Review Article
Prevalence of multiple primary carcinomas in patients with Merkel cell carcinoma: a meta-analysis of cohort studies

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Abstract: Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer that may be associated with multiple primary carcinomas (MPCs). However, there are few studies proving whether MCC can increase the risk of MPCs. Here, the literature was searched on Medline, Web of Science, EMBASE, Cochrane, Ovid, and Science Direct databases systematically for reports on the incidence of MPCs in patients with MCC before June 2018. Five cohort studies provided primary data for the analysis, which were derived from 504 papers. A random-effects meta-analysis for the pooled prevalence of MPCs in patients with MCC was performed. A total of 3,356 patients with MCC from 1978 to 2010 in different countries were selected for the meta-analysis. The pooled prevalence of all trials combined was 12.06% (95% confidence interval (CI), 0.0856-0.1673), but heterogeneity was found in these prevalence estimates (I^2=91.4%). After sensitivity analysis, they were divided into two subgroups. The pooled prevalence of MPCs in patients with MCC in the first subgroup (≤27 years) was 9.44% (95% CI, 0.0833-0.1068). The incidence in the second subgroup (all investigated times (≥27 years)) was 17.64% (95% CI, 0.1536-0.2019). The total standardized incidence ratio of MPCs in patients with MCC compared with the general population in different places from where these studies were extracted was about 1.10 to 2.34. In these studies, MPCs of the digestive system (8.89%-22.13%), integumentary system (3.28%-50.63%), and hematological system (5.07%-29.17%) accounted for a large proportion. The prevalence of MPCs in patients with MCC was high. MCC has a strong connection with MPCs. Organs of the digestive system and integumentary systems were prone to second tumors after MCC. Particular attention should be paid to patients with MCC, which might cause MPCs, in clinics.
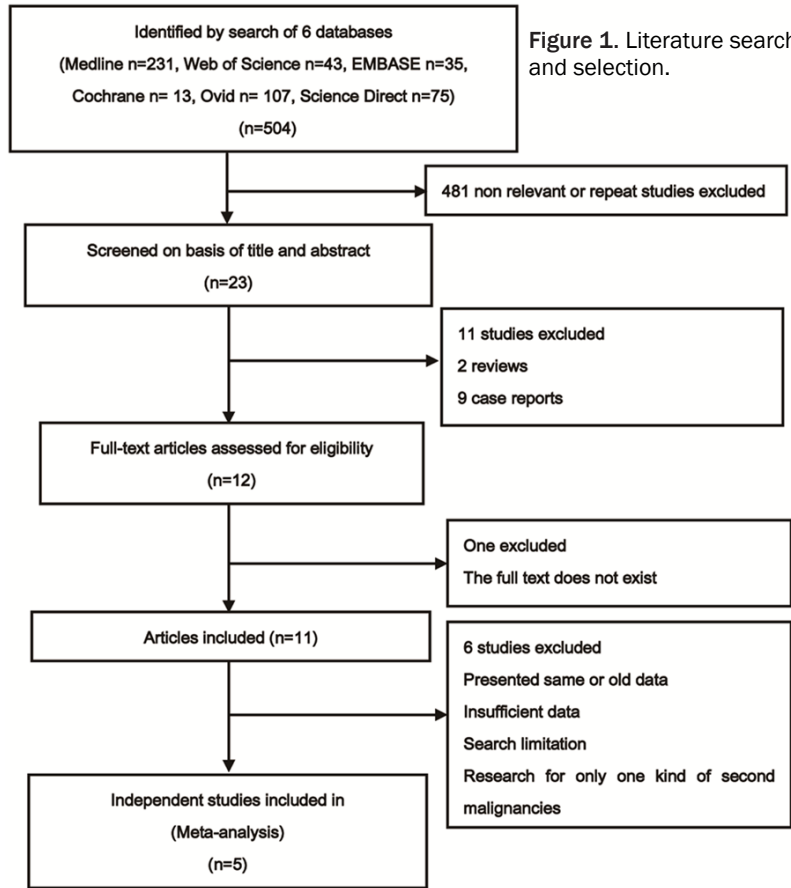
Keywords: Multiple primary carcinomas, Merkel cell carcinoma, prevalence meta-analysis

Introduction

Merkel cell carcinoma (MCC) is not only a rare kind of neuroendocrine carcinoma, but also a highly malignant carcinoma of the skin. It was first reported in 1972 [1]. MCC is more common among elderly people [2]. The approximate incidence of MCC in France was 0.57 to 0.74 per 100,000 persons from 2006 to 2010 [3]. By 2011, the incidence of MCC was about 0.79 per 100,000 years in the United States. However, Queensland, Australia had an even higher incidence of MCC: 1.6 per 100,000 persons in 2000, for example [4, 5]. Although MCC is rare, according to recent records, it is always followed by multiple primary carcinomas (MPCs).

Besides, it has a high incidence in different regions, like Australia and Europe [6-10]. Lip cancer and lymphoid leukemia in Queensland, Australia in patients with MCC showed a high correlation (standardized incidence ratio (SIR) >8) [9]. In addition, 27 patients with MCC in one hospital comprised 19 patients (70%) with MPCs after MCC [11]. The incidence of MCC increased steadily in the last few decades and so was that of MPCs. In 1975, 4,805 (7.2%) cases of MPCs from the International Agency for Research on Cancer (IARC)/International Association of Cancer Registries (IACR) database, and 5,222 (7.8%) MPC cases among 62,136 cases of first primary MCCs from the Surveillance, Epidemiology, and End Results

Figure 1. Literature search and selection.

cer cells [17]. Immunotherapy and its related mechanisms are a current area of research.

Methods

Search strategy and selection criteria

Medline, Web of Science, EMBASE, Cochrane, Ovid, and Science Direct databases were searched. All literature was searched until June 2018 for spatial distributions of MPCs and MCC in the world. For the research, "Merkel Cell Carcinoma" or "MCC" were used. The second group of search words were "multiplicity carcinomas", "multiple primary Cancers", "second cancers", "second tumors", "second neoplasm", "second carcinomas" or "second malignanc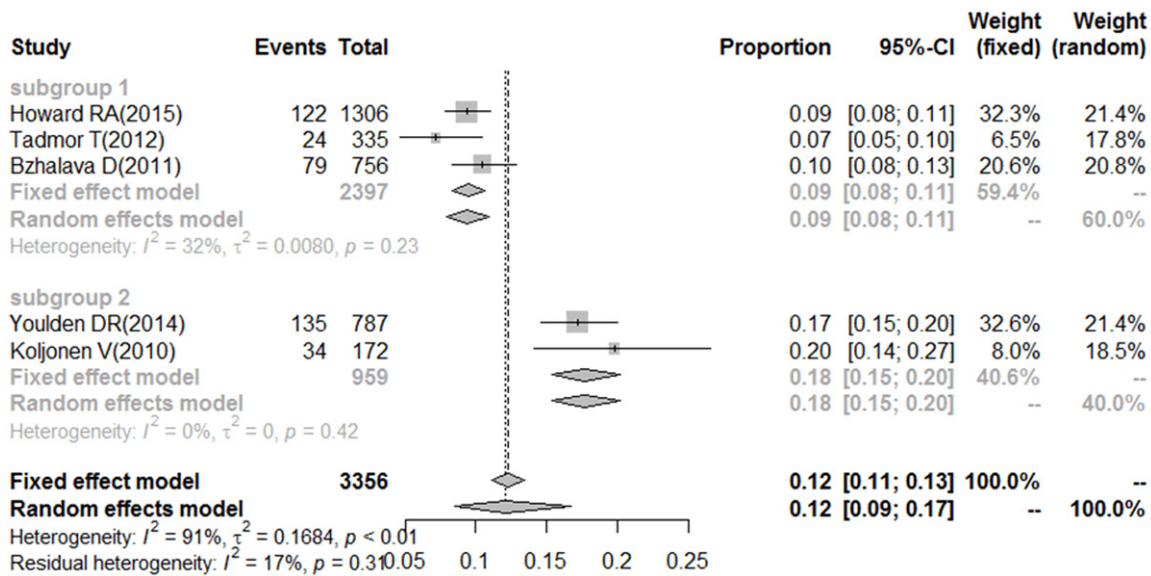ies" Another group was "incidence", "occurrence", "risk" or "prevalence". All the cohorts were from population-based cancer registries.

Articles were required to meet the inclusion criteria: (1) cohort studies or large-scale epidemiological studies, (2) data searched by the National Cancer Registry of countries or cancer registries of the SEER, (3) studies of more than one kind of second malignancy, (4) details of baseline information for patients and complete data collection, (5) recent data for epidemiological studies, and (6) definite diagnosis of MPCs and SIRs between different carcinomas. When related messages were updated, old data were replaced with the most recent data for the same studies. The overall diagram of the literature search is described in **Figure 1**.

Quality assessment and data extraction

For the entire study, quality was assessed independently by two investigators according to the inclusion criteria above. One reviewer extracted data for the study setting and samples (number, age, sex, carcinoma types, countries, data

(SEER) database were reported in the world. Meanwhile, in 2011, there were 16.7% and 19.7% of MPCs among all carcinomas [12, 13].

It is generally believed that Merkel cell polyoma-virus (MCPyV) is the cause of MCC, and ultraviolet ray exposure may be involved in virus-mediated and non-viral carcinogenic processes by promoting immunosuppression or DNA damage [14]. Surgery, chemotherapy, radiotherapy, and recently emerging immunotherapy are the main treatments for MCC. For example, avelumab (an anti-programmed death-ligand 1 drug) was approved by the United States Food and Drug Administration in 2017 as a drug for the treatment of advanced MCC [15, 16]. The mechanism of MPCs caused by MCC is not clear. The secondary diseases might be caused by chemotherapy, radiotherapy, or immunodepression. Reports have suggested that several patients with MCC were able to achieve complete remission on their own, or they may relapse after a period of remission. Researchers believe that MCPyV provides an inherent immune-stimulatory signal to the can-

Figure 2. Pooled analysis with summary estimates (random-effects meta-analysis) for the prevalence of multiple primary carcinomas in patients with Merkel cell carcinoma.

sources, SIRs), while the other reviewer verified the accuracy.

Statistical analysis

The prevalence rates and their 95% confidence intervals (CIs) were determined using the extracted raw data. The I^2 test (ranges from 0% to 100%) was used to quantify the effects of heterogeneity, which represented the proportion of inter-study variability that can be contributed to heterogeneity. While $I^2 > 50\%$ and $P < 0.05$ in the forest plot (**Figure 2**), showed the heterogeneity of the data. Thus, it was divded into two subgroups by study time (all investigated times were greater than 27 years or not). At the same time, a random-effects meta-analysis was considered to estimate the pooled proportions, and a fixed-effect meta-analysis was selected for each subgroup. Moreover, SIRs were collected to evaluate the risk of MPCs in MCC. In this meta-analysis, all statistical analyses were performed using R software version 3.5.1.

Results

Of the total of 504 articles collected, we screened 5 papers for the prevalence rate of MPCs, as shown in **Figure 1** [6-10]. All studies were cohort studies. Across 5 cohorts, the total number of patients ranged from 172 to 1,306. The results of the meta-analysis showed that the

prevalence of MPCs in patients with MCC was especially high. Because $I^2 = 91.4\%$ (P<0.001) was based on the forest plots, a bias between the cohorts was found. The cohort studies were then divided into two subgroups, as shown in **Figure 2**. The sample size of the first subgroup was 2,397, and that of the other was 959. In the first subgroup, $I^2 = 31.7\%$ (P=0.2311), and in the second subgroup, $I^2 = 0\%$ (P=0.4155). Thus, no obvious heterogeneity appeared in the cohort studies. Furthermore, P=0.0944 (95% CI, 0.0833-0.1068) in the first subgroup, and P= 0.1764 (95% CI, 0.1536-0.2019) in the other group. A fixed-effect model of meta-analysis was used for each subgroup.

SIRs in the cohort studies ranged from 1.10 to 2.34 for total samples or sample of sex [6-10]. Five studies were extracted from the United States, Israel, Denmark, Norway, Sweden, Australia, and Finland. Older patients had a higher risk of MPCs in the study, especially among those older than 60 years. Skin carcinomas were one kind of high-occurrence disease after MCC (3.28%-50.63%), as well as hematological malignancies (5.07%-29.17%), carcinomas of digestive organs (8.89%-22.13%), carcinomas of the genital tract (16.40%), and other malignancies, like lung cancer (6.33%-15.57%), prostate carcinoma (3.80%-11.11%), or breast cancer (5.74%-11.76%). All data are listed in **Tables 1**-**3**.

Table 1. Characteristics of patients among the included studies

Study	Publication Year	Population	Study type	Data source	Diagnosed Age (%) or Median		No. of first diagnosed Cancer (MCC)	No. of MPCs	All carcinomas SIR (95% CI)
Howard RA	2015	US (1986-2002)	Cohort Studies	SEER	<60	72 (13.2)	1306	122	1.22 (1.01-1.45)
					60-69	246 (18.8)			
					70+	888 (68.0)			
Tadmor T	2012	Israeli (1989-2010)	Cohort Studies	INCR	72	8 (35.2-86.4)	335	24	Male 1.15 (0·53-1.78)
									Female 1.10 (0.45-1·76)
Bzhalava D	2011	Denmark (1980-2007)	Cohort Studies	Cancer registries	<60	45 (5.95)	756	79	1.4 (1.1-1.72)
		Norway (1990-2007)			60-74	181 (23.94)			
		Sweden (1990-2007)			75+	30 (70.11)			
Youlden DR	2014	Australia (1982-2010)	Cohort Studies	QCR	75 (29-104)		787	135	2.19 (1.84-2.60)
Koljonen V	2010	Finland (1979-2006)	Cohort Studies	FCR	<60	18 (10.47)	172	34	2.34 (1.62-3.27)
					60-74	50 (29.1)			
					75+	104 (60.5)			

SIR: standardized incidence ratio; SEER: cancer registries of the Surveillance, Epidemiology, and End Results; NCR: Israeli National Cancer Registry; QCR: Queensland Cancer Registry; FCR: Finnish Cancer Registry.

Table 2. Numbers of patients with multiple primary carcinomas after the diagnoses of MCC and types of carcinoma

Study	Digestive organs	Lung	Breast	Female genital tract	Male genital tract	Prostate	Bladder	Kidney	Brain	Skin, malignant melanoma
Howard RA	27 (22.13%)	19 (15.57%)	7 (5.74%)	6 (4.92%)	14 (11.48%)	-	7 (5.74%)	3 (2.46%)	3 (2.46%)	4 (3.28%)
Tadmor T	-	-	-	-	-	-	-	-	-	-
Bzhalava D	9 (11.39%)	5 (6.33%)	6 (7.59%)	-	-	3 (3.80%)	3 (3.80%)	1 (1.27%)	1 (1.27%)	40 (50.63%)
Youlden DR	12 (8.89%)	13 (9.63%)	9 (6.67%)	-	-	15 (11.11%)	-	5 (3.70%)	-	29 (21.48%)
Koljonen V	7 (20.59%)	-	4 (11.76%)	-	-	-	-	-	-	11 (32.35%)

Table 3. Numbers of patients with multiple primary carcinomas after the diagnoses of MCC and types of carcinoma

Study	Non-Hodgkin lymphoma	Multiple myeloma	CLL	ALL	Hairy cell leukaemia	Other cancers	Total
Howard RA	10 (8.20%)	1 (0.82%)	3 (2.46%)	-	-	18 (14.75%)	122 (100%)
Tadmor T		7 (29.17%)				17 (70.83%)	24 (100%)
Bzhalava D	1 (1.27%)	-		3 (3.80%)	-	7 (8.86%)	79 (100%)
Youlden DR	5 (3.7%)	-	-	-	-	47 (34.81%)	135 (100%)
Koljonen V	2 (5.88%)	-	2 (5.88%)	-	-	8 (23.53%)	34 (100%)

CLL: Chronic lymphocytic leukemia; ALL: Acute lymphoblastic leukemia.

Conclusions

This might be the first meta-analysis to describe the prevalence of MPCs in patients with MCC. In this study, MCC and MPCs were strongly associated and that MCC can increase the risk of MPCs. The included studies showed that the prevalence of MPCs was increasing rapidly in recent times for unknown reasons. Older patients were at high risk of developing MPCs in this study, and this might be linked to their immune systems. The United States, Israel, Denmark, Norway, Sweden, Australia, and Finland comprised the main population with these diseases, which may be related to their lifestyle, geographical conditions or genes.

There was a related report of carcinomas of the salivary gland (SIR, 11.55) and biliary sites other than the liver and gallbladder (SIR, 7.24) in

1,306 patients with first primary MCC [18]. These tumors were analyzed for association with the digestive system and this system was determined to be at high risk of harboring second primary cancers in countries. Additionally, the risk of developing carcinomas in other systems were not the same. Hematological malignancies, carcinomas of the urinary system, and other cancers like skin malignancies, lung cancers, and female breast cancers also had high levels of risk.

The use of population-based data is appropriate for assessing the relative risk of being diagnosed with a second primary cancer. While the research for MCC and MPCs were likely to be published as case reports, the overall incidence of populations in different regions was difficult to determine [19-21]. In contrast, details can be systematically obtained through national databases or related institutions, but few data exist currently. Most reports also originated from developed countries, and they might have some limitations. Through all the investigations of populations across the world, it was hypothesized that MCC-associated diseases are related to race, chemotherapy, radiotherapy, and immunosuppression.

There are several limitations in the study. First, there has been little research of the relation between MCC and MPCs. Only several countries had reported detailed information of the prevalence of MCC and MPCs, although case reports originated from many countries. These studies may have regional limitations in the global context. Second, the mechanism behind the studies was not yet clear, and a considerable number of theories were hypothetical. Therefore, more research must be conducted to further substantiate these hypotheses. Last, in this meta-analysis, all studies together had great heterogeneity. Heterogeneity might have been derived from regions or the investigated time period.

As described above, the results of this analysis showed that MCC can increase the risk of MPCs, the prevalence of which was high. More attention should be paid to patients with MCC who might develop second primary cancers in clinics. The conclusion of the theories above still need more multi-center research, large samples, and prospective research to prove them.

Disclosure of conflict of interest

None.

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