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Original Article

Is High Altitude an Emergent Occupational Hazard for Primary Malignant Brain Tumors in Young Adults? A Hypothesis

Abstract

Introduction: Brain cancer accounts for approximately 1.4% of all cancers and 2.3% of all cancer-related deaths. Although relatively rare, the associated morbidity and mortality affecting young- and middle-aged individuals has a major bearing on the death-adjusted life years compared to other malignancies. Over the years, we have observed an increase in the incidence of primary malignant brain tumors (PMBTs) in young adults. This observational analysis is to study the prevalence and pattern of brain tumors in young population and find out any occupational correlation. **Materials and Methods:** The data were obtained from our tertiary care cancer institute's malignant diseases treatment center registry from January 2008 to January 2018. A total of 416 cases of PMBT were included in this study. **Results:** Our analysis suggested an overall male predominance with most PMBTs occurring at ages of 20–49 years. The glial tumors constituted 94.3% while other histology identified were gliosarcoma (1) gliomatosis cerebri (1), hemangiopericytoma (3), and pineal tumors (3). In our institute, PMBT constituted 1% of all cancers while 2/416 patients had secondary glioblastoma multiforme with 40% showing positivity for O-6-methylguanine-DNA-methyltransferase promoter methylation. **Conclusions:** Most patients belonged to a very young age group without any significant family history. A probable hypothesis could be excessive cosmic radiation exposure to persons staying at high altitude areas due to occupational exigencies for which in-depth case–control epidemiological studies are required to reach any conclusion.

Keywords: *Cosmic radiation, epidemiology, high altitude, primary malignant brain tumor*

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Introduction

Brain tumors are a mixed group of neoplasms varying from benign to malignant which originates from the intracranial tissues and meninges. The most common malignant neoplasms in the brain are metastatic lesions while primary malignant brain tumors (PMBTs) are relatively uncommon. Gliomas account for >70% of all brain tumors and of these, glioblastoma multiforme (GBM WHO Grade IV) is the most frequent and malignant histologic type.[1] There is a tendency toward a higher incidence of gliomas in developed, industrialized countries. Some reports indicate that Caucasians have a higher incidence than African or Asian populations. The development of intracranial malignancy is also associated with several hereditary diseases such as Neurofibromatosis Type-1 and Type-2, but the prevalence of these syndromes is very low. Many environmental, occupational, and dietary factors have been reported to be associated with an elevated risk of central nervous system (CNS) tumors. Farmers and petrochemical workers have been shown to have a higher incidence of PMBTs, but the only factor unequivocally associated with an increased risk is therapeutic X-ray-irradiation.[1] In particular, children treated with X-ray-irradiation for acute lymphoblastic leukemia show a significantly elevated risk of developing gliomas and primitive neuroectodermal tumors, often within 10 years after exposure.[2]

Many analyses have examined the incidence rate of gliomas to assess whether rates are increasing. The results of these have generally shown the incidence of glioma overall and glioma subtypes to be fairly stable over the time periods assessed.[3-6] An examination of the annual age-adjusted incidence in Nordic countries between 1979 and 2008 found no clear trend in glioma incidence rates during this period although there was a slight increase in brain tumor incidence rates overall. Various Indian

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studies have quoted that there has been a rising trend in the intracranial neoplasms in both males and females in Indian population.[7] After a detailed retrospective analysis over the years, we have also observed a relative increase in the incidence of PMBTs in our younger population. There have been various studies world over to find out the correlation between PMBT and various etiological factors such as ionizing radiation. In our study, subset analysis for the possible etiology for high prevalence in young population has not been done; however, a probable hypothesis for increase in the incidence of PMBTs in the young people staying at high altitude areas for a definite duration due to occupational exigencies could be continuous exposure to cosmic radiation at high altitudes. Apart from the possible etiological factors, we have also tried to find out various other epidemiological parameters such as age, gender distribution, topography, and histopathological distribution of PMBTs in the young population.

Materials and Methods

The data on PMBTs were obtained from the database of our tertiary cancer care hospital's malignant diseases treatment center (MDTC) registry. A total of 416 cases of PMBTs were identified for the present analysis which included young men and women who reported at our institute. In this study, we have excluded the data of benign brain tumors, metastatic lesions, spinal cord tumors, meningeal tumors (excluding mesenchymal tumors), lymphomas, and tumors of sellar region.

While handling the data about patient particulars and their disease characteristics, utmost confidentiality of information was maintained. The data utilized for this study covers the period from January 2008 to January 2018, with topography of PMBTs identified by coding according to the International Statistical Classification of Diseases –10 (C71.0–C71.9) and histopathological type of PMBTs was identified as per the WHO classification of tumors of the CNS, 2007.[2]

Results

Overall 39,437 cases of various malignancies that were registered by hospital MDTC registry over this duration and a total of 416 cases of PMBTs fulfilling the criteria of our study were identified. The chronological distribution of patients reported at our institute from the afore-mentioned study period has been shown in Table 1. Our analysis suggested an overall male preponderance with males constituting 91.83% (382/416) and females 8.17% (34/416). The incidence of PMBTs was observed to be highest in 30–39 years of the age group in males (116/382) as well as females (7/34) [Table 2]. The age of the patients ranged from 22 months to 78 years the median age of males was 39.44 years, and for females, it was 41.02 years. Table 3 shows the distribution of patients according to their gender and age in relation to altitude. 183/416 (43.99%) of young males had a history of living at high altitude at some point of time due to occupational exigencies. Since no females were staying at these altitudes over varied duration as these stations are not family stations, hence this relation cannot be demonstrated in their dependents and females.

Table 1: Year wise chronological distribution of total primary malignant brain tumors s reported from January 2008 to January 2018

Year	Total PMBTs reported (*n*)
2008	44
2009	25
2010	23
2011	54
2012	53
2013	33
2014	39
2015	19
2016	56
2017	70
Total	416

PMBT – Primary malignant brain tumors

Table 2: Distribution of total primary malignant brain tumors by age group and gender from January 2008 to January 2018

Age group (years)	Gender	
	Males	Females
0-4	9	0
5-9	6	2
10-14	3	2
15-19	2	0
20-24	21	3
25-29	45	2
30-34	54	3
35-39	62	4
40-44	49	3
45-49	36	1
50-54	27	3
55-59	21	5
≥60	47	6
Total	382	34

The most common anatomic sites involved by PMBT were overlapping lesions, i.e., lesion involving two or more contiguous sites of brain (149/416, 35.81%) followed by frontal lobe (116/416, 27.88%). The least common sites were occipital lobe and pineal region with both amounting to 0.8% and cerebellum 1.08% of cases as shown in Table 4. As illustrated in Table 5, most of the PMBTs were found to be of glial origin (94.3%). Further subset analysis for various histopathology of PMBTs show that most often encountered histological subtypes were GBM (165/416, 39.66%) [Figure 1], diffuse astrocytoma (112/416, 26.92%) [Figure 2], anaplastic astrocytoma (39/416, 9.30%), oligodendroglial

Table 3: Distribution of total primary malignant brain tumors by age group and gender from January 2008 to January 2018 occurring at high altitudes

Age group (years)	PMBTs reported (*n*) in males at high altitude	PMBTs reported (*n*) in females at high altitude (no females were staying at high altitude areas)
0-4	-	-
5-9	-	-
10-14	-	-
15-19	-	-
20-24	16	0
25-29	27	0
30-34	48	0
35-39	38	0
40-44	30	0
45-49	19	0
50-54	5	0
55-59	-	-
≥60	-	-
Total	183	00

PMBT – Primary malignant brain tumors

Table 4: Topographical distribution according to anatomic sites

Anatomic sites	Percentage
Frontal lobe	27.88
Temporal lobe	16.04
Parietal lobe	9.06
Occipital lobe	0.8
Cerebral ventricle	1.0
Cerebellum	1.08
Brain stem	8.25
Overlapping lesions	35.81
Pineal region	0.8

tumors (22/416, 5.28%), oligoastrocytic tumors (22/416, 5.28%), ependymal tumors (21/416, 5.04%), and embryonal tumors Medulloblastoma (13/416 3.12%) while very rare histological subtypes reported were Gliosarcoma (1/416), gliomatosis cerebri (1/416), central neurocytoma (1/416), hemangiopericytoma (3/416) [Figure 3], and tumors of pineal region (4/416) [Figure 4]. Two patients developed secondary GBM from Grade II astrocytoma over a period of 4–5 years. About 40% were positive for promoter methylation (O-6-methylguanine-DNA-methyltransferase [MGMT]). In 183 patients who had a history of exposure to high altitude areas also glial tumors dominated. 92/183 patients had GBM while 59/183 patients had diffuse astrocytoma as shown in Table 6. On subset analysis of patients posted at high altitude, we found that maximum number (48/183) of patients belonged to 30–34 years of age group as shown in Table 7. Table 8 shows the distribution of patients according to altitude and duration of stay. We did not find any difference in the distribution of patients according to altitude. At all altitudes, glial tumors were the most common.

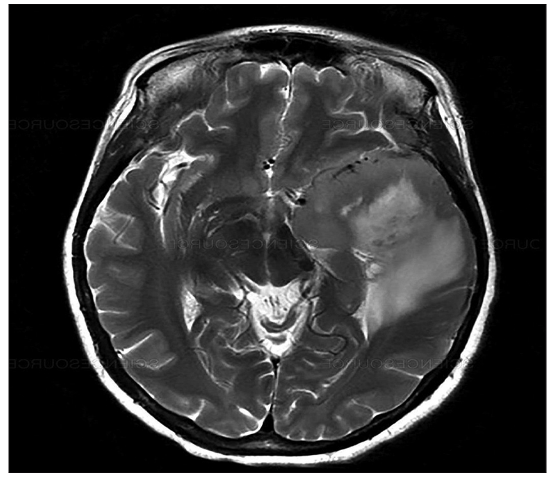

Figure 1: Magnetic resonance imaging of glioblastoma multiforme

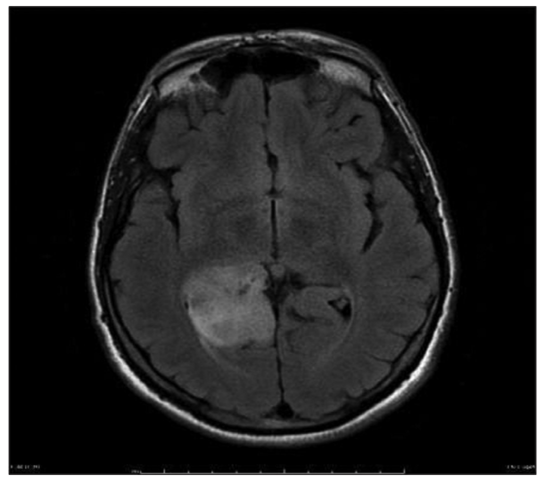

Figure 2: Magnetic resonance imaging of diffuse astrocytoma Grade II

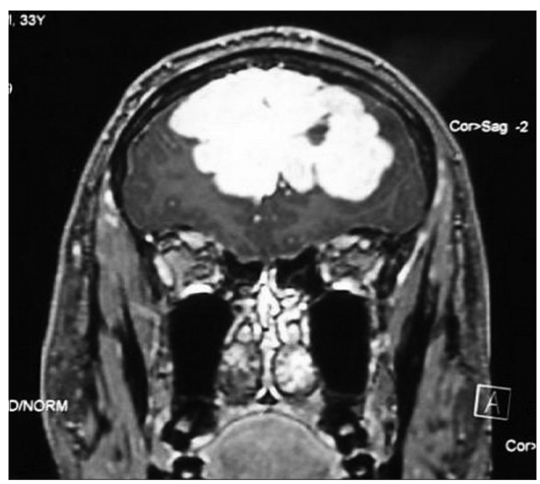

Figure 3: Magnetic resonance imaging of hemangiopericytoma

Discussion

Brain tumors although are not frequent can lead to significant morbidity and mortality in view of proximity to vital centers. Review of various articles denotes prevalence of PMBTs to be around 1%–2% of all adult cancers[8,9]

Table 5: Distribution of total primary malignant brain tumors as per their histological patterns reported from January 2008 to January 2018

Histological pattern	Distribution (*n*)
Neuroepithelial tumors	
A. Astrocytic tumors	
a. Pilocytic astrocytoma	1
b. Diffuse astrocytoma	112
c. Anaplastic astrocytoma	39
d. Glial tumors	
GBM	165
Gliosarcoma	1
Gliomatosis cerebri	1
Oligodendroglial tumors	
a. Oligodendroglioma	18
b. Anaplastic oligodendroglioma	4
Oligoastrocytic tumors	
a. Oligoastrocytoma	15
b. Anaplastic oligoastrocytoma	7
Ependymal tumors	
a. Myxopapillary ependymoma	1
b. Ependymoma	11
c. Anaplastic ependymoma	9
Neuronal and mixed neuronal glial tumors	
a. Anaplastic ganglioglioma	7
b. Central neurocytoma	1
Tumors of pineal region	
a. Pineocytoma	1
b. Pineoblastoma	2
c. Pineal papillary tumor	1
Embryonal tumors	
a. Medulloblastoma	13
Mesenchymal tumors: Hemangiopericytoma	3
Germ cell tumors: Germinoma	4

GBM – Glioblastoma multiforme

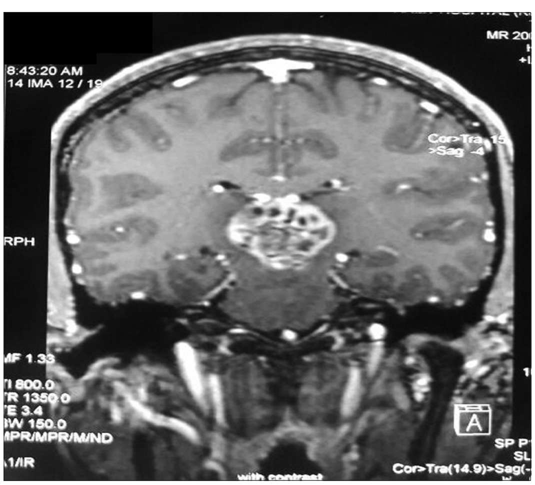

Figure 4: Magnetic resonance imaging of pineal tumor

Table 6: Distribution of primary malignant brain tumors as per their histological patterns occurring in high altitude areas

Histological pattern	Distribution (*n*)
Neuroepithelial tumors	
A. Astrocytic tumors	
a. Pilocytic astrocytoma	0
b. Diffuse astrocytoma	59
c. Anaplastic astrocytoma	5
d. Glioblastoma	
GBM	92
Gliosarcoma	0
Gliomatosis cerebri	0
B. Oligodendroglial tumors	
a. Oligodendroglioma	14
b. Anaplastic oligodendroglioma	1
C. Oligoastrocytic tumors	
a. Oligoastrocytoma	7
b. Anaplastic oligoastrocytoma	2
D. Ependymal tumors	
a. Myxopapillary ependymoma	0
b. Ependymoma	0
c. Anaplastic ependymoma	0
E. Neuronal and mixed neuronal glial tumors	
a. Anaplastic ganglioglima	0
b. Central Neurocytoma	0
F. Tumors of pineal region	
a. Pineocytoma	0
b. Pineoblastoma	1
c. Pineal papillary tumor	0
Embryonal tumors	
a. Medulloblastoma	0
Mesenchymal tumors: Hemangiopericytoma	2
Germ cell tumors: Germinoma	0

and incidence of brain tumor are reported to be around 3.9/100,000 in males while 2.4/100,000 in females.[5] The prevalence of PMBTs in our study was observed to be around 1.05% (416/39,437) of all cancers reported which is nearly similar with the world literature. An estimated 79,270 new cases of primary malignant and nonmalignant brain tumors are expected to be diagnosed in the United States in the US in 2017.[10] The US incidence rate for primary brain and nervous system tumors in adults aged 20 years or older is estimated to be 4.67–5.73/100,000 persons.[11]

Our analysis suggested a male preponderance in overall incidence rates in all the age groups which is also in agreement with several other studies reported from various parts of the world. In a study by Yole BB in five Indian cancer registries including Mumbai, Delhi, Bengaluru, Chennai, and Bhopal also found a greater incidence of malignant brain tumors in males while benign tumors such as meningiomas were more common in females.[7] Out of 416 cases of PMBTs, 75 cases are on regular follow-up with our institute. We have observed only seven cases had a recurrence in due course of their illness and were offered optimum management according to the standard

Table 7: Distribution of total primary malignant brain tumors s as per their histological patterns by age group from January 2008 to January 2018 at high altitude

Age group (years)	Histological pattern	Distribution (*n*)
20-24	Diffuse astrocytoma	11
	Oligodendroglioma	3
	Oligoastrocytoma	2
25-29	Diffuse astrocytoma	21
	Oligodendroglioma	4
	Oligoastrocytoma	1
	Hemangiopericytoma	1
30-34	Diffuse astrocytoma	8
	Anaplastic astrocytoma	1
	Oligodendroglioma	2
	Oligoastrocytoma	2
	GBM	34
	Hemangiopericytoma	1
35-39	Diffuse astrocytoma	7
	Anaplastic astrocytoma	4
	Oligodendroglioma	1
	Anaplastic oligodendroglioma	1
	Oligoastrocytoma	1
	Anaplastic oligoastrocytoma	1
	GBM	22
	Pineoblastoma	1
40-44	Diffuse astrocytoma	5
	Oligodendroglioma	2
	Oligoastrocytoma	1
	Anaplastic oligoastrocytoma	1
	GBM	21
45-49	Diffuse astrocytoma	6
	Oligodendroglioma	1
	GBM	12
50-54	Diffuse astrocytoma 1	1
	Oligodendroglioma 1	1
	GBM 3	3
55-59	-	-
≥60	-	-
Total		183

GBM – Glioblastoma multiforme

guidelines followed at our institute. Interesting finding in our study was that maximum patients were young males, belonging to an age group of 30–39 years. In a similar study by Dasgupta *et al.*,[12] they observed that the median age of glial tumors was seen to be at least a decade earlier than reported in the Western population, which could be partially explained by the lower life expectancy and a higher proportion of the younger population in India. Most common histopathology which we observed in our study was GBM which constituted almost 40% of all tumors which is in accordance with the worldwide literature. While in the similar study by Dasgupta *et al.*,[12] the most common tumor was astrocytoma (34.7%) followed by medulloblastoma and supratentorial peripheral neuroectodermal tumors (22.4%) and craniopharyngioma. In the USA, the incidence of anaplastic astrocytomas and GBM increase with age, peaking in the 75–84 age groups. There also gliomas are more common in men than women with the exception of pilocytic astrocytomas which occur at similar rates in men and women.[13]

The association between various occupational risk factors such as ionizing radiation, electromagnetic radiation need to be studied further. No comprehensive review of occupational risk factors for brain tumors has been published since 1986 but some issues discussed then are relevant even today. Since the report of Wertheimer and Leeper in 1979[14] of an increased incidence of brain tumors in children living in homes with an expected higher exposure to power-frequency electric and magnetic fields, exposure to electromagnetic fields have become an area of interest in the study of factors affecting brain tumor risk. Only few studies found clear indication of an association between radio frequency (RF) exposure and brain tumors. Out of this one was a cohort study by Kyrylenkos *et al.*,[15] and two were case–control studies.[16,17] Although brain tumors are rare and the population attributed to risk is low assuming 13% of adults being occupationally exposed to RF fields assuming a relative risk of 1.3, about 4% of brain tumors can be attributed to RF exposure, i.e., 2200 cases per year in US.[18] Last few decades universal increase in the use of mobile phones emitting continuous RF radiation (non-Ionizing radiation) has created a lot of scientific buzz in area of epidemiological research for the keens to prove or disprove whether there is any association between brain tumors and exposure to RF radiation of which most of the studies quoted no any association between the both.

A probable hypothesis for increase in the incidence of PMBTs in the young persons in our study could be excessive exposure to cosmic radiation at high altitudes as they are regularly been deployed at various hilly regions of Jammu-Kashmir and North East India due to service exigencies, with the maximum altitude deployment at around 6400 meters (≈21,000 feet). Average background radiation in an Individual at ground level is approximately 370 mRem/year which increases to 1 mRem/year with every 200 feet ascent in altitude. Although the cumulative exposure does not cross the average safety limit, a continuous low-dose exposure could be one of the reasons for the *de novo* changes.[19,20]

Various studies have found an association between low-dose radiation exposure and malignancies are going on at present world over. Except for therapeutic X-rays, no environmental or lifestyle factor has unequivocally been established as risk factor or brain tumors. During the last decades of the 20th century, some types of brain tumors show a steady increase of a few percentage per year, which might be some extent related to the introduction

Table 8: Distribution of total primary malignant brain tumors as per their histological patterns by duration from January 2008 to January 2018 at different stages of high altitude

Altitude (feet)	Duration of stay (years)	Duration wise PMBTs reported (*n*)	Altitude wise histological distribution (*n*)
High (8000-12,000)	<1	23	Diffuse astrocytoma (31)
	1-2	31	Anaplastic astrocytoma (2)
	>2	33	Oligodendroglioma (9)
			Oligoastrocytoma (5)
			GBM (37)
			Pineoblastoma (1)
			Hemangiopericytoma (2)
Very high (12,000-18,000)	<1	37	Diffuse astrocytoma (28)
	1-2	31	Anaplastic astrocytoma (3)
	>2	26	Oligodendroglioma (5)
			Anaplastic oligodendroglioma (1)
			Oligoastrocytoma (2)
			Anaplastic oligoastrocytoma (2)
			GBM (53)
Extremely high (>18,000)	<1	2	GBM (2)
	1-2		
	>2		

GBM – Glioblastoma multiforme; PMBT – Primary malignant brain tumors

of computed tomography and other high-resolution neuroimaging methods. In a study by Bondy *et al*.,[21] found that even the comparatively low doses (averaging 1.5 Gy) used to treat tinea capitis have been associated with relative risks of 18.10 and 3 for nerve sheath tumors, meningiomas, and gliomas, respectively. There was increased mortality among airline pilots was reported due to brain tumors possibly implicating exposure to cosmic radiation at high altitude in the same study.[21] Occupational risk findings from atomic energy and airline employees were equivocal. A small but statistically significant elevated risk of 1.2 for the occurrence of brain tumors in nuclear facility employees and nuclear materials production workers has been reported by Hodges *et al*.[22] While the similar study by Gundestrup and Storm,[23] noticed that although malignant melanoma and skin cancer were in excess in cockpit crew members, there was no increased risk of brain cancers in pilots.

A latest research by the National Aeronautics and Space Administration has revealed the results of a major new study into the effect of radiation at high altitude. Cosmic rays from the sun and space crash into molecules in the atmosphere, causing particle decay, and radiation which can be harmful to our health. The new study, using weather balloons, took some of the first radiation measurements of their kind at altitudes from 26,000 feet to over 120,000 feet above earth. While we are mostly safe from this radiation on the ground, pilots, and aircrew are exposed to the dangerous radiation as are astronauts. Earth's magnetosphere acts as a magnetic shield and blocks most of the radiation from reaching the planet. However, particles with enough energy can penetrate the magnetosphere and the atmosphere and can harm the people getting exposed.[24]

Apart from other factors, the concept of different genetic pathways leading to cancer has gained considerable acceptance as far as GBMs are concerned. Two main types have been described primary GBMs which mainly occur in elderly patients and are characterized by mutation in the phosphate and tensin homolog gene and epidermal growth factor receptor while secondary GBMs are a feature of the younger population and have P53 and platelet-derived growth factor mutations.[12] We had two cases of secondary GBMs, and both our cases were P53 positive. Promoter methylation (MGMT) was positive in 40% of our patients. The frequency of methylation status reported in the literature varies probably because each laboratory uses a slightly different technique. Various methods for quantitative measurement of MGMT methylation are being formulated to remove this discrepancy.

Conclusions

A major task which is still not accomplished over the years in descriptive brain tumor epidemiology is the explanation of gender and ethnic differences for gliomas and meningiomas. Further analytic studies of various factors such as diet, occupational factors, and potentially relevant polymorphism are likely to improve our understanding of this devastating disease. Since currently established or suggested risk factors do not account for most cases, novel concepts of neurocarcinogenesis are required before a comprehensive picture of the natural history and pathogenesis of brain tumors can be formed. Given these formidable challenge, future epidemiologic research on brain tumors is likely to be exciting. Although brain tumors are rare and nothing concrete has been found about its etiological factors, several predisposing risk factors postulated by various studies are white race, family history of brain cancer, certain chemical exposures, and exposure to ionizing radiation. In our study, we have postulated a hypothesis of increased incidence of PBMT in younger population due to exposure to cosmic radiation at high altitude which needs to be explored further.

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Conflicts of interest

There are no conflicts of interest.

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