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Primary malignant brain tumors following systemic malignancies: a population-based analysis

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Running title: Brain tumors following cancer

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Abstract
BACKGROUND: Several reports have described glioma following different cancers. We assessed the prevalence of primary malignant brain tumors afterwards systemic malignancies in patients in the United States based on SEER program data.
METHODS: The detailed data of patients with primary malignant brain tumors following an initial malignant tumor outside the central nervous system were extracted from SEER. Descriptive statistics were used to analyze patient demographic and clinical characteristics. We also extracted standardized incidence ratios (SIRs) stratified by age, race, sex, history of radiation or chemotherapy, histology findings and primary cancer site.
RESULTS: We identified 5212 patients diagnosed with primary malignant brain tumors following systemic malignancies. Most patients had prostate cancer, breast cancer and skin melanoma as the primary cancer. The median duration between the first diagnosis of cancer and that of the subsequent malignant brain tumor was 53 months. Glioblastoma was the most common subsequent malignant brain tumor type. The prognosis after subsequent malignant brain tumor diagnosis was poor. The SIRs differed most by race, cancer site, and cancer type. Patients with acute lymphocytic leukemia had the highest risk of developing primary malignant brain tumors.
CONCLUSION: Our study provides a comprehensive analysis of clinical data and the SIRs of patients with primary malignant brain tumors afterwards other systemic malignancies. Genetic relationships might play a key role in subsequent malignant brain tumor origin. Our data provide directions for future studies exploring the hidden associations between systemic malignancies and primary malignant brain tumors.

Keywords
Primary brain tumor, Glioma, Cancer, SEER Program, CNS disease.

Introduction

Glioma accounts for almost 30% of all primary brain tumors and 80% of malignant tumors, and it is responsible for the majority of deaths from primary brain tumors[1] . Although numerous studies have contributed to a greater understanding of the genesis of glioma [2], the origin of glioma remains a topic of controversy in cancer research [3]. There are several reports describing glioma following different kinds of systemic malignancies, such as breast cancer [4-8] and acute lymphocytic leukemia (ALL) [9-14]. We have also encountered such cases during our clinical work. Is there a relationship between systemic malignancies and primary malignant brain tumors? Whether the prevalence of primary brain tumors is higher among patients with systemic malignancies? The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48% of the U.S. population [15]. Multiple primary standardized incidence ratios (MP-SIR) are the analytic measurements used to perform multiple primary analyses and to test hypotheses that explore theoretical links in the etiology of two cancers. A defined cohort of persons previously diagnosed with cancer is followed through time to compare their subsequent cancer experience to the number of cancers that would be expected based on incidence rates for the general population. We sought to determine whether the prevalence of primary brain tumors is higher among patients with systemic malignancies.

Method

The detailed data of patients with primary malignant brain tumors following a primary malignant tumor outside the central nervous system were extracted from the MP-SIR session of the SEER database. Malignancy was defined according to the behavior code of the International Classification of Diseases for Oncology 3 (ICD-O-3), and in situ disease was included. Patients of an unknown age were excluded. Death certificate only and autopsy only cases were also excluded. To avoid potential events being ignored, the latency exclusion period was set as two months. Single outcome analysis was chosen as the analysis type. Subjects exited the study based on the following dates, whichever occurred first: the date of their first event (diagnosis of any malignant brain tumor), the date of their death, the date at which they were lost to follow-up, or the end date of the study. Descriptive statistics were used to analyze the demographic and clinical characteristics of these patients. We extracted the standardized incidence ratios (SIRs) of the MP-SIR session using the SIR table mode, with the patients stratified by age, race, sex, history of radiation or chemotherapy, histology findings and primary cancer site. The SIR was evaluated based on the observed value, expected value, O/E ratio, and 95% confidence interval (CI). A history of radiation or chemotherapy was identified according to the variable “therapy”. The histology findings were extracted according to the variable “Histology recode - Brain groupings”. The primary tumor site was defined according to the variable “ICD-O-3/WHO 2008 individual sites only”. To make the results more specific, we also extracted the SIRs for patients with particular primary cancers according to a history of radiation or chemotherapy. Finally, we analyzed the pathological type of the subsequent malignant brain tumor, which was defined according to ICD-O-3. The research period was a diagnosis within Jan 2000 to Dec 2018. All the data were obtained by using the SEER*Stat 8.3.9 program. The latest database of Incidence - SEER Research Plus Data, 18 Registries (November 2020 submission) [16] was adopted.

Results

We indexed 6,061,265 patients with primary malignant or in situ cancer outside of the central nervous system. Of these, we identified only 5212 patients (0.09%) with primary malignant brain tumors following systemic malignancies. Only 0.16% of the patients with prostate cancer developed brain tumors, which was the highest percentage of all primary cancers studied. The percentages for patients with breast cancer, melanoma of the skin and ALL were 0.07%, 0.15% and 0.10%, respectively (Table 1). Among the 5212 patients, most were first diagnosed with prostate cancer (n=1469, 28.2%), breast cancer (n=776, 14.9%) or melanoma of the skin (n=587, 11.3%).

The median duration between the initial cancer diagnosis and the development of a subsequent malignant brain tumor was 53 months, and the median age at diagnosis of the subsequent malignant brain tumor was 70 years old. The prognosis after the diagnosis of subsequent malignant brain tumor was poor, and the median survival month was 6 months. Most of the patients were male (n=3256, 62.5%) and non-Hispanic white (n=4376, 84.0%). The SIR was found to be significantly higher for male patients than for general population. We then stratified the

patients for analysis by race and origin, and the results indicated that the SIR for Hispanic individuals was significantly lower than that for non-Hispanic individuals (Table 2).

We listed the SIRs for the primary cancers based on histology for the cancers with the top 15 observed values in Table 3. Patients with codes “9950-9969: chronic myeloproliferative disorders”, “9820-9839: lymphoid leukemias”, “8720-8799: nevi and melanomas” and “8140-8389: adenomas and adenocarcinomas” had significantly higher SIRs, while patients with codes “8500-8549: ductal and lobular neoplasms” and “8050-8089: squamous cell neoplasms” had lower SIRs. We listed the SIRs for the primary cancers based on site for the cancers with the top 25 observed values in Table 4. We found that patients with ALL, small intestine cancer, other nonepithelial skin cancers, extranodal non-Hodgkin lymphoma, thyroid cancer, kidney and renal pelvis cancer, and melanoma of the skin had a significantly higher risk of developing primary malignant brain tumors. Patients with breast cancer, laryngeal cancer and rectosigmoid junction cancer had a lower risk.

In the whole cohort, patients who did not receive chemotherapy or radiation for primary cancer had a significantly higher incidence of subsequent primary malignant brain tumors. We analyzed the response to radiation therapy and chemotherapy among patients with prostate cancer, breast cancer, melanoma of the skin and ALL, but we did not find any evidence to prove that patients who received radiation or chemotherapy had higher incidence ratios than their counterparts who did not receive radiation or chemotherapy (Table 5). The subsequent malignant brain tumor types are listed in Table 6. Almost 94% of them were gliomas, and glioblastoma was the most common pathological type of subsequent malignant brain tumor, accounting for 68.4% of all tumors (n=3563).

Discussion

Glioma is the most common primary malignant central nervous system tumor, and the prognosis is very poor, especially for patients with high-grade glioma [17]. The origin of glioma remains controversial [3]; several centers have also reported high-grade glioma following different kinds of systemic malignancies. We therefore wondered whether a connection exists between the development of primary malignant brain tumors and other systemic malignancies. The SEER program covers approximately 48% of the United States population [15], and the MP-SIR session of the database was designed to aid in comparisons of the incidence of cancer in a defined cohort of persons previously diagnosed with cancer with the incidence of cancer in the general population to test hypotheses that explore theoretical links between the etiology of two cancers. Therefore, we conducted this population-based analysis to investigate the prevalence of brain tumors among patients with systemic malignancies in the United States. We intended to use the diagnosis of primary brain glioma as the end point of the study. However, this is not possible with the SEER program, so we chose a diagnosis of primary malignant brain tumor instead. In this cohort, 93.9% of the subsequent primary malignant brain tumors were found to be gliomas. We also found that 68.6% of all brain tumors in this cohort were glioblastomas according to ICD-O-3. This result is consistent with a previous report that most secondary glioma is high-grade [5, 13]. To the best of our knowledge, this is the largest population-based analysis of subsequent primary malignant brain tumors to date, and the results provide a better understanding of such situation, especially secondary brain gliomas.

Based on the results shown in Table 1, we found that only 0.09% of all patients with primary cancers outside the brain developed primary malignant brain tumors, and the highest percentage among cancers was just 0.16%. Thus, the development of subsequent malignant brain tumors seems to be a sporadic event, as previously reported [4]. The median duration between the diagnosis of the first cancer and subsequent malignant brain tumor was 53 months. Perhaps because of the poor prognosis of patients with systemic cancer, few primary malignant brain tumors can be detected before the patient’s death. We also found that the SIRs differed most by race, cancer site, and cancer type. For example, patients with ALL and endocrine gland cancer had very higher SIRs. Therefore, we believe there might be a potential connection between systemic malignancies and primary malignant brain tumors. For the SIR results stratified by cancer site and cancer type, we listed the results with higher observed values. It should be noted that the SEER program data were collected by numerous workers, and the SIRs for cancers with lower observed values were more easily affected by potentially inaccurate data.

Glioma following breast cancer has been reported several times [4-8]. In our cohort, we found that 713 of 5212 patients developed primary malignant brain tumors following ductal and lobular neoplasms, and 776 of 5212

patients suffered from primary malignant brain tumors afterwards breast cancer. However, the SIR for patients with breast cancer or ductal and lobular neoplasms was lower than that for the general population. This association could be related to the favorable long-term survival of breast cancer patients, which contributes to the development of glioma [4, 8]. Primary brain glioma following ALL has been commonly reported [9-14]. Yamanaka et al conducted a systematic review to characterize the etiology of secondary glioma in ALL patients [13]. The researchers found 98 cases of glioma following ALL in the period between 1964 and 2014, and radiation therapy was administered in 92 cases. Brain radiation therapy, intrathecal and intravenous chemotherapy and genetic predisposition are believed to be causative factors responsible for subsequent central nervous system tumors in pediatric ALL, and the most important risk factors are believed to be brain radiation therapy and intrathecal chemotherapy [18-21, 13]. We identified 24 patients with glioma following ALL in our cohort, but radiation therapy was administered to only 5 patients. The ALL patients who did not receive radiation therapy also had a higher SIR, with an O/E value of 4.36, which was significantly higher than that of the general population. Chemotherapy was administered to 21 patients, but we could not confirm whether these patients had received intrathecal chemotherapy or intravenous chemotherapy. However, the SIR of ALL patients who did not receive chemotherapy was also significantly higher than that of the general population. In this study, we did not find any evidence to prove that radiation or chemotherapy caused increased the risk of developing subsequent malignant brain tumors in patients in the whole cohort or those with prostate cancer, breast cancer, ALL or melanoma of the skin. Therefore, we cannot conclude that radiation therapy and chemotherapy play key roles in the development of primary malignant brain tumors. We believe that it is more likely that genetic predisposition is the most important risk factor. Scarbrough et al also explored the association between melanoma and glioma risk and concluded that a common genetic predisposition may be responsible for the detected association [22].

We also found that patients with endocrine gland cancer had a significantly higher risk of developing primary malignant brain tumors than the general population. Hormone replacement therapy has been reported to be associated with an increased risk of glioma [23]. In addition, growth hormones have been reported to have autocrine or paracrine actions in the development and progression of glioma [24]. Thus, we cannot ignore the potential association between hormones and glioma. Wang et al analyzed the incidence of second primary malignancy in patients with malignant astrocytoma and found that patients with malignant astrocytoma had a significantly higher risk of developing thyroid cancer and leukemia [25]. Thus, it may be worthwhile to focus on the common genetic predisposition of patients with glioma and patients with thyroid cancer or ALL in the future.

There are several limitations of our report that must be considered. First, the prognosis varies greatly for patients with different pathological types of cancer and systemic malignancies. The median duration to the detection of subsequent primary malignant brain tumors was 53 months, and our analysis might have missed a potential relationship between primary malignant brain tumors and some tumors with a very poor prognosis. Second, we were unable to obtain some pertinent details of radiation therapy and chemotherapy, such as how many Grays were used and whether intrathecal chemotherapy was administered. Therefore, we could not explore the effect of radiation therapy and chemotherapy on the development of primary malignant brain tumors in depth. Third, among our cohort, a few patients had more than 2 primary tumors before the detection of subsequent malignant brain tumors, but we only collected and analyzed the data related to the first index tumor and the following brain tumor. This could also affect the comprehensiveness of our study. Despite these limitations, our study represents the most comprehensive retrospective analysis of subsequent primary malignant brain tumors to date. Our results can provide new information regarding the epidemiology of subsequent primary malignant brain tumors in the United States and provide directions for future studies exploring potential genetic associations between systemic malignancies and primary malignant brain tumors.

Conclusion

Our study provides a comprehensive analysis of the clinical data and SIRs of patients with primary malignant brain tumors following other systemic malignancies. Genetic relationships might play a key role in the origin of subsequent primary malignant brain tumors. Our data provide directions for future studies exploring potential hidden associations between systemic malignancies and primary malignant brain tumors.

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Conflicts of Interest: None.

Statement of Ethics
All the data were extracted from the SEER database. Because the data of the SEER database were available to the public, the ethics committee and informed consent were not necessary for this study.

Author Contributions
YBW drafted the manuscript. YBW, ZQW and CH acquired the data and conducted the analysis. YX, YQL, GZ and YBW designed the study. All authors critically revised the manuscript.

Data Availability Statement
All the data were obtained using the SEER*Stat 8.3.9 program extracted from the SEER database. They can be accessed from SEER (https://seer.cancer.gov/).

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Table 1 The number of patients studied and the number of patients with subsequent primary malignant brain tumors.

Sites	Persons with Event	Persons indexed	Percentage
all sites	5212	6,061,265	0.09%
Prostate	1,469	917,369	0.16%
Breast	776	1,112,058	0.07%
Melanoma of the Skin	587	419,253	0.14%
Urinary Bladder	238	229,544	0.10%
Kidney and Renal Pelvis	207	186,735	0.11%
Lung and Bronchus	178	592,935	0.03%
Corpus Uteri	156	187,403	0.08%
Thyroid	144	167,942	0.09%
NHL - Nodal	137	155,573	0.09%
Sigmoid Colon	105	116,004	0.09%
Miscellaneous	105	155,162	0.07%
NHL - Extranodal	90	78,527	0.11%
Rectum	86	128,344	0.07%
Chronic Lymphocytic Leukemia	78	60,122	0.13%
Cecum	69	83,298	0.08%
Ascending Colon	58	70,601	0.08%
Myeloma	56	78,659	0.07%
Ovary	40	82,901	0.05%
Small Intestine	31	24,488	0.13%
Soft Tissue including Heart	31	41,128	0.08%
Other Non-Epithelial Skin	31	21,946	0.14%
Tongue	28	42,803	0.07%
Larynx	27	45,748	0.06%
Rectosigmoid Junction	26	43,553	0.06%
Acute Lymphocytic Leukemia	24	23,297	0.10%
Vulva	23	38,949	0.06%
Descending Colon	22	23,114	0.10%
Others	390	933,809	0.04%

Table 2 Demographic and clinical characteristics of the patients with subsequent primary malignant brain tumors.

Variables	Numbers (%)	Observed	Expected	O/E	95% CI
Age at diagnosis of first malignant tumor (years)					
Mean±SD	63.49±0.341				
Median	65				
Age at diagnosis of secondary malignant brain tumor (years)					
Mean±SD	68.86±0.179				
Median	70				
Months between first cancer and secondary brain tumor					
Mean±SD	64.48±0.685				
Median	53				
Survival months after diagnosis of malignant brain tumor					
Mean±SD	14.15±0.341				
Median	6				
Sex					
Female	1956(37.5)	1,956	1,946.77	1	0.96-1.05
Male	3256(62.5)	3,256	3,069.14	**1.06#**	1.02-1.1
Race and origin recode					
Hispanic (All Races)	343(6.6)	343	432.72	**0.79#**	0.71-0.88
Non-Hispanic White	4376 (84.0)	4,376	4,174.43	**1.05#**	1.02-1.08
Non-Hispanic Black	297(5.7)	297	260.5	**1.14#**	1.01-1.28
Non-Hispanic Asian or Pacific Islander	179(3.4)	179	140.37	**1.28#**	1.1-1.48
Non-Hispanic American Indian/Alaska Native	17(0.3)	17	7.9	**2.15#**	1.25-3.45

 # means P < 0.05

Table 3 The SIRs of patients stratified by histology findings.

Histology record-broad groups	Observed	Expected	O/E	95% CI
8140-8389: adenomas and adenocarcinomas	2536	2,427.74	**1.04#**	1-1.09
8500-8549: ductal and lobular neoplasms	713	810.21	**0.88#**	0.82-0.95
8720-8799: nevi and melanomas	593	451.13	**1.31#**	1.21-1.42
8120-8139: transitional cell papillomas and carcinomas	255	268.81	0.95	0.84-1.07
8050-8089: squamous cell neoplasms	197	280.69	**0.7#**	0.61-0.81
9670-9699: nhl - mature b -cell lymphomas	173	148.55	1.16	1-1.35
9820-9839: lymphoid leukemias (C42.1)	101	72.32	**1.4#**	1.14-1.7
8440-8499: cystic, mucinous and serous neoplasms	96	101.45	0.95	0.77-1.16
8010-8049: epithelial neoplasms, NOS	78	87.71	0.89	0.7-1.11
9730-9739: plasma cell tumors	56	44.24	1.27	0.96-1.64
9950-9969: chronic myeloproliferative disorders (C42.1)	49	32.54	**1.51#**	1.11-1.99
8000-8009: unspecified neoplasms	29	24.63	1.18	0.79-1.69
9590-9599: malignant lymphomas, NOS or diffuse	29	21.05	1.38	0.92-1.98
9980-9989: myelodysplastic syndrome	29	27.69	1.05	0.7-1.5
8550-8559: acinar cell neoplasms	25	23.46	1.07	0.69-1.57

 # means P < 0.05

Table 4 The SIRs of patients stratified by cancer site.

Site	Observed	Expected	O/E	95% CI
Prostate	1,469	1,418.71	1.04	0.98-1.09
Breast	776	878.65	**0.88#**	0.82-0.95
Melanoma of the Skin	587	442.05	**1.33#**	1.22-1.44
Urinary Bladder	238	256.76	0.93	0.81-1.05
Kidney and Renal Pelvis	207	149.89	**1.38#**	1.2-1.58
Lung and Bronchus	178	199.04	0.89	0.77-1.04
Corpus Uteri	156	138.01	1.13	0.96-1.32
Thyroid	144	102.59	**1.4#**	1.18-1.65
NHL - Nodal	137	124.38	1.1	0.92-1.3
Sigmoid Colon	105	108.72	0.97	0.79-1.17
Miscellaneous	105	86.72	1.21	0.99-1.47
NHL - Extranodal	90	62.98	**1.43#**	1.15-1.76
Rectum	86	104.87	0.82	0.66-1.01
Chronic Lymphocytic Leukemia	78	63.64	1.23	0.97-1.53
Cecum	69	71.74	0.96	0.75-1.22
Ascending Colon	58	62.45	0.93	0.71-1.2
Myeloma	56	44.06	1.27	0.96-1.65
Ovary	40	37.8	1.06	0.76-1.44
Small Intestine	31	17.31	**1.79#**	1.22-2.54
Soft Tissue including Heart	31	24.17	1.28	0.87-1.82
Other Non-Epithelial Skin	31	19.7	**1.57#**	1.07-2.23
Tongue	28	31.64	0.88	0.59-1.28
Larynx	27	41.02	**0.66#**	0.43-0.96
Rectosigmoid Junction	26	38.54	**0.67#**	0.44-0.99
Acute Lymphocytic Leukemia	24	5.14	**4.67#**	2.99-6.95

 # means P < 0.05

Table 5 The effect of chemotherapy and radiation therapy on the development of primary malignant brain tumors.

Site and treatment		Observed	Expected	O/E	95% CI
All sites					
Chemotherapy record	yes	901	904.73	1	0.93-1.06
	none/unknown	4,311	4,111.19	**1.05#**	1.02-1.08
Radiation record	yes	1,419	1,460.83	0.97	0.92-1.02
	none/unknown	3,793	3,555.08	**1.07#**	1.03-1.1
Prostate		1,469	1,418.71	1.04	0.98-1.09
Chemotherapy record	yes	11	6.48	1.7	0.85-3.04
	none/unknown	1,458	1,412.23	1.03	0.98-1.09
Radiation record	yes	565	556.12	1.02	0.93-1.1
	none/unknown	904	862.59	1.05	0.98-1.12
Breast		776	878.65	**0.88#**	0.82-0.95
Chemotherapy record	yes	232	245.95	0.94	0.83-1.07
	none/unknown	544	632.7	**0.86#**	0.79-0.94
Radiation record	yes	379	446.47	**0.85#**	0.77-0.94
	none/unknown	397	432.18	0.92	0.83-1.01
Melanoma of the Skin		587	442.05	**1.33#**	1.22-1.44
Chemotherapy record	yes	3	2.19	1.37	0.28-4
	none/unknown	584	439.86	**1.33#**	1.22-1.44
Radiation record	yes	7	2.57	**2.73#**	1.1-5.62
	none/unknown	580	439.48	**1.32#**	1.21-1.43
Acute Lymphocytic Leukemia		24	5.14	**4.67#**	2.99-6.95
Chemotherapy record	yes	21	4.87	**4.31#**	2.67-6.59
	none/unknown	3	0.27	**11.3#**	2.33-33.02
Radiation record	yes	5	0.78	**6.42#**	2.08-14.99
	none/unknown	19	4.36	**4.36#**	2.62-6.81

 # means P < 0.05

Table 6 Pathology data of the subsequent primary malignant brain tumors.

Histology recode according to ICD-O-3	Number	Percentage()
9440/3: Glioblastoma, NOS	3563	68.4
9401/3: Astrocytoma, anaplastic	292	5.6
8000/3: Neoplasm, malignant	279	5.4
9380/3: Glioma, malignant	278	5.3
9400/3: Astrocytoma, NOS	233	4.5
9450/3: Oligodendroglioma, NOS	107	2.1
9442/3: Gliosarcoma	82	1.6
9451/3: Oligodendroglioma, anaplastic	64	1.2
9382/3: Mixed glioma	59	1.1
9391/3: Ependymoma, NOS	41	0.8
9420/3: Fibrillary astrocytoma	41	0.8
9421/3: Pilocytic astrocytoma, malignant	34	0.7
9441/3: Giant cell glioblastoma	30	0.6
9411/3: Gemistocytic astrocytoma	20	0.4
9473/3: Primitive neuroectodermal tumor	12	0.2
Others	77	1.5