RESEARCH ARTICLE

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Epidemiology, Pattern, and Survival of Multiple Primary Malignant Neoplasms in Southeast Iran: Results of Kerman Population-Based Cancer Registry 2014-2020

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Abstract

Purpose: Cancer survivors may experience a subsequent primary cancer that affects their survival and quality of life. This study aimed to investigate the epidemiology of multiple primary malignant neoplasms (MPMNs) in Kerman province, southeast Iran during 2014-2020. **Materials and Methods:** In this retrospective cohort study, all patients who had been diagnosed with primary cancers and registered with the Kerman Cancer Registry Program (KPBCR) during 2014-2020 were included. MPMNs were defined as primary malignant tumors arising in different sites and/or were of different histological or morphological origins. If the second malignancy was diagnosed within the first six months from the diagnosis of the first tumor it was considered synchronous, and if after six months it was defined as metachronous. Logistic regression was used to analyze the relationship between age, sex, and primary cancer site with incidence and survival of secondary in the entire population. **Results:** Of 26,315 patients registered with a primary cancer diagnosis, 492 (1.86%) developed subsequent primary cancers. The most common type of secondary cancer was skin and mucosa (n=131, 26.63%) followed by urogenital (n=115, 23.37%), followed by, gastrointestinal (n=62, 14.45%), and breast neoplasms (n=57, 11.59%). Most patients had metachronous tumors (n=350, 71.13%). The primary cancer site (Skin and mucosa, urogenital, and breast) was significantly associated with developing subsequent cancer among cancer survivors. The overall 5-year survival of MPMNs cases was over 50%. Older age at diagnosis (HR= 1.02) and having synchronous tumors (HR=1.41) were negatively associated with the survival time of patients with MPMNs. Conclusion: Both patients and physicians should be taught about the importance of prevention and the provision of care and screening services among cancer survivors. Studying the epidemiology, susceptibility, and risk factors of MPMNs among cancer survivors will open windows to a better understanding of this phenomenon and policy making.

Keywords: Multiple primary malignant neoplasms- neoplasms- second primary- survival- Iran- Kerman

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Introduction

Over the last decades, advances in early diagnosis and treatment of cancer have contributed to considerable improvements in the overall survival [1] and life expectancy rates of patients with malignant cancers in most regions of the world with an overall estimated 5-year survival rate of 66% for cancer patients [2]. Cancer survivors may experience a subsequent primary cancer that affects their survival and quality of life. Compared to the general population, it is estimated that cancer survivors have a 14% higher risk of developing subsequent primary cancers [2, 3]. The increased risk is significantly associated with a combination of shared lifestyle, genetic and environmental factors [4]. Additionally, radiotherapy and the late effects of treatments may also result in an increased risk of developing subsequent cancers [4].

Multiple primary malignant neoplasms (MPMNs) refer to neoplasms with different morphologies arising in one patient and were first introduced by Billroth in 1889 [5]

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and then described by Warren and Gates in 1932 [6]. Since that time, the term "multiple primaries" has been widely used in the cancer literature [7-11]. According to the interval between the first and second primary neoplasm, MPMNs are classified as synchronous or metachronous, with synchronous defined as neoplasms occurring within six months, and metachronous neoplasms occurring beyond 6 months of the first primary diagnosis [12].

With the accompanying trends of developing subsequent primary cancers, there is increased recognition of the need to prioritize effective screening methods, prevention strategies, and counseling for cancer survivors. While developing subsequent primary cancers among cancer survivors may confer higher mortality and reduced quality of life, studying the epidemiologic aspects of this phenomenon seems logical. In this context, identifying the characteristics of cancers that have an elevated risk of occurring together can shed light on key questions about MPMNs pattern in different populations. The aim of the present study was to analyze the epidemiology, pattern and survival of the MPMNs cases from a population-based cancer registry program in Kerman Province, South-East Iran.

Materials and Methods

This study was approved by the Research Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1400.178).

In this retrospective cohort study, all 26,956 patients who have been diagnosed with malignant primary cancers and registered by the Kerman Cancer Registry Program (KPBCR) [13] during 2014-2020 were included. The KPBCR collects data on malignant cancers in Kerman, the largest and most developed city in the southeast of Iran with a population of 3,166 million in 2016.

The cases of MPMNs were defined as primary malignant neoplasms arising in different sites and/or were of different histological or morphological origins. According to International Agency for Research on Cancer(IARC) recommended rules, primary neoplasm is one that originates in a primary site or tissue and is not an extension, nor a recurrence, nor a metastasis. In addition, neoplasms with different morphologies should be regarded as MPMNs, even if they are diagnosed simultaneously in the same site [14]. In this study, the first site was defined as the first primary cancer reported during 2014-2020. Cases without histopathological verification were excluded from the analysis.

According to the interval between the first and the second primary cancer, MPMNs were classified as synchronous or metachronous. Synchronous defined as neoplasms occurred within six month, and metachronous neoplasms occurred beyond 6 months of the first primary diagnosis. For the data analysis, we created a datasheet in Stata 17.0. The demographic and clinical profile of each patient including age at diagnosis, date of diagnosis, topography, morphology and date of last follow up were extracted. We stratified the data by site of the first primary cancer, site of the second primary cancer, sex and age at the first primary and the second primary cancer diagnosis. An expert pathologist was asked to distinguish MPMNs cases from suspected metastatic or recurrent cases.

Univariate and multivariate logistic regression models were used to explore the association between clinical characteristics of patients (age at first diagnosis, sex, and site of the primary cancer) and developing a subsequent cancer in the entire population (patients diagnosed with cancer during 2014-2020 in Kerman province). The survival time of different MPMNs subgroups was calculated on February 2023 using the Kaplan-Meier method, and statistical significance was analyzed using Chi square or Fisher's exact test. The factors associated with the overall survival were identified using univariate and multivariate Cox proportional hazard regression model analyses. Stata (StataCorp, USA) was used for data analysis. A P value <0.05 was considered as statistically significant.

Results

This study used REPCAN (Guideline for REporting Population-based CANcer Registry Data) for analysis and reporting data [15].

Baseline characteristics of patients with MPMNs

In total, 26,316 patients were diagnosed with cancer during 2014-2020 in Kerman province, Iran. Over half of patients were male (n=14,022, 53.3%). Of this population registered by KPBCR during this period, 492 (1.87%) developed subsequent primary cancers (MPMNs). Among these MPMNs patients, 280 cases (56.9%) were men and the ratio of males to females was 1.31: 1. The average age(±standard deviation) at diagnosis for all patients diagnosed with primary cancer was 60.7 (±15.4) years. The average age at diagnosis for all patients with secondary cancers (MPMNs) was 58.5 (±16.7) years. Urogenital (n=4978, 18.91%), gastrointestinal (n=3883, 14.75%) and skin and mucosa cancers (n=3066, 11.65%) were the most common primary cancer site categories among all patients diagnosed with primary cancers. Among patients with MPMNs, the most common primary cancer site was Skin and Mucosa (n=131, 26.63%) urogenital system (n=115, 23.37%) (Table 1).

As shown in Table 1, 350 patients (71.14%) were metachronous multiple primary neoplasms (mMPMNs) and 142 patients (28.86%) were synchronous multiple primary malignant neoplasms (sMPMNs). The interval between the first and second primary tumor in mMPMNs cases ranged from 7 to 81 months with an average of 23.6 (± 17.1) and a median of 22 months. The average age was 55.6 (±14.3) years in patients with sMPMNs, and 58.85 (±16.9) years in those with mMPMNs.

Squamous cell carcinoma was the most common pathological type of the primary and secondary cancers including 8.64% of primary cancers and 19.51% of secondary cancers, adenocarcinoma (13.50% of primary cancers and 13.21% of secondary cancers) and basal cell carcinoma (6.13% of primary cancers and 11.38% of secondary cancers) (Table 1).

Logistic regression analysis was used to estimate the association of age, sex, and the primary cancer site with

Table 1. Baseline Characteristics of Patients Diagnosed with Primary and Secondary Cancers in Kerman Province, Iran, 2014-2020

Categories	Patients registered with primary cancer (N=26,315)	Patients registered with secondary cancers (synchronous) (n=142)	Patients registered with secondary cancers (metachronous) (n=350)	Total Patients registered with secondary cancers (N=492)
Sex (%)				
Male	14022 (53.3)	80 (56.34)	200 (57.14)	280 (56.8)
Female	12293 (46.7)	62 (43.66)	150 (42.86)	212 (43.2)
Age at first diagnosis (years)			58.85 (16.9)	
Average (Standard Deviation)	60.7 (15.4)	55.6 (14.3)		58.5 (16.7)
Primary cancer site (%)				
Gastrointestinal	3883 (14.75)	16 (11.27)	46 (13.14)	62 (14.45)
Breast	3087 (11.73)	14 (9.86)	43 (12.28)	57 (11.59)
Skin & mucosa	3066 (11.65)	39 (27.46)	92 (26.29)	131 (26.63)
Respiratory system	2961 (10.22)	8 (5.63)	27 (7.71)	35 (7.11)
Bone and soft tissue	502 (1.90)	3 (2.11)	7 (2.0)	10 (2.03)
Hematopoietic system	1880 (7.14)	14 (9.86)	17 (4.86)	31 (6.30)
Nervous system	1352 (5.13)	0	11 (3.14)	11 (2.24)
Urogenital	4978 (18.91)	32 (22.54)	83 (23.71)	115 (23.37)
Endocrine system	3834 (14.56)	10 (7.04)	14 (4.0)	24 (4.88)
Lymph node	826 (3.13)	5 (3.52)	9 (2.57)	14 (2.85)
Primary cancer morphology (%)				
Infiltrating Ductal Carcinoma	2628 (9.99)	9 (6.34)	32 (9.14)	41 (8.33)
Adenocarcinoma	3552 (13.50)	21 (14.78)	44 (12.57)	65 (13.21)
Myeloma	373 (1.42)	2 (1.41)	7 (2.0)	9 (1.83)
Leukemia	1325 (5.03)	8 (5.63)	12 (3.43)	20 (4.06)
Non-Hodgkin lymphoma	33 (0.12)	3 (2.11)	4 (1.14)	7 (1.42)
Hodgkin lymphoma	293 (1.11)	1 (0.70)	3 (0.86)	4 (0.81)
Squamous Cell Carcinoma	2273 (8.64)	28 (19.72)	68 (19.43)	96 (19.51)
Basal Cell Carcinoma	1612 (6.13)	14 (9.86)	42 (12)	56 (11.38)
Malignant Melanoma	112 (0.43)	2 (1.41)	3 (0.86)	5 (1.01)
Papillary Thyroid Carcinoma	951 (3.61)	5 (3.52)	8 (2.26)	13 (2.64)
Urothelial carcinoma	1884 (7.16)	5 (3.52)	31 (8.86)	36 (7.32)
Renal Cell Carcinoma	212 (0.81)	4 (2.82)	2 (0.57)	6 (1.22)
Endometrioid adenocarcinoma	292 (1.11)	2 (1.41)	11 (3.14)	13 (2.64)
Serous cystadenocarcinoma	158 (0.60)	2 (1.41)	8 (2.29)	10 (2.03)
Unknown	6243 (23.72)	12 (8.45)	26 (7.43)	38 (7.72)
Others	4374 (16.62)	24 (16.90)	49 (14.0)	73 (14.84)

developing a secondary cancer among the entire patients diagnosed with primary cancers in Kerman province during 2014-2020. Bivariate logistics regression model indicated a small but positive association between age at first cancer diagnosis and developing a subsequent cancer (OR=1.01, P=0.01). In other words, the odds of developing a subsequent cancer increases if the age at first cancer diagnosis rises. Patients who primarily diagnosed with skin and mucosa (OR=3.44, P<0.0001) or urogenital (OR=1.88, P<0.0001) cancers were more likely to develop a subsequent cancer. Findings from the multivariate logistic regression model confirmed the significant association of having skin and mucosa (OR=3.47, P<0.0001) or urogenital (OR=1.88, P<0.0001) cancers with an elevated risk of developing a subsequent cancer among patients in Kerman province (Table 2).

Clinical Characteristics

The most incident combinations of MPMNs based on their sites are presented in Figure 1. Skin and mucosa-skin and mucosa (n=45, 9.1%) and urogenital-urogenital (n=35, 7.1%) were the most common combinations (Figure 1). Squamous cell carcinoma- Squamous cell carcinoma (n=26, 5.3%) were the most incident morphological pairs occurring in patients. Males and females represented different forms of combinations. The most common multiple pairs in men were skin and mucosa-skin and mucosa (n=39, 13.92%), skin and mucosa – urogenital (n=19, 6.78%), and urogenital – urogenital (n=19, 6.78%) (Appendix 1, Table A). In women urogenital-breast (n=34,

Table 2. Bivariate and Multivariate Analysis

Variable	Crude Odds Ratio (95% Confidence interval)	P-value	Adjusted Odds Ratio (95% Confidence Interval)	P-value
Age at the first diagnosis (years)	1.01 (1.00 – 1.01)	0.01	1 (0.99 – 1.00)	0.16
Sex				
Male	1	--	1	--
Female	0.86 (0.72 – 1.03)	0.1	0.84 (0.68 – 1.02)	0.09
Primary cancer site				
Gastrointestinal	1	--	1	--
Breast	1.38 (0.95 – 1.98)	0.08	1.6 (1.08 -2.36)	0.01*
Skin & mucosa	3.44 (2.54 – 4.64)	P<0.0001*	3.47 (2.57 – 4.69)	P<0.0001*
Respiratory	1.02 (0.68 – 1.53)	0.89	1 (0.67 – 1.50)	0.99
Bone and soft tissue	1.44 (0.71 – 2.91)	0.3	1.57 (0.77 – 3.21)	0.21
Hematologic	1.28 (0.82 – 1.97)	0.26	1.35 (0.87 – 2.11)	0.17
Nervous system	0.76 (0.42 – 1.39)	0.38	0.81 (0.44 – 1.48)	0.5
Urogenital	1.88 (1.39 – 2.55)	P<0.0001*	1.88 (1.38 – 2.55)	P<0.0001*
Endocrine system	1.08 (0.64 – 1.83)	0.75	1.26 (0.73 – 2.17)	0.4
Lymph node	1.46 (0.83 – 2.57)	0.18	1.54 (0.87 – 2.73)	0.14

16.03%) and urogenital-urogenital (n=19, 8.96%) were among the most common multiple pairs (Appendix 1, Table B).

Prognosis

In this study, 199 out of the 492 (40.44%) patients were still surviving in February 2023, but 293 (59.55%) deceased. The survival time of the patients with MPMNs was calculated as the time from the time of diagnosis of primary cancer to death or end of follow-up (February 2023). Five years survival was 52.4% (47.5%-57%), which was highest for breast cancer (64.5% (95% CI: 50.1% -75.8%)) and lowest for Respiratory system cancer (31.7% (95% CI: 16.2%-48.5%)) based on primary site. Five years survival for patients with sMPMNs was lower than patients with mMPMNs (52.8% vs 53.3%) (Table 3,

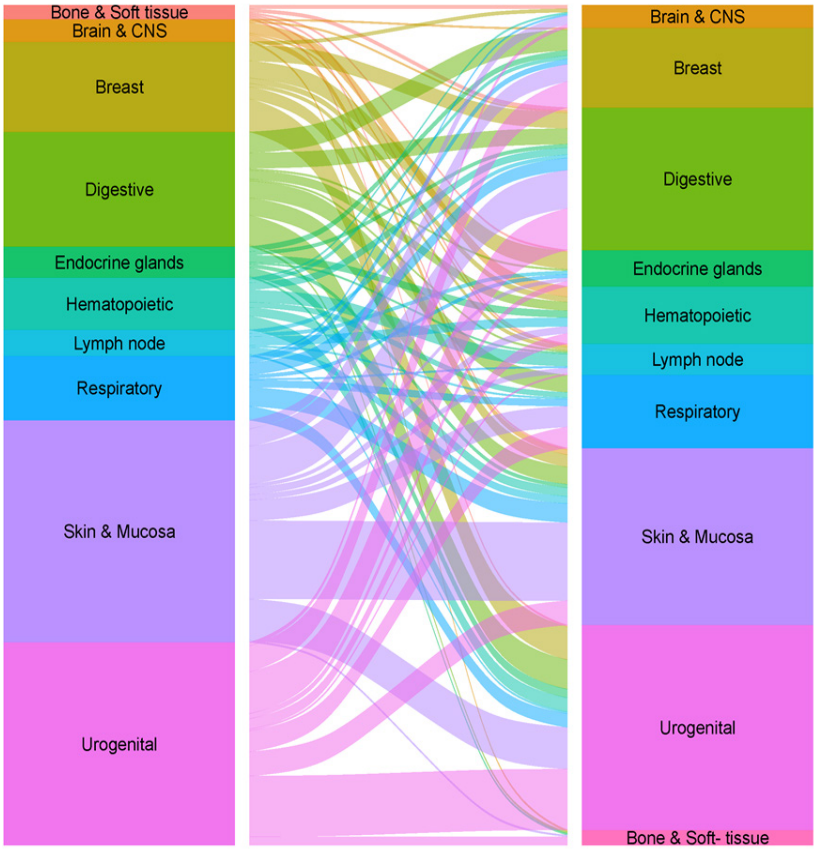

Figure 1. The Most Incident Primary Site Combinations among Patients Diagnosed with Multiple Primary Malignant Neoplasms in Kerman Province, 2014-2020.

Table 3. 5-Year Survival Rates of Patients with Secondary Cancers

Category	Patients with secondary cancers (N=492)	Deaths (N=293)	Alive (N=199)	5 years survival % (95% Confidence Interval)
Primary Cancer site (%)				
Skin & Mucosa	131 (26.63)	66 (25.53)	51 (25.63)	50.6 (41.2- 59.3)
Urogenital	115 (23.37)	57 (19.45)	43 (21.61)	52.0 (41.4-61.5)
Gastrointestinal	62 (12.60)	31 (10.58)	29 (14.57)	54.2 (40.5-66.0)
Breast	57 (11.59)	23 (7.85)	31 (15.58)	64.5 (50.1 -75.8)
Respiratory system	35 (7.11)	25 (8.53)	6 (3.02)	31.7 (16.2-48.5)
Hematopoietic	31 (6.30)	16 (5.46)	12 (6.03)	40.1 (18.0-61.4)
Endocrine system	24 (4.88)	12 (4.10)	12 (6.03)	57.1 (34.6-74.3)
Lymph node	14 (2.85)	7 (2.39)	6 (3.02)	50.5 (20.6-74.4)
Nervous system	11 (2.24)	5 (1.71)	4 (2.01)	48.0 (16.1-74.5)
Bone & Soft tissue	10 (2.03)	6 (2.05)	4 (2.01)	50 (18.4-85.3)
Multiple primary status (%)				
Metachronous	350 (71.14)	213 (76.70)	137 (68.84)	53.3 (47.7-58.6)
Synchronous	142 (28.86)	80 (27.30)	62 (31.16)	52.8 (43.4- 61.3)

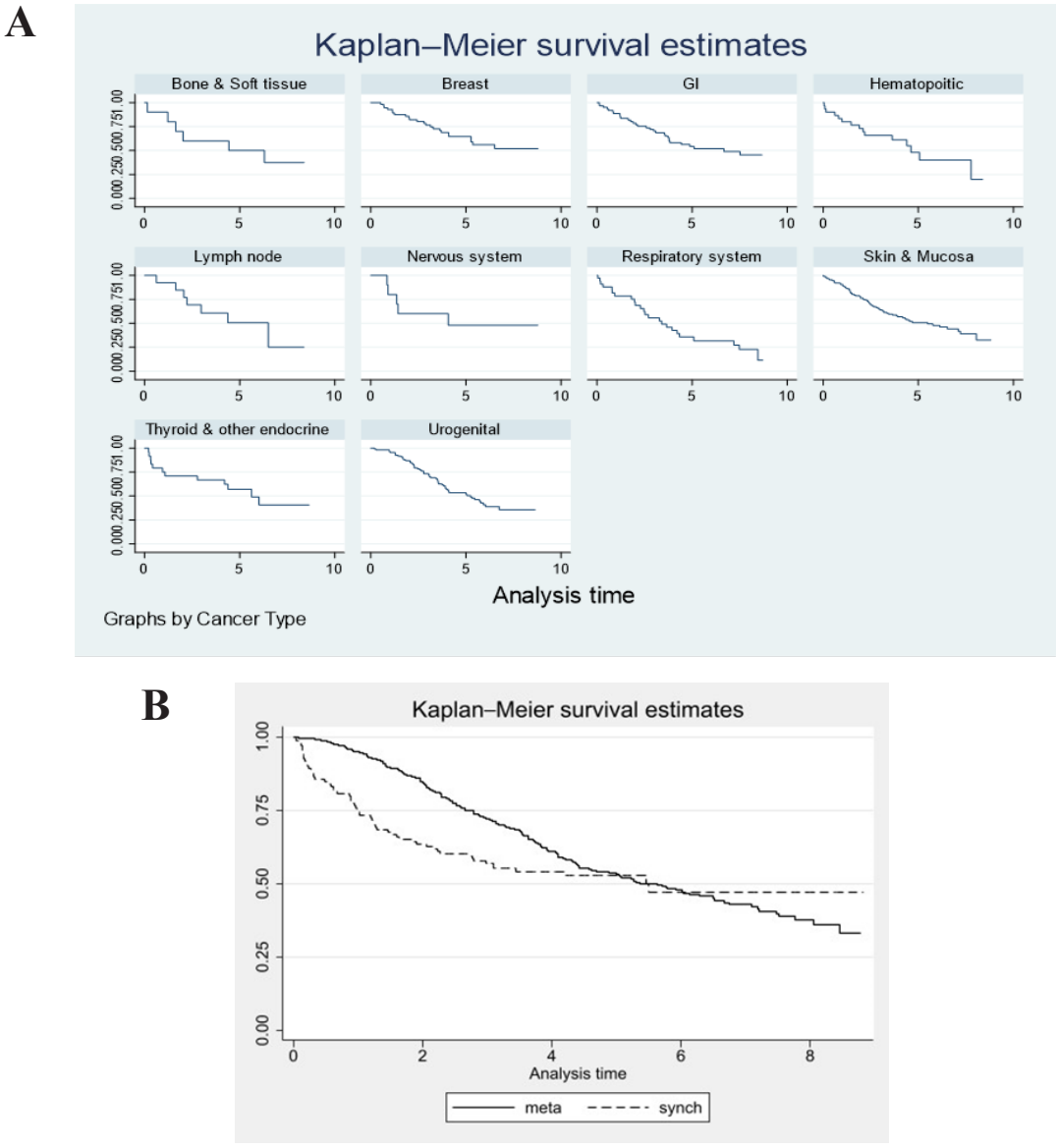

Figure 2. Kaplan-Meier Survival Curve of Patients with Multiple Primary Malignant Neoplasms based on Primary cancer (A), and its comparison between synchronous and metachronous tumors (B)in Kerman province 2014-2020

Table 4. Effect of Age, Gender, Type, and Tumor Type on Hazard of Death among Patients with Secondary Cancers

Variable	Hazard Ratio	95% Confidence Interval
Age	1.02	1.01-1.03
Sex (ref: male)	0.9	0.67-1.22
Multiple primary status (ref: Metachronous)	1.41	1.05-1.90
Primary cancer site		
Bone & Soft tissue (reference)	-	-
Breast	0.61	(0.24-1.54)
Gastrointestinal	0.58	0.24- 1.43)
Hematopoietic	0.84	0.32-2.19
Lymph node	0.83	0.28-2.48
Nervous system	0.83	0.28-2.48
Respiratory system	1.12	0.33-3.76
Skin & Mucosa	1.16	0.47-2.88
Endocrine system	0.69	0.29-1.63
Urogenital	0.88	0.33-2.37

Figure 2).

Further investigation of data showed that according to the bivariate Cox proportional hazard regression analysis, age at diagnosis had significant effect on the survival time of patients with MPMNs (HR= 1.02). In addition, patients with sMPMNs (HR=1.41) indicated higher risk of death than the entire cancer survivors with MPMNs (Table 4).

Discussion

The data from this study indicated a considerable prevalence of MPMNs among cancer survivors in Kerman province, Iran. Most secondary cancers were metachronous tumors, independent of age and sex, although higher frequencies of secondary cancers were observed in older patients and in males. The risk of developing a secondary cancer was different according to the primary cancer site. Patients with primary skin and mucosa, urogenital and breast cancer indicated higher rates of developing a secondary cancer than the entire cancer survivors. Moreover, 5-year survival of patients with secondary cancers was significantly reduced in patients with older ages, and synchronous tumors.

Our findings indicated that around two out of 100 primary cancer survivor, experience a new secondary cancer. Existing evidence suggested an overall prevalence of 0.7 to 17% [16-18] depending on different regions and databases. The diverse incidence of MPMNs across different countries and geographical regions might be associated with genetic factors, environmental factors, diagnostic methods, longer follow-up duration and inclusion of autopsy series in these studies [19, 10, 20]. Furthermore, factors such as improvement in diagnostic tests, sophisticated treatment which increases survival of cancer survivors, medical surveillance and availability of screening tests affect the prevalence [21]. So, the low prevalence of MPMNs in low and middle-income countries including Iran is likely associated with incomplete coverage of cancer registries in these regions, low availability of screening tests and low survival rate of cancer survivors. Another explanation for this low prevalence may be that we reported the cases just in the time period of seven years which is relatively short [22].

In the present study, the average age at diagnosis among MPMNs cases was lower than the entire cancer survivors. Although MPMNs may occur at any age, existing evidence suggests that the overall incidence of MPMNs cases in lower ages may be associated with the early onset of breast and female genital cancers in women in developing countries [23, 20]. With the progress in the diagnosis and treatment of breast cancer, the 5-year survival for cancer survivors with primary breast cancer increased markedly with time in most countries [24, 1], therefore, the number of cancer survivors would increase.

Current findings indicated that skin and mucosa was the most common primary cancer site among MPMNs cases in Iran. According to the national estimates, skin cancer is among the most common types of cancers in the Iranian population [25]. Sun exposure is the main risk factor of skin cancer. Evidences support the increased risk of subsequent malignant melanoma in patients with primary malignant melanoma [26]. This may be as the result of UV radiation in sun exposed areas. In addition, host susceptibility factors such as genetic [27], family history of melanoma [28] and history of atypical moles [29] has been associated with the increased risk of second melanoma among melanoma survivors. Therefore, intensive surveillance of skin cancer survivors especially among individuals with positive family history and history of atypical moles is recommended. In addition, existing evidence showed increased risk of secondary primary cancers in different organs in skin cancer survivors. In our study, skin-urogenital pair was a common pair of MPMNs cases. Both of these cancers are among the most common types of cancers in Kerman [13]. The increased risk of bladder cancer following the skin cancer has been addressed in various studies [30]. Common risk factors of these cancers may justify the finding that indicated that smoking which is a well-known risk factor of bladder cancer [31], is also an independent risk factor for squamous cell carcinoma of skin [32].Exposure to arsenic, a chemical that widely uses in pesticide production, car batteries and electronic devices, is another common risk factor for these two cancers [33-36].

According to our findings, the overall 5- year survival rates of patients with sMPMNs and mMPMNs in Iran was higher than 50%. Older age at diagnosis, and having sMPMNs were associated with poor prognosis among MPMNs cases in Kerman. Poor prognosis of MPMNs cases in older ages was previously reported in other countries[37].

To our knowledge, this is the first report of patient with secondary malignant neoplasms in Iran and our findings have important implications for public health practice. Nevertheless, our results may be subject to some limitations: First, due to rapidly progressive nature of some cancers such as cancer of lung, occurrence of death in a short period of time preclude the occurrence of

second primary cancer (competing risk) may affects our understanding about the true picture of MPMNs. Second, Due to limited number of MPMNs cases in Kerman and subsequent low precision, we couldn't calculate the incidence of secondary primary cancer related to specific primary cancer site among MPMNs compared to general population. Third, as the coverage of cancer registry in Iran is not complete, under-estimation of cases is probable. Finally, Due to limited follow-up period, estimation of lifetime incidence of MPMNs was not possible.

In conclusion, with the advent of early screening and more efficient treatments and consequently increased survival of cancer patients, MPMNs would be an issue within the next years. Patients should be educated well about the importance of prevention, life style modification and necessity of screening tests after the diagnosis of first cancer. Future researches in Iran should focus on risk estimation of second primary cancer in patients with MPMNs and underlying risk factors and efficacy of preventive interventions in cancer survivors.

Author Contribution Statement

RMA contributed to the project concept and manuscript design, data collection and interpretation, critical review of the manuscript writing and discussion of the manuscript. BM worked on data analysis, data interpretation and writing of the manuscript. MSB worked on data analysis, data interpretation and writing of the manuscript. SM worked on data analysis, data interpretation and writing of the manuscript. AZK worked on data analysis, data interpretation and writing of the manuscript. MNR worked on data analysis, data interpretation and writing of the manuscript. HM worked on data analysis, data interpretation and writing of the manuscript. AS worked on data analysis, data interpretation and writing of the manuscript. AB worked on the project concept and manuscript design, supervising, critical review of the manuscript writing and discussion the manuscript. AB is responsible for the overall content as the guarantor. All authors read and approved the final manuscript.

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Ethical considerations

This study is approved by the Research Ethics Committee of Kerman University of Medical sciences (IR.KMU.AH.REC.1400.178).

Conflicts of interests

None.

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