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Early Preventive Strategies and CNS Meningioma — Is This Feasible? A Comprehensive Review of the Literature

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■ BACKGROUND: Meningiomas are one of the most common benign primary brain tumors; however, there is a paucity of literature on potential preventability. This comprehensive review aimed to explore the existing evidence for the potential risk factors that may contribute to meningioma development and to discuss early prevention strategies.

■ METHODS: Literature search was conducted via MEDLINE, Embase, Web of Science, and Cochrane Database to retrieve existing literature on various environmental exposures and lifestyle behaviors that are potential risk factors for the development of meningiomas.

■ RESULTS: Significant risk factors included exposure to ionizing radiation and certain environmental chemicals. Notably, this study also identified that cigarette smoking and obesity are associated with the development of meningiomas. To date, wireless phone usage, hormonal exposures, dietary factors, and traumatic brain injury remain inconclusive. Early prevention strategies should primarily be family-driven, community-based, and public health-endorsed strategies. Targeting unhealthy behaviors through healthcare organizations could execute a pivotal role in the maintenance of an optimum lifestyle, reducing the development of risk factors pertinent to meningiomas.

■ CONCLUSIONS: To our knowledge, this is the first study that offers a perspective on prevention of meningiomas. A causal relationship of risk factors in developing meningiomas cannot be directly established with the current evidence. We are aware of the limitations of the hypothesis, but we believe that this study will raise more awareness and our findings could potentially be endorsed by organizations promoting health across the globe. Further prospective and retrospective studies will shed more light on this topic and help establish a definitive relationship.

INTRODUCTION

Accounting for approximately 39% of all primary central nervous system (CNS) tumors and 54.5% of all nonmalignant tumors, meningiomas are the most common primary CNS neoplasm subtype, with their incidence increasing worldwide.[1,2] Meningiomas arise in the meninges from arachnoid cap cells, cellular components of the pia mater, arachnoid mater, and the septae and trabeculae of the subarachnoid space.[3] Disease severity of meningiomas is stratified according to the World Health Organization criteria, which includes grades I, II, and III, starting with benign histology and indolent behavior progressing to atypical or malignant tissue appearances and aggressive tissue infiltration. Classically, meningiomas are slow-growing benign tumors, with the most recent statistical report from the Central Brain Tumor Registry of the United States showing that 79.8% of meningiomas are grade I.[2] When symptomatic, patients present clinically with neurological deficits depending on location, such as focal or generalized seizure disorders, psychomotor symptoms, or behavioral disturbances.[4] A proportion of patients remain asymptomatic, and the diagnosis is incidental, especially with greater use of advanced imaging techniques in modern medicine; studies[5-7] have shown that approximately 1%—3% of the population harbor incidental meningiomas, with the prevalence higher in older patients.

Nevertheless, as meningiomas are relatively rare compared to other cancers, previous studies have encountered several obstacles, such as incomplete reporting, selection bias and detection bias, among others.[8] Therefore, it may not be surprising that little is known about established risk factors contributing to the natural history of meningioma tumorigenesis. Whether prevention of meningiomas is a possibility as a new route to explore or is there sufficient evidence to support this endeavor are questions to be answered.

Epidemiology

The incidence of meningiomas increases with age, with a dramatic increase after the age of 65 years.[2] The incidence rate in patients aged 20–34 years is 1.51/100,000; 17.82/100,000 in ages 55–64 years and 59.67/100,000 in ages 85+ years.[2] Benign and malignant meningiomas are 2.3 times and 1.1 more common in females compared to males, respectively.[2] While age and sex are nonmodifiable risk factors for meningiomas, it is even more crucial to focus on the modifiable risk factors and the preventive strategies that could make a substantial change in the progression of meningioma cases.

METHODS

A broad systematic search strategy was employed to capture the emerging risk factors in meningioma tumorigenesis. The key terms included combinations and synonyms of the following: "meningioma" and ("obesity," "overweight," "genetics," "hormone," "cigarette smoking," "head injury," "ionizing radiation," "mobile phone," or "diet"). We first conducted searches of the following online databases in February of 2023: Medline and EMBASE via Ovid, Web of Science Core Collection (Clarivate), and Cochrane Database of Systematic Reviews. All retrieved references were uploaded into RefWorks ProQuest online interface and duplicates automatically and manually, if required, were removed.

Studies were eligible for inclusion if they were 1) a meta-analysis and/or systematic review evaluating the association between the respective risk factor and the development of meningioma and 2) if there were no available studies to fulfil criteria 1), studies were included if randomized-control trials, cohort or case-control studies were available for the respective risk factor-meningioma association. Exclusion criteria were 1) studies published before the year 2000 and 2) studies written in non-English language. Two independent authors, D.S. and A.C., screened titles and abstracts for relevancy from the database search and excluded articles that were deemed insignificant. From the included studies, the authors then evaluated the full-text articles for further data extraction.

RESULTS AND DISCUSSION

Before exploring various risk factors that may contribute to the development of meningiomas, it is worth reviewing the different levels of prevention and the corresponding modes of intervention in the natural progression of any disease. Primordial prevention consists of actions to minimize future hazards to health and hence inhibits the establishment of factors that are known to increase the risk of disease. It addresses broad health determinants rather than preventing personal exposure to risk factors, which is the goal of primary prevention. Primary prevention seeks to prevent the onset of specific diseases via risk reduction by altering behaviors or exposures that can lead to disease or by enhancing resistance to the effects of exposure to a disease agent. These are collectively referred to as early prevention strategies.

Obesity

In 2016, the International Agency for Research on Cancer Handbook Working Group concluded that there is sufficient evidence to establish the association between a low body fat percentage and a decreased meningioma risk in humans.[9] These studies had satisfactory evidence and statistical power to suggest the benefits of a reduced body fat percentage and prevention of meningiomas, even after excluding the effects caused by chance, confounding variables, and bias.[10]

Several other authors have also investigated the relationship between excess body fat and meningiomas (Table 1). In a meta-analysis that was carried out in 2014, which included 6 studies, an overall relative risk of 1.12 (95% CI 0.98–1.28) for overweight and 1.45 (95% CI 1.26–1.67) for obesity was obtained. However, on subgroup analysis by gender, a significant association was detected for obese women only.[14] Another meta-analysis including 16 studies carried out by Sergentanis and colleagues showed that there is an overall relative risk of 1.27 (95% CI 1.13–1.43) among females and 1.58 (95% CI 1.22–2.04) among males associated with overweight status or obesity and meningioma risk.[13] In addition, a meta-analysis pooling 2982 meningioma patients from 12 eligible case-control and cohort studies also reported positive associations: the overall relative risk for the overweight group was 1.21 (95% CI 1.01–1.43), and for obesity, 1.54 (95% CI 1.32–1.79).[12] A more recent meta-analysis of studies with longer follow-up durations concluded that the association between obesity and meningioma in relative risk yields an overall value of 1.48 (95% CI, 1.30–1.69; P < 0.001). This dose-response meta-analysis also showed that for every 5 kg/m² increments in body mass index, the relative risk for meningiomas was 1.19 (1.14–1.25) (P < 0.001), whilst ruling out any evidence of publication bias and heterogeneity.[15]

Overall, given the growing body of evidence, body fat percentage plays a role in the development of meningiomas. Meningiomas join the growing cluster of cancers that are highly likely associated with obesity, including cancers of the oesophagus, pancreas, colorectum, endometrium, kidney, and breast in postmenopausal women.[16] Thus, there is potential for strategies that lower body fat composition for its primordial and primary preventions.

Indeed, the prevalence of obesity worldwide is growing. If recent research has revealed the likely association between meningioma risk and obesity, is it reasonable to assume that the increasing number of meningioma cases is due to obesity as opposed to less common risk factors, such as ionizing radiation (IR) or genetic predispositions? However, obesity is a result of a constellation of environmental factors and establishing a cause-effect relationship is complex. Obesity may not even be the primary causative modifiable factor for meningioma, as it is perhaps the result of other causative factors, such as unhealthy lifestyles, behaviors and sex hormones. An unhealthy lifestyle has been well documented in the literature[14] to be an essential risk factor for different types of cancer, thus, could these be addressed and potentially reverse the trajectory of meningiomas?

Although it is agreed that body mass index is a strong suspect in the development of meningioma, the aetiological mechanisms that drive the direct link between obesity and meningioma are unclear. Therefore, further research and larger studies could examine the possible parameters in depth.[8]

Table 1. Overview of the Meta-Analyses Examining the Association Between Excess Body Fat and Meningioma

Reference Study Topic	Study Design Participants	Results	Conclusions
Zhang et al., 2021[11] Relationship between BMI and meningiomas Normal weight BMI = 18.5—24.9 kg/m^2 Overweight BMI = 25.0 to 29.9 kg/m^2 Obesity BMI $\geq$ 30.0 kg/m^2	Meta-analysis Cohort = 9 Case-control = 7 N = 11,614 Control = 3,887,156	Obesity (5 case-control + 6 cohort) RR = 1.48 (95% CI: 1.30—1.69) $P < 0.001$ Moderate heterogeneity I^2 = 35.8% $P = 0.112$ Publication bias was not detected by Egger's test ($P = 0.339$) Overweight (4 case-control + 5 cohort) RR = 1.18 (95% CI: 1.07—1.31) $P = 0.001$ No heterogeneity I^2 = 0 $P = 0.454$ Publication bias was not detected by Egger's test ($P = 0.929$) Underweight (1 case-control + 2 cohort) RR = 1.03 (95% CI: 0.64—1.64) $P = 0.9$ No heterogeneity I^2 = 0 $P = 0.74$ Publication bias was not detected by Egger's test ($P = 0.632$) Dose-response analysis (4 case-control + 1 nested case-control + 6 cohort) No evidence of a nonlinear relationship with BMI and meningioma For every 5 mg/m^2 increment of BMI RR = 1.19 (1.14—1.25) $P < 0.001$ No heterogeneity I^2 = 0% $P = 0.529$ Publication bias was not detected by Egger's test ($P = 0.412$)	Excess weight (overweight and obesity) was associated with an increased risk of development of meningiomas. Linked to a 48% increase in the risk of meningiomas. No significant association between underweight and risk of meningiomas. For every 5 mg/m^2 increase in BMI, there was a 19% increment in the risk of meningioma.
Niedermaier et al., 2015[12] Association between overweight/ obesity and risk of meningiomas Normal weight BMI = 18.5—24.9 kg/m^2 Overweight BMI = 25.0 to 29.9 kg/m^2 Class I obesity BMI = 30.0—34.9 kg/m^2 Class I — III obesity BMI $\geq$ 30.0 kg/m^2 Class II — III obesity BMI $\geq$ 35.0 kg/m^2 Combined = both women and men	Meta-analysis Cohort = 6 Case-control = 3 N = 2982	Overweight versus normal weight (combined) RR = 1.21 (95% CI: 1.01—1.43) Class I obesity versus normal weight (combined) RR = 1.92 (95% CI: 1.41—2.60) Class II—III obesity versus. normal weight (combined) RR = 1.55 (95% CI: 1.05—2.30) Class I — III obesity versus. normal weight (combined) RR = 1.54 (95% CI: 1.32—1.79) Begg test and Egger test indicated no statistically significant evidence of publicationbias (all P values $\geq$ 0.16) No between-study heterogeneity for any of the analysis (all P values $\geq$ 0.44) Dose-response relation of BMI to meningioma is nonlinear (P linearity <0.001) Statistically significant positive association in men ($P = 0.02$) Statistically significant positive association in women ($P < 0.001$) Statistically significant positive association in combined ($P < 0.001$)	Moderate increase in risk of meningioma in overweight individuals compared to individuals with normal weight. Substantial increase in risk of meningioma in obese individuals compared to individuals with normal weight. Dose-response curve showed statistically significant positive association between BMI and meningioma in women, men and combined.

BMI: Body mass index

Table 1. Continued

Reference Study Topic	Study Design Participants	Results	Conclusions
Sergentanis et al., 2015[13] Association between being overweight/obese and risk of meningioma in women and men Normal weight BMI = 18.5—24.9 kg/m^2 Overweight BMI = 25.0 to 29.9 kg/m^2 Obesity BMI $\geq$ 30.0 kg/m^2	Meta-analysis Cohort = 6 Case-control = 5 N = 3, 296	Overweight versus normal weight in women Pooled RR = 1.11 (95% CI: 0.99—1.25) I^2 = 8.3% P = 0.366 Obesity versus normal weight in women Pooled RR = 1.48 (95% CI: 1.28—1.71) I^2 = 0.0% P = 0.546 Overweight versus normal weight in men Pooled RR = 1.39 (95% CI: 0.95—2.03) I^2 = 29.0% P = 0.238 Obesity in versus normal weight men Pooled RR = 1.78 (95% CI: 1.22—2.61) I^2 = 29.6% P = 0.224 Overweight and obese pooled together in women Pooled RR = 1.27 (95% CI: 1.13—1.43) I^2 = 35.7% P = 0.0.78 Overweight and obese pooled together in men Pooled RR = 1.58 (95% CI: 1.22—2.04) I^2 = 27.2% P = 0.202 Dose-response analysis between overweight/obesity status versus risk of meningioma in women BMI in increments of 5 kg/m^2 Exponentiated coefficient = 1.15 (95% CI: 1.03—1.28) P = 0.018	Overweight and obesity were significantly associated with the development of meningioma in women. Overweight and obesity were significantly associated with the development of meningioma in men.
Shao et al., 2014[14] Association between excess body weight and risk of meningioma Normal weight BMI = 18.5—24.9 kg/m^2 Overweight BMI = 25.0 to 29.9 kg/m^2 Obesity BMI $\geq$ 30.0 kg/m^2	Meta-analysis Cohort = 4 Case-control = 2 N = 1376 Control = 1,212,889	Obesity versus normal weight in women RR = 1.46 (95% CI: 1.26—1.69) I^2 = 0.0% P for heterogeneity 0.515 Obesity versus normal weight in men RR = 1.30 (95% CI: 0.64—2.62) I^2 = 0.0% P for heterogeneity 0.427 Obesity versus normal weight in combined RR = 1.45 (95% CI: 1.26—1.67) I^2 = 0.0% P for heterogeneity 0.550 Overweight versus normal weight in combined RR = 1.12 (95% CI: 0.98—1.28) I^2 = 0.0% P for heterogeneity 0.722	A statistically significant link between the risk of meningioma and obesity in women was observed. No statistically significant link between the risk of meningioma and obesity in men. An association between an increased risk of meningioma and obesity in the population was identified. No significant association between risk of meningioma and overweight.

BMI: Body mass index

Ionising Radiation

It is well established that exposure to IR significantly increases the risk of developing meningiomas, with studies quoting an increase of up to 10-fold.[17] Exposure to higher radiation doses corresponds to shorter latency periods, but exposure to lower doses also carries a considerable risk. Due to the physiological and latency period differences, studies[18-21] show that exposure to moderate-to-high IR (>0.5 Gy) during childhood is associated with a higher incidence of meningiomas later in life. In addition, at lower doses, 1 meta-analysis[22] revealed a positive dose-response relationship. If IR exposure occurs during adulthood, the latest systematic review[23] reported no association between IR and the risk of CNS tumors, including meningiomas. Further studies are essential to expand our understanding of IR and meningiomas.

Genetics

Over the last decade, several genetic biomarkers that characterise meningiomas have been identified.[24] Although these biomarkers may be used to predict tumor behavior, prognosis and clinical management, there are instances where they may also be applied in early detection, monitoring, or even, genetic counselling.

To date, the most significant genetic finding is the neurofibromatosis 2 (NF2) gene, a tumor suppressor gene, located on chromosome 22q12 that is mutated or deleted in approximately half of all sporadic meningioma cases.[25,26]

If the gene alteration is acquired as a germline mutation, it may lead to neurofibromatosis type II (NF2), an autosomal dominant familial syndrome in which approximately 50% of NF2 patients develop multiple, aggressive intracranial meningiomas[27] in their lifetime, with the onset of their first lesion typically occurring at an average of 30 years of age.[28] NF2 patients could receive regular medical check-ups and/or screenings, genetic testing for early detection and management, and genetic counselling based on individual risk factors with genetic profiles. Other familial syndromes of significance include Gorlin,[27] Cowden,[29] and Werner[30] syndromes.

In contrast, NF2 alterations may occur as somatic mutations, leading to sporadic tumors. Approximately, 40%−60% of sporadic meningioma cases are driven by non-NF2 mutations (Figure 1).[27] Other pertinent somatic non-NF2 mutations associated with the development of meningiomas are shown in Figure 1. In addition, the accumulation of chromosomal instabilities and cytogenetic aberrations are also associated with meningioma World Health Organization grade, aggressiveness, and recurrence shown in Figure 1.

However, limited genomic and epigenetic studies have been carried out to elucidate the genetic basis of meningioma development. Large-scale genome-wide association studies and high-throughput sequencing are needed to determine susceptibility to meningioma in patients at an earlier stage.[38]
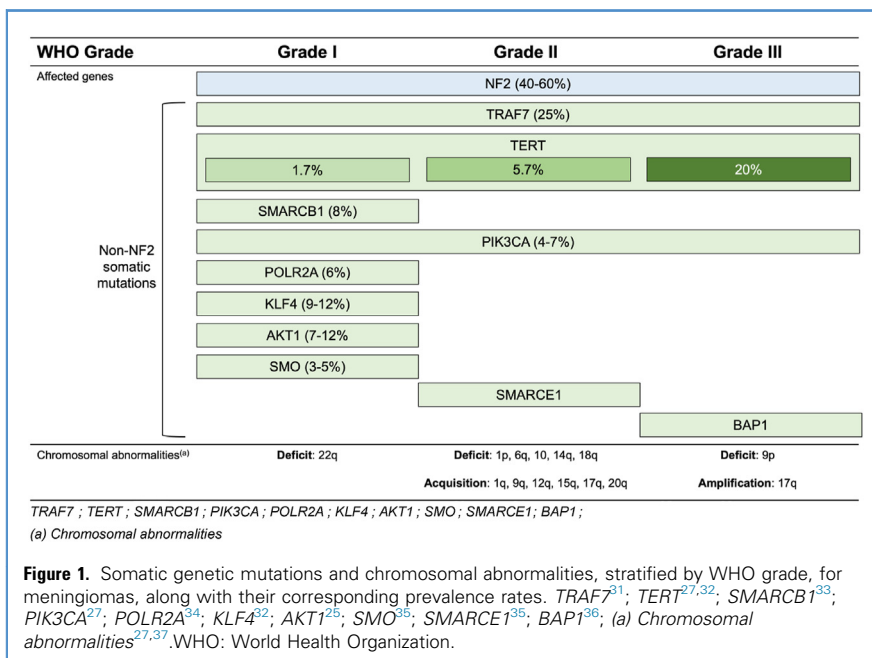
Hormonal Exposure

Considering the increased incidence in females and the substantial proportion of cases demonstrating somatostatin, progesterone, estrogen, and androgen receptors, it has been previously hypothesized that hormones play a role in meningioma development.[17,39-41]

Studies pertaining to meningioma risk in patients taking exogenous sex hormones have given discordant results. A recent meta-analysis suggested that the use of oral contraceptives is not related to the risk of meningioma.[42] Conversely, consistent evidence from observational studies found that menopausal hormone replacement therapy was associated with an increased risk of meningioma.[11] In addition, age of menarche, age at menopause, and age at first birth did not significantly contribute to the risk of developing meningioma, however postmenopausal status and parity were statistically significant.[43] Clarifying these associations through larger, prospective studies would help provide insights into the risk of meningiomas and their connection to sex hormones.

Wireless Phone Usage

A widely debated risk factor for meningioma is wireless phone usage. Wireless phones emit radiofrequency electromagnetic field signals, which may play a role in the tumorigenesis of meningiomas. To date, the published literature is heterogeneous without any definitive correlations. There is no consistent evidence of an increased risk of meningioma among mobile phone users as current observation periods are too short.[44,45] Of note, the most recent systematic review and meta-analysis suggested that wireless phone usage is associated with a decreased meningioma risk.[46] However, further high-

WHO Grade	Grade I	Grade II	Grade III
Affected genes			
	NF2 (40-60%)		
	TRAF7 (25%)		
	TERT		
	1.7%	5.7%	20%
	SMARCB1 (8%)		
	PIK3CA (4-7%)		
	POLR2A (6%)		
	KLF4 (9-12%)		
Non-NF2 somatic mutations	AKT1 (7-12%)		
	SMO (3-5%)		
		SMARCE1	
			BAP1
Chromosomal abnormalities[(a)]	Deficit: 22q	Deficit: 1p, 6q, 10, 14q, 18q	Deficit: 9p
		Acquisition: 1q, 9q, 12q, 15q, 17q, 20q	Amplification: 17q

TRAF7 ; TERT ; SMARCB1 ; PIK3CA ; POLR2A ; KLF4 ; AKT1 ; SMO ; SMARCE1 ; BAP1 ;
(a) Chromosomal abnormalities

Figure 1. Somatic genetic mutations and chromosomal abnormalities, stratified by WHO grade, for meningiomas, along with their corresponding prevalence rates. *TRAF7*[31]; *TERT*[27,32]; *SMARCB1*[33]; *PIK3CA*[27]; *POLR2A*[34]; *KLF4*[32]; *AKT1*[25]; *SMO*[35]; *SMARCE1*[35]; *BAP1*[36]; (a) Chromosomal abnormalities[27,37].WHO: World Health Organization.

Table 2. Overview of the Meta-Analyses Examining the Relationship Between Cigarette Smoking and Meningioma

Reference Study Topic	Study Design Participants	Results	Conclusions
Chao et al., 2021[47] Association between active cigarette smoking and the risk of developing meningioma in women, men and combined	Meta-analysis cohort = 2 Case-control = 10 N = 2255 control = 1,207,912	Women RR = 0.92 (95% CI: 0.73—1.16) Men RR = 1.42 (95% CI: 1.16—1.74) Combined, women and men RR = 1.09 (95% CI: 0.90—1.33)	In women, active smoking was not a significant risk factor for meningioma. In men, active smoking was a significant risk factor for meningioma. In the whole population, active cigarette smoking did not increase the risk of developing meningiomas.
Zhong et al., 2021[48] Association between smoking and risk of meningiomas in women	Meta-analysis cohort = 1 Case-control = 6 N = 2132 Control = 1,178,959	Ever versus never smoking Pooled OR = 0.83 (95% CI: 0.90—1.33) P for heterogeneity 0.085 USA studies (3 studies) Pooled OR 0.77 (95% CI: 0.68—0.87) P for heterogeneity, 0.362 Worldwide (non-USA) (4 studies) Pooled OR 0.99 (95% CI: 0.73—1.35) P for heterogeneity, 0.100 Current versus never smoking Pooled OR = 0.78 (95% CI: 0.66—0.93) P for heterogeneity 0.229 Past versus never smoking Pooled OR = 0.82 (95% CI: 0.71—0.94) P for heterogeneity 0.679	Ever, current, and past smoking were associated with a significantly reduced risk of meningioma in women. Note, according to subgroup analysis, a decreased risk of developing meningiomas in women ever smokers was observed in USA studies only.
Claus et al., 2012[49] Effect of gender on the association between cigarette smoking and risk of intracranial meningiomas	Meta-analysis Case-control = 7 N = 2614 Control = 1,179,686	Ever versus never smoking in women Pooled OR = 0.82 (95% CI: 0.68—0.98) Ever versus never smoking in men Pooled OR = 1.39 (95% CI: 1.08—1.79)	In terms of women, ever smokers were at significantly decreased risk of meningioma relative to never smokers. In terms of men, ever smokers were at significantly increased risk of meningioma relative to never smokers.
Fan et al., 2012[50] Relationship between cigarette smoking and the development of meningioma in men, women, and combined	Meta-analysis Cohort = 2 Case-control = 7 N = 1376 Control = 1,212,889	Ever versus never smoking combined (6 case-control + 2 cohort) Risk estimate = 0.95 (95% CI: 0.87—1.05) P for heterogeneity 0.177 Current versus never smoking combined (4 case-control) Risk estimate = 0.79 (95% CI: 0.50—1.25) P for heterogeneity 0.069 Past versus never smoking combined (3 case-control) Risk estimate = 0.84 (95% CI: 0.69—1.03) P for heterogeneity 0.177 Ever versus never smoking in women (4 case-control + 1 cohort) Risk estimate = 0.86 (95% CI: 0.65—1.13) P for heterogeneity 0.019 Ever versus never smoking in men (4 case-control) Risk estimate = 1.49 (95% CI: 1.06—2.09) P for heterogeneity 0.210	No significant association was seen for ever, current, and past smokers in the whole population. Ever smoking was associated with an increased risk of meningioma in men but not in women.

quality, robust studies are required to establish a definitive relationship.

Carcinogens

Cigarette Smoking. Our search strategy yielded a total of 4 meta-analyses that studied the association between tobacco smoking and the development of meningiomas (Table 2). Chao et al. concluded that tobacco smoking did not significantly increase the risk of developing meningiomas in the population.[47] However, in the subgroup analysis, the risk in males who smoked cigarettes was 42% higher compared to their controls, which is statistically significant. In contrast, smoking reduces the likelihood of meningioma development by 8% in females. Three other meta-analyses agreed with similar findings; ever,[48-50] current[48] and past[48] smoking were associated with a significantly reduced risk of meningioma in women. On the contrary, in terms of men, ever[49,50] smokers are at significantly increased risk of meningioma relative to never smokers.

DIETARY FACTORS

Inconsistent results have been widely observed when studies have investigated the relationship between meningiomas and diet, which includes the consumption of cured meat and fruits/vegetables. N-nitroso compounds have been hypothesized to play a critical role in the development of meningioma.[51] Furthermore, the International Agency for Research on Cancer has classified N-nitroso compounds as probable human carcinogens, as experimental research has demonstrated the formation of N-nitroso compound derivatives able to induce brain tumors in animals.[52] The primary source of dietary N-nitroso compounds is cured meat and precursors.[53]

One international case-control study observed no clear patterns of significant dietary associations between leafy green vegetables, yellow-orange vegetables, cured meat, noncured meat, fresh fish, eggs, grains, and citrus fruits with the aetiology of meningiomas.[54] In comparison to previous research, there was also an inconsistent association between cured meat and the risk of

meningioma.[54] A considerable number of studies have combined the histological subtypes of brain tumors to explore dietary risk factors, resulting in a heterogeneous case group.

KETOGENIC DIET

Emerging studies have proposed that a ketogenic diet could be a therapeutic option in primary brain tumors, as tumor cells lose the ability to convert from glucose-to ketone-dependent metabolism.[55] This has been suggested in case reports and cohort studies that investigated the antitumoral effects of a ketogenic diet in gliomas, however, the evidence remains unclear.[55-58] In addition, a correlation between serum glucose and meningioma risk has been suggested in several studies,[12,59-61] as reviewed by Selke and colleagues.[62] Based on this analysis, it can be argued that there is potential for the ketogenic diet to be used in primordial prevention and is worthy of future study to explore its application in meningiomas.

Occupation

Several studies have attempted to find an association between the role of occupational exposure and meningioma carcinogenesis; however, the findings have been inconsistent up to date. It is important to note that a larger proportion of studies have directed their attention on the association between occupational factors and the risk of all brain tumors or on the risk of glioma, therefore there is a lack of evidence in the meningioma subgroup. Although findings have been inconsistent, 1 case-control study, which examined lifetime work history from 197 cases of meningioma observed a significantly elevated risk of meningioma in individuals who worked as automobile body painters, designers and decorators, military occupations, industrial production supervisors, teachers, and managers.[63] In addition, in genetically susceptible individuals, there was a clear association between the risk of meningioma and lead exposure in individuals carrying the ALAD2 allele.[64] Bhatti and colleagues further provided evidence that lead exposure increases the risk of meningioma by inducing the production of reactive oxygen species and diminishing antioxidant proteins.[65]

Interestingly, a French prospective cohort (AGRICAN) investigated the associations between the incidence of meningioma and lifetime agricultural exposures to carbamate herbicides and fungicides over a period of 8 years (2005−2013).[66] For meningiomas, there was a statistically increased risk when exposed to the following carbamate herbicides: chlorpropham and/or propham and diallate. In terms of fungicide carbamates, everexposed individuals were at an increased risk of developing meningioma. Regarding fungicide, a significant association was observed with cuprobam exposure.[66]

Traumatic Brain Injury (TBI)

The incidence of TBI is much higher than the incidence of brain tumors and most individuals with TBI do not develop brain neoplasms. A recent systematic review demonstrated that no definite link can be established between the two entities.[67] Although there is a growing number of publications aiming to explore the relationship between the two, the quality of evidence is moderate-to-low since the majority are retrospective cohort, case-control studies, and case reports with a level of evidence of III, IV, and V respectively. Currently, no randomized or prospective comparative studies have been published. This is possibly due to multiple, intrinsic variables that control the post-TBI meningioma development causal relationship, therefore becoming unlikely to conduct studies with a higher quality of evidence. The limitations faced by all studies reviewed by Shah et al., were recall bias, selection bias, generalizability, and insufficient sample sizes. In addition, Shah et al. reported that the average time between head trauma and the diagnosis of brain tumors, including meningioma, had a latency period of 12.9 years ± 10.7. Noteworthy, the most common brain tumors that were reported were meningiomas, representing over half of all cases (24/45−53.3%). Overall, there is no statistical significance that could be drawn from current literature.

Potential Strategies for Effective Early Prevention of Meningiomas

From the modifiable risk factors associated with the development of meningiomas discussed, it is the question of

whether preventive strategies can be implemented within the population and how these preventive efforts can be maximized. Despite a lack of high-quality, robust clinical trials, the review authors propose the following discussion points regarding strategies for effective primordial and primary prevention (Figure 2).

Research has shown that perhaps the best stage for introducing early prevention strategies is in childhood, as implementing good behaviors in children is easier because of greater neuroplastic potential. According to Bronfenbrenner's ecological systems theory, a child's development adds up to the aggregation of genetic, biological, psychological, and environmental factors that are determined by the immediate environment, such as the family nucleus, and more peripheral environments, like schools and the wider community.[68] For instance, with regards to cigarette smoking, literature shows that ever smokers commence smoking before reaching young adulthood with a majority based on social influence.[69] Schools are also considered critical environments for preventing childhood obesity, as they offer the opportunity to provide healthy dietary patterns, nutritional education, and increased physical activity to children.[70]

Theories regarding biological processes also provide another rationale for early primordial intervention, with an emphasis particularly on obesity. It has been shown that the growth trajectory to obesity is initiated in early childhood,[71] where initial screening is recommended in children 6—12 years of age.[72] However, emerging evidence suggests that prenatal, early infancy and early childhood factors contribute to the surfacing of obesity in at-risk populations, and perhaps primordial efforts should start earlier. Fleming and colleagues have suggested that a multigenerational mechanism characterizes the aetiology of obesity. Ideally, strategies for all risk factors should aim to optimize conditions at all stages from preconception, in utero, early infancy, to school age in order to effectively mitigate the predisposition to unhealthy behaviours.[73-77] A meta-analysis assessed primordial prevention strategies in childhood obesity and favorable outcomes were identified in the child's growth trajectory when counselling regarding breastfeeding, complementary feeding, diet advice, physical activity, and sleep was provided to parents in a clinical setting and or through community visits.[78]

To be most successful, health promotion strategies perhaps ought to be targeted at the various levels that influence child development including 1) the individual, 2) family, 3) the community, and 4) the nation. At both individual and community levels, holistic approaches that aim to improve health education and literacy should empower children to make informed decisions and adopt healthy behaviors from an early stage.[79,80]

The prevention of unhealthy behaviors cannot merely be summed up by the implementation of a single intervention but instead requires a broader set of approaches[81] and a focus on complex systems.[82,83] According to Rutter and colleagues, the complex systems model of evidence is defined mainly by three sets of properties: emergence, feedback, and adaptation.[84] For a national primordial intervention to be effective, it must take into consideration all three properties and their intricate interactions. Further research is therefore necessary to decipher the complex mechanisms that co-ordinate the inception of unhealthy behaviors to ensure its effectiveness.

Limitations

Residual confounding may have impacted the results obtained from the studies reviewed, as cohort and case-control
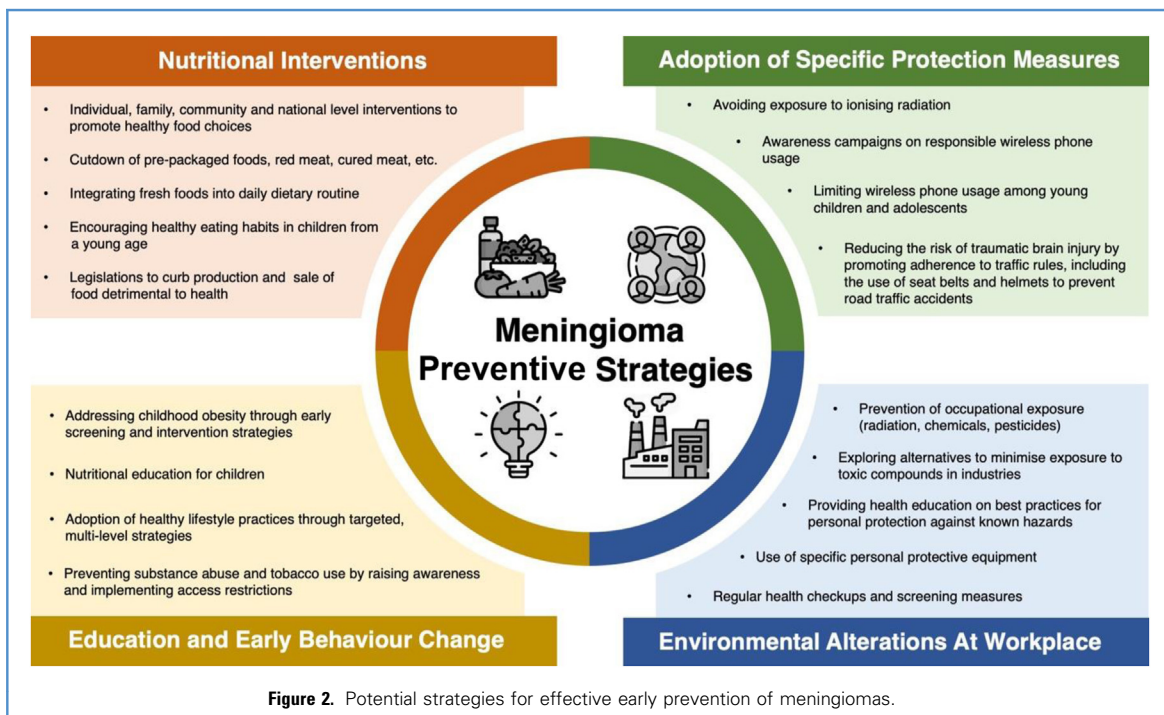

Figure 2. Potential strategies for effective early prevention of meningiomas.

studies are prone to bias with confounding variables that cannot be adjusted for. Moreover, a causal effect cannot be determined with certainty, particularly in case-control studies which represents a significant limitation.

Additionally, most of the studies included in this review were conducted in Western countries, making it difficult to generalize the findings to a wider population with potentially different socio-economic backgrounds or biological reserves. Thus, caution ought to be exercised when interpreting and validating these results and applying them to other settings.

CONCLUSION

Is prevention of meningioma possible at the primordial and primary levels? Our review has suggested that the evidence base for the role of early prevention in meningiomas remains limited. The causality of what we believe as the potential contributors remains highly debatable but nonetheless forms a basis for future epidemiological research. We believe that our study will bring awareness in this regard. Global health-promoting organizations and national health strategies could potentially focus on implementing change in current healthcare policies and actively promote healthy lifestyle promotion. There is sufficient evidence for the association of obesity, cigarette smoking, and ionizing radiation as risk factors for meningioma development, which may provide a rationale for future prospective studies investigating primordial and primary prevention. We believe that the focus on primordial and primary prevention of meningioma will remain a forerunner to explore this concept and address this issue and its feasibility for future generations.

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REFERENCES

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol. 2019;21(Suppl 5): vi-v100.

2. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. Neuro Oncol. 2021;23(12 Suppl 2):iii1-iii105.

3. Weller RO. Microscopic morphology and histology of the human meninges. Morphologie. 2005;89: 22-34.

4. Whittle IR, Smith C, Navoo P, Collie D. Meningiomas. Lancet. 2004;363:1535-1543.

5. Nakasu S, Hirano A, Shimura T, Llena JF. Incidental meningiomas in autopsy study. Surg Neurol. 1987;27:319-322.

6. Rausing A, Ybo W, Stenflo J. Intracranial meningioma–a population study of ten years. Acta Neurol Scand. 1970;46:102-110.

7. Helseth A. Incidence and survival of intracranial meningioma patients in Norway 1963-1992. Neuroepidemiology. 1997;16:53-59.

8. Rajaraman P. Hunting for the causes of meningioma–obesity is a suspect. Cancer Prev Res (Phila). 2011;4:1353-1355.

9. The International Agency for Research on Cancer. Absence of Excess Body Fatness. In: IARC Handbooks of Cancer Prevention. 16. France: International Agency for Research on Cancer: Lyon; 2019: 401-410.

10. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer–viewpoint of the IARC working group. N Engl J Med. 2016;375:794-798.

11. Zhang G, Chen J, Luo Y, et al. Menopausal hormone therapy and women's health: an umbrella review. PLoS Med. 2021;18:e1003731.

12. Niedermaier T, Behrens G, Schmid D, Schlecht I, Fischer B, Leitzmann MF. Body mass index, physical activity, and risk of adult meningioma and glioma: a meta-analysis. Neurology. 2015;85: 1342-1350.

13. Sergentanis TN, Tsivgoulis G, Perlepe C, et al. Obesity and risk for brain/CNS tumors, gliomas and meningiomas: a meta-analysis. PLoS One. 2015;10:e0136974. https://doi.org/10.1371/journal.pone.0136974.

14. Shao C, Bai L, Qi Z, Hui G, Wang Z. Overweight, Obesity and Meningioma Risk: A Meta- Analysis. PLoS One. 2014;9:e90167.

15. Zhang D, Chen J, Wang J, et al. Body mass index and risk of brain tumors: a systematic review and dose-response meta-analysis. Eur J Clin Nutr. 2016; 70:757-765.

16. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371: 569-578.

17. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. J Neuro Oncol. 2010; 99:307-314.

18. Braganza MZ, Kitahara CM, Berrington de González A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. Neuro Oncol. 2012;14:1316-1324.

19. Ron E, Modan B, Boice JDJ, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med. 1988;319:1033-1039.

20. Taylor AJ, Little MP, Winter DL, et al. Population-based risks of CNS tumors in survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol. 2010;28:5287-5293.

21. Yeh H, Matanoski GM, Wang N, Sandler DP, Comstock GW. Cancer incidence after childhood nasopharyngeal radium irradiation: a follow-up study in Washington county, Maryland. Am J Epidemiol. 2001;153:749-756.

22. Abalo KD, Rage E, Leuraud K, et al. Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis. Pediatr Radiol. 2021;51:45-56.

23. Lopes J, Baudin C, Leuraud K, Klokov D, Bernier M. Ionizing radiation exposure during adulthood and risk of developing central nervous system tumors: systematic review and meta-analysis. Sci Rep. 2022;12:16209.

24. Proctor DT, Ramachandran S, Lama S, Sutherland GR. Towards molecular classification of meningioma: evolving treatment and diagnostic paradigms. World Neurosurg. 2018;119: 366-373.

25. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013;339:1077-1080.

26. Goutagny S, Kalamarides M. Meningiomas and neurofibromatosis. J Neuro Oncol. 2010;99:341-347.

27. Lee YS, Lee YS. Molecular characteristics of meningiomas. J Pathol Transl Med. 2020;54:45-63.

28. Smith MJ. Germline and somatic mutations in meningiomas. Cancer Genet. 2015;208:107-114.

29. Kerr K, Qualmann K, Esquenazi Y, Hagan J, Kim DH. Familial syndromes involving meningiomas provide mechanistic insight into sporadic disease. Neurosurgery. 2018;83:1107-1118.

30. Lauper JM, Krause A, Vaughan TL, Monnat RJJ. Spectrum and risk of neoplasia in Werner syndrome: a systematic review. PLoS One. 2013;8: e59709.

31. Zotti T, Scudiero I, Vito P, Stilo R. The emerging role of TRAF7 in tumor development. J Cell Physiol. 2017;232:1233-1238.

32. Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: novel therapeutic opportunities. Nat Rev Neurol. 2018;14:106-115.

33. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet. 2013;45:285-289.

34. Clark VE, Harmancı AS, Bai H, et al. Recurrent somatic mutations in POLR2A define a distinct subset of meningiomas. *Nat Genet.* 2016;48: 1253-1259.

35. Pereira BJA, Oba-Shinjo SM, de Almeida AN, Marie SKN. Molecular alterations in meningiomas: literature review. *Clin Neurol Neurosurg.* 2019; 176:89-96.

36. Shankar GM, Abedalthagafi M, Vaubel RA, et al. Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. *Neuro Oncol.* 2017; 19:535-545.

37. Karsy M, Azab MA, Abou-Al-Shaar H, et al. Clinical potential of meningioma genomic insights: a practical review for neurosurgeons. *Neurosurg Focus.* 2018;44:E10.

38. De La Garza-Ramos R, Flores-Rodríguez JV, Martínez-Gutiérrez JC, Ruiz-Valls A, Caro-Osorio E. Current standing and frontiers of gene therapy for meningiomas. *Neurosurg Focus.* 2013;35: E4.

39. Baldi I, Engelhardt J, Bonnet C, et al. Epidemiology of meningiomas. *Neurochirurgie.* 2018;64: 5-14.

40. Wu W, Zhou Y, Wang Y, et al. Clinical significance of somatostatin receptor (SSTR) 2 in meningioma. *Front Oncol.* 2020;10:1633.

41. Delgado-López PD, Cubo-Delgado E, González-Bernal JJ, Martín-Alonso J. A practical overview on the molecular biology of meningioma. *Curr Neurol Neurosci Rep.* 2020;20:62.

42. Yang X, Liu F, Zheng J, Cheng W, Zhao C, Di J. Relationship between oral contraceptives and the risk of gliomas and meningiomas: a dose-response meta-analysis and systematic review. *World Neurosurg.* 2021;147:e148-e162.

43. Qi Z, Shao C, Huang Y, Hui G, Zhou Y, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: a meta-analysis. *PLoS One.* 2013;8:e83261.

44. Ahlbom A, Feychting M, Green A, et al. Epidemiologic evidence on mobile phones and tumor risk: a review. *Epidemiology.* 2009;20:639-652.

45. Dubey RB, Hanmandlu M, Gupta SK. Risk of brain tumors from wireless phone use. *J Comput Assist Tomogr.* 2010;34:799-807.

46. Chen F, Wang P, Lan J, et al. Wireless phone use and adult meningioma risk: a systematic review and Meta-analysis. *Br J Neurosurg.* 2021;35:444-450.

47. Chao H, Cheng Y, Shan J, et al. A meta-analysis of active smoking and risk of meningioma. *Tob Induc Dis.* 2021;19:34-38.

48. Zhong P, Lin Y, Chen T. A decreased risk of meningioma in women smokers was only observed in American studies rather than studies conducted in other countries: a systematic review and meta-analysis. *Chin Neurosurg J.* 2021;7:1-45.

49. Claus EB, Walsh KM, Calvocoressi L, et al. Cigarette smoking and risk of meningioma: the effect of gender. *Cancer Epidemiol Biomarkers Prev.* 2012;21: 943-950.

50. Fan Z, Ji T, Wan S, et al. Smoking and risk of meningioma: a meta-analysis. *Cancer Epidemiol.* 2012;37:39-45.

51. Boeing H, Schlehofer B, Blettner M, Wahrendorf J. Dietary carcinogens and the risk for glioma and meningioma in Germany. *Int J Cancer.* 1993;53: 561-565.

52. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: some N-nitroso compounds. *IARC Monogr Eval Carcinog Risk Chem Man.* 1978;17:1-349.

53. Preston-Martin S, Pogoda JM, Mueller BA, Holly EA, Lijinsky W, Davis RL. Maternal consumption of cured meats and vitamins in relation to pediatric brain tumors. *Cancer Epidemiol Biomarkers Prev.* 1996;5:599-605.

54. Terry MB, PhD, Howe G, et al. An international case-control study of adult diet and brain tumor risk: a histology-specific analysis by food group. *Ann Epidemiol.* 2009;19:161-171.

55. Artzi M, Liberman G, Vaisman N, et al. Changes in cerebral metabolism during ketogenic diet in patients with primary brain tumors: 1H-MRS study. *J Neuro Oncol.* 2017;132:267-275.

56. Champ CE, Palmer JD, Volek JS, et al. Targeting metabolism with a ketogenic diet during the treatment of glioblastoma multiforme. *J Neuro Oncol.* 2014;117:125-131.

57. Schwartz K, Chang HT, Nikolai M, et al. Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature. *Cancer Metab.* 2015;3:3.

58. Strowd RE, Cervenka MC, Henry BJ, Kossoff EH, Hartman AL, Blakeley JO. Glycemic modulation in neuro-oncology: experience and future directions using a modified Atkins diet for high-grade brain tumors. *Neurooncol Pract.* 2015;2:127-136.

59. Michaud DS, Bove G, Gallo V, et al. Anthropometric measures, physical activity, and risk of glioma and meningioma in a large prospective cohort study. *Cancer Prev Res.* 2011;4:1385-1392.

60. Edlinger M, Strohmaier S, Jonsson H, et al. Blood pressure and other metabolic syndrome factors and risk of brain tumour in the large population-based Me-Can cohort study. *J Hypertens.* 2012;30: 290-296.

61. Wiedmann M, Brunborg C, Lindemann K, et al. Body mass index and the risk of meningioma, glioma and schwannoma in a large prospective cohort study (The HUNT Study). *Br J Cancer.* 2013; 109:289-294.

62. Selke P, Rosenstock P, Bork K, Strauss C, Horstkorte R, Scheer M. Glycation of benign meningioma cells leads to increased invasion. *Biol Chem.* 2021;402:849-859.

63. Rajaraman P, Roos AJD, Stewart PA, et al. Occupation and risk of meningioma and acoustic neuroma in the United States. *Am J Ind Med.* 2004; 45:395-407.

64. Rajaraman P, Stewart PA, Samet JM, et al. Lead, genetic susceptibility, and risk of adult brain tumors. *Cancer Epidemiol Biomarkers Prev.* 2006;15: 2514-2520.

65. Bhatti P, Stewart PA, Hutchinson A, et al. Lead exposure, polymorphisms in genes related to oxidative stress, and risk of adult brain tumors. *Cancer Epidemiol Biomarkers Prev.* 2009;18:1841-1848.

66. Piel C, Pouchieu C, Carles C, et al. Agricultural exposures to carbamate herbicides and fungicides and central nervous system tumour incidence in the cohort AGRICAN. *Environ Int.* 2019;130: 104876.

67. Shah DS, Sanan A, Morell AA, et al. Traumatic brain injury and subsequent brain tumor development: a systematic review of the literature. *Neurosurg Rev.* 2022;45:3003-3018.

68. Vélez-Agosto NM, Soto-Crespo JG, Vizcarrondo-Oppenheimer M, Vega-Molina S, García Coll C. Bronfenbrenner's bioecological theory revision: moving culture from the macro into the micro. *Perspect Psychol Sci.* 2017;12:900-910.

69. Muttarak R, Gallus S, Franchi M, et al. Why do smokers start? *Eur J Cancer Prev.* 2013;22:181-186.

70. World Health Organization. *Taking action on childhood obesity* (Publication No. WHO/NMH/PND/ECHO/18.1). World Health Organization; 2018:1-8. Available at: https://iris.who.int/handle/10665/274792. Accessed February 20, 2023.

71. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017; 390:1211-1259.

72. Daniels SR, Jacobson MS, McCrindle BW, Eckel RH, Sanner BM. American heart association childhood obesity research summit report. *Circulation.* 2009;119:489.

73. Fleming TP, Watkins AJ, Velazquez MA, et al. Origins of lifetime health around the time of conception: causes and consequences. *Lancet.* 2018;391:1842-1852.

74. Shafei AE, Nabih ES, Shehata KA, et al. Prenatal exposure to endocrine disruptors and reprogramming of adipogenesis: an early-life risk factor for childhood obesity. *Child Obes.* 2018;14:18-25.

75. Gillman MW, Rifas-Shiman SL, Kleinman K, Oken E, Rich-Edwards JW, Taveras EM. Developmental origins of childhood overweight: potential public health impact. *Obesity.* 2008;16:1651-1656.

76. Stettler N. Nature and strength of epidemiological evidence for origins of childhood and adulthood obesity in the first year of life. *Int J Obes.* 2007;31: 1035-1043.

77. Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk factors for childhood obesity in the first 1,000 Days: a systematic review. *Am J Prev Med.* 2016;50:761-779.

78. Blake-Lamb TL, Locks LM, Perkins ME, Woo Baidal JA, Cheng ER, Taveras EM. Interventions for childhood obesity in the first 1,000 Days A systematic review. *Am J Prev Med.* 2016;50:780-789.

79. Chari R, Warsh J, Ketterer T, Hossain J, Sharif I. Association between health literacy and child and adolescent obesity. *Patient Educ Counsel*. 2014;94: 61-66.

80. Yin HS, Johnson M, Mendelsohn AL, Abrams MA, Sanders LM, Dreyer BP. The health literacy of parents in the United States: a nationally representative study. *Pediatrics*. 2009;124(Suppl 3):289.

81. The Academy of Medical Sciences. *Improving the health of the public by 2040*. United Kingdom: The Academy of Medical Sciences: London; 2016:4-9.

82. Diez Roux AV. Complex systems thinking and current impasses in health disparities research. *Am J Publ Health*. 2011;101:1627-1634.

83. Fink DS, Keyes KM. Wrong answers: when simple interpretations create complex problems. In: El-Sayed AM, Galea S, eds. *Systems Science and Population*. New York, NY: Health Oxford University Press; 2017.

84. Rutter H, Savona N, Glonti K, et al. The need for a complex systems model of evidence for public health. *Lancet*. 2017;390:2602-2604.