohort, we had patients with even 5 primary cancers. Five thousand thirteen of 5796 patients had 2 primary cancers, 357 of 5796 patients had 3 primary cancers, 16 of 5796 patients had 4 primary cancers, and lastly, 10 of 5796 patients had 5 primary cancers.

MPCs are generally more common in men than in women. Baba et al reported male and female rates 89% and 11%, respectively [16]. Xu and Gu [11] and Utaha et al [17] showed similar male dominance in the incidence of MPCs. In our study, we found that MPCs were seen significantly more frequently in men than in women (p<0.001). When we compared the MPCs incidence according to age at diagnosis of the first primary cancer, MPCs were commonly seen between 60-69 years for males and between 50-59 years for females. The incidence rates distribution for both genders seemed to be statistically significant (p<0.001).

Another important issue is the preference site of MPCs dependence. The preference site of MPCs differs according to the tumor distribution regions and the hereditary status of patients. In the Chinese data from Xu and Gu, the original tumor sites were most commonly observed in the gastrointestinal tract, followed by the breast, respiratory system, reproductive system, and head and neck [11]. Previous studies reported that the most common first primary tumor organ is the uterus, followed by the breast, esophagus, and lung, whereas the most common second primary cancer tumor site is the lung, followed by the esophagus, breast, uterus, and rectum [17]. In this study, the primary tumor originated frequently in the gastrointestinal tract, followed by the gastrointestinal tract and lung, whereas the second primary occurred most frequently in the genitourinary tract followed by the genitourinary track, as well. This data was compatible with the current literature regarding MPCs.

Lung cancer, which is the most common cancer in men, was followed by other respiratory system cancers as a second primary cancer diagnosis. Bladder cancers were seen commonly with lung cancer. This issue was thought to be related to persistent

smoking. Breast cancer, which is the most common cancer in women, was followed by endometrium, ovary, and thyroid cancers as MPCs. It was thought that hormonal factors for endometrial cancer and genetic factors for ovarian cancer might have an important role in these results. Corso et al aimed to assess the frequency of second primary non-breast cancer after breast cancer diagnosis and treatment, and its correlation with clinicopathological features [18]. Data from 21,527 patients with primary breast cancer were collected retrospectively in a single cancer center; 4.1% of the women developed a second non-breast cancer. The most frequently observed second primary tumor affected the digestive tract (27.8%). Breast cancer survivors in hormonal therapy are at higher risk for developing a second thyroid cancer [HR 4.00 (1.46-10.9)]. They concluded that clinical surveillance is required to prevent ovarian and thyroid cancers, respectively, in patients with positive family history and triple negative breast cancer [18]. Cybulski et al. evaluated the MPCs as a guide to heritability and they showed similar concordance between the breast and the thyroid and also between the breast and the ovarian cancers [19].

Weir et al evaluated the effect of SEER and IARC/IACR rules on cancer incidence rates and trends using data from the SEER Program [20] and showed that there was a certain increase in the incidence of MPCs. They concluded that Cancer Registries collecting incidence data using SEER rules may consider including incidence rates and trends using IARC/IACR rules to facilitate international data comparisons. We should present some additional prevention and protection rules according to registered data [20]. In our study, similar to current literature, it was seen that the incidence of MPCs increased significantly during the 25-year period ($p<0.001$).

Applied treatments are accepted as an important issue in terms of MPCs occurrence. In the current literature, there is a couple of trials showing the relation between the incidence of MPCs and the applied therapy to primary cancer [19]. Petru and Schmähl [21] evaluated the incidence of second malignancies assessed by retrospectively analyzing data from previous studies in well-defined and closely followed patient cohorts [21]. They showed a significant relationship between the applied chemotherapy and the risk of MPCs. In our cohort, MPCs were seen commonly in cancer patients treated both with radiotherapy ($p<0.001$) and/or chemotherapy ($p<0.001$) compared to patients treated with surgery alone.

An interesting result was obtained by Warschkow et al trial, who used the SEER data, comparing the MPCs incidence in the patients with resected rectal carcinoma according to the usage of radiotherapy as a part of their treatment [22]. The authors found a decrease in the incidence of prostate cancer for men ($p<0.001$) and an increase in the risk of endometrial cancer for women. Additionally, they saw an increased risk of lung cancer ($p<0.001$), bladder cancer ($p<0.001$), and lymphoma ($p=0.026$) for the patients needed to be treated with both radiotherapy and resection [22].

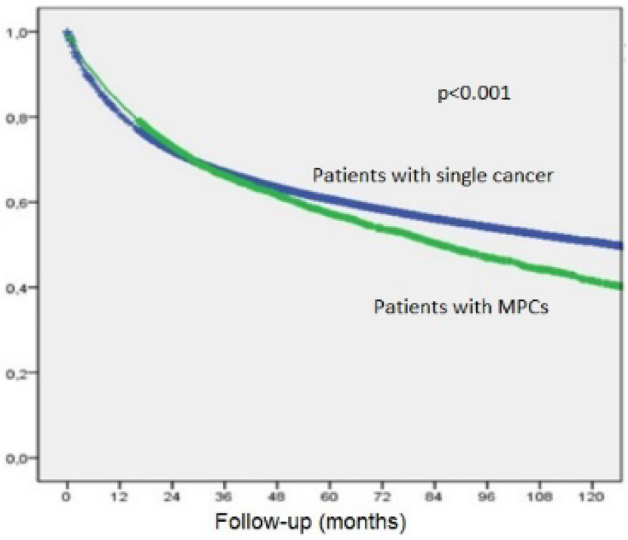

Figure 1. Cumulative survival curves of patients having both single and multiple cancer diagnosis.

Hegemann et al evaluated the risk of second cancer following radiotherapy for prostate cancer in a population-based analysis with 19,538 cases [23] and found the incidence rates of second cancer for the patients treated with radiotherapy alone, radical prostatectomy alone, and combined radiotherapy and surgery were 15.9, 10.5, and 13.2%, respectively ($p<0.001$). The smokers treated with radiotherapy developed significantly more lung, bladder, and non-melanoma skin cancers than the non-smokers [23].

In the retrospective evaluation of MPCs by Xu and Gu [11], the 1-, 3-, and 5-year cumulative survival rates in their 170 patients were 68.8, 39.1, and 25.2%, respectively [11]. Their median survival time was 24 months. In this current study cohort, we had 36 months median survival time. The 5-, and 10-year cumulative survival rates in 4,987 (only the patients whose last status was known, were included) were 28.1 and 12.4%, respectively (Figure 1).

Conclusions

We identified approximately 5% MPCs among 117,139 patients registered to Ege University Can-

cer database. According to the age group of primary cancer diagnosed, MPCs are more common in males aged 60-69 years and in females aged 50-59 years. There is a statistically significant increase in MPCs over the years. Applied treatments such as radiotherapy and/or chemotherapy generate a significant risk for MPCs occurrence. Survival in MPCs is worse compared with the single primary, and as the number of multiple cancers increases, survival is getting worse. The persistence of the (1) factors which play a role in the etiology of primary cancer in the development, (2) habits such as nutrition, smoking, hormonal and genetic predispositions, and (3) treatments such as RT and CT used in cancer treatments may facilitate the development of MPCs.

Conflict of interests

The authors declare no conflict of interests.

References

1. Fitzmaurice C, Allen C, Barber RM. Global Burden of Disease Cancer Collaboration trialists: Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524-48.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
3. Zhai C, Cai Y, Lou F et al. Multiple Primary Malignant Tumors - A Clinical Analysis of 15,321 Patients with Malignancies at a Single Center in China. J Cancer 2018;9:2795-801.
4. Cigna E, Gradilone A, Sorvillo V, Scuderi N. ABCB5 in peripheral blood of a patient affected by multiple primary malignancies. Ann Ital Chir 2011;82:49-53.
5. Papajík T, Mysliveček M, Sedová Z et al. Synchronous second primary neoplasms detected by initial staging F-18 FDG PET/CT examination in patients with non-Hodgkin lymphoma. Clin Nucl Med 2011;36:509-12.
6. National Cancer Institute. New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000. Bethesda: NHI PUbl, 2006.
7. Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. Am J Clin Oncol 2003;26:79-83.
8. Warren S, Gates O. Multiple primary malignant tumors. A survey of the literature and statistical study. Am J Cancer 1932;16:1358.
9. Liu F, Qin D, Wang Q. Clinical pathological analysis of 172 cases with multiple primary carcinoma. Chin J Oncol 1979;1:113-9.
10. Breslow NE, Day NE. Statistical methods in cancer research. Volume II– The Design and Analysis of Cohort Studies. Lyon: IARC Sci Publ, 1987.
11. Xu LL, Gu KS. Clinical retrospective analysis of cases with multiple primary malignant neoplasms. Genet Mol Res 2014;13:9271-84.
12. Mao R, Chen T, Zhou F et al. The burdens of lung cancer involved multiple primary cancers and its occurring patterns-SEER Analysis between 1973 and 2006. Sci Rep 2017;7:6451.
13. Shibahara Y, Sugawara Y, Miki Y et al. Analysis of multiple primary cancer autopsy cases associated with breast cancer: 2002-2010. Pathol Int 2016;66:695-700.
14. Rosso S, Terracini L, Ricceri F, Zanetti R. Multiple primary tumours: incidence estimation in the presence of competing risks. Popul Health Metr 2009;7:5.
15. Filali K, Hédelin G, Schaffer P et al. Multiple primary cancers and estimation of the incidence rates and trends. Eur J Cancer 1996;32A:683-90.
16. Baba Y, Yoshida N, Kinoshita K et al. Clinical and Prognostic Features of Patients With Esophageal Cancer and Multiple Primary Cancers: A Retrospective Single-institution Study. Ann Surg 2018;267:478-83.
17. Utada M, Ohno Y, Hori M, Soda M. Incidence of multiple primary cancers and interval between first and second primary cancers. Cancer Sci 2014;105:890-6.
18. Corso G, Veronesi P, Santomauro GI et al. Multiple primary non-breast tumors in breast cancer survivors. J Cancer Res Clin Oncol 2018;144:979-86.
19. Cybulski C, Nazarali S, Narod SA. Multiple primary cancers as a guide to heritability. Int J Cancer 2014;135:1756-63.
20. Weir HK, Johnson CJ, Ward KC, Coleman MP. The effect of multiple primary rules on cancer incidence rates and trends. Cancer Causes Control 2016;27:377-90.
21. Petru E, Schmähl D. Cytotoxic chemotherapy-induced second primary neoplasms: clinical aspects. Neoplasma 1991;38:147-55 (Review).
22. Warschkow R, Güller U, Cerny T, Schmied BM, Plasswilm L, Putora PM. Secondary malignancies after rectal cancer resection with and without radiation therapy: A propensity-adjusted, population-based SEER analysis. Radiother Oncol 2017;123:139-46.
23. Hegemann NS, Schlesinger-Raab A, Ganswindt U et al. Risk of second cancer following radiotherapy for prostate cancer: a population-based analysis. Radiat Oncol 2017;12:2.