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Toenail selenium, genetic variation in selenoenzymes and risk and outcome in glioma

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ABSTRACT

Background: Selenium is an essential trace element obtained through diet that plays a critical role in DNA synthesis and protection from oxidative damage. Selenium intake and polymorphisms in selenoproteins have been linked to the risk of certain cancers though data for glioma are sparse.
Methods: In a case-control study of glioma, we examined the associations of selenium in toenails and genetic variants in the selenoenzyme pathway with the risk of glioma and patient survival. A total of 423 genetic variants in 29 candidate genes in the selenoenzyme pathway were studied in 1547 glioma cases and 1014 healthy controls. Genetic associations were also examined in the UK Biobank cohort comprised of 313,868 persons with 322 incident glioma cases. Toenail selenium was measured in a subcohort of 300 glioma cases and 300 age-matched controls from the case-control study.
Results: None of the 423 variants studied were consistently associated with glioma risk in the case-control and cohort studies. Moreover, toenail selenium in the case-control study had no significant association with glioma risk (p trend = 0.70) or patient survival among 254 patients with high grade tumors (p trend = 0.70).
Conclusion: The present study offers no support for the hypothesis that selenium plays a role in the onset of glioma or patient outcome.

1. Introduction

Gliomas represent the majority of primary intracranial tumors; approximately 80% of malignant brain tumors arise from the glial cells of the brain [1]. Mortality from glioma is high with only 5% survival at 5 years in glioblastoma multiforme (GBM), the most aggressive and common subtype of glioma (WHO Grade IV) [1]. Gliomas occur more frequently in males, and in Caucasians when compared to other racial groups [2]. Genetic susceptibility [3], as well as rare Mendelian disorders including neurofibromatosis, tuberous sclerosis, and Li-Fraumeni syndrome also contributes to disease [4–6]. A history of chicken pox, allergies, or atopic disease has a protective association with glioma suggesting that the immune response may play a role in glioma development [7,8]. A prolonged adolescent growth phase is positively associated with glioma risk [9], as is a higher BMI during adolescence [10], and a later age at menarche in women [11,12]. The only known environmental risk factor is ionizing radiation [13]. The role of diet in glioma including trace elements such as selenium is poorly studied.

Selenium (Se) is an essential trace element obtained through diet that plays a critical role in reproduction, thyroid hormone metabolism, DNA synthesis, and protection from oxidative damage and infection [14]. Se is naturally present in many foods and is also available as a dietary supplement. Concentrations of Se in foods vary with Se in the soil in which food is produced [14]. Toenail concentrations of Se offer a useful measure of dietary exposure and reflect long-term dietary intake [15]. In the brain, Se and the selenoproteins play a central role in brain

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function and neuroprotection [16–19]. Se stores in the body reflect not only diet but GI absorption and tissue uptake, and vary according to alcohol consumption and cigarette smoking which may deplete Se stores in the body by contributing to oxidative stress [20].

Epidemiologic studies have suggested a protective association between Se and cancer risk though data are inconsistent [21]. A Cochrane meta-analysis of prospective observational studies showed lower cancer incidence among patients with higher Se exposure for cancers of the prostate, gastric cardia, bladder, and lung, but not for breast or colon [21]. In contrast, randomized clinical trials have not found evidence that Se supplementation is associated with risk reduction for primary liver cancer, non-melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma, prostate cancer, lung, bladder, or colorectal cancer, and with cancer-related mortality; it is speculated that supplementation may not reduce cancer in persons already replete for Se as would apply to the majority of persons in the US [21]. Two studies have examined Se levels and brain tumor risk in human populations. One small study (N = 22) found no difference in Se levels in cerebrospinal fluid of patients with glioma as compared to patients with benign tumors of the brain (meningioma), or diagnosed with hydrocephalus, arterial malformation, aneurysm, or headaches [22]. Another study examined serum levels of Se in patients with malignant brain tumors (n = 139) compared to healthy adult individuals (n = 294) and found lower Se serum levels in the glioma patients [23]; however, as concentrations of Se in blood reflect recent Se intake [24], Se in the serum of cases may have reflected recent changes in diet related to the glioma diagnosis.

Selenium's actions in the body are exerted through its incorporation as the amino acid selenocysteine into 25 selenoproteins thought to exert most of the functions of Se in the body [14]. Nearly all of the well-characterized selenoproteins possess a role in antioxidant function and redox status in the cell [25]. A number of other genes exert effects on bioavailability and action of Se in the cell. Among them, SEPSECS is involved in the regulation of selenoprotein synthesis [26]. SEPHS1 is one of two selenophosphate synthases in mammals; unlike SEPSH2, a known selenoprotein, the function of SEPHS1 has not been determined though it is hypothesized to play a role in cell differentiation and proliferation [27]. Interactions of SPECSECS and SEPHS1 with SEPHS2 play a role in selenocysteine biosynthesis [28]. GCLC and GCLM are subunits of GCL (glutamate cysteine ligase) which is the first rate-limiting enzyme of glutathione biosynthesis [29]. Single-nucleotide polymorphisms (SNP) in selenium pathway genes have been linked to the risk of colorectal, prostate, lung or breast cancers [30] but are poorly studied in glioma.

The aim of this study was to investigate the association between toenail Se concentrations and genetic variants in selenoproteins and related genes in relation to glioma risk and survival in a US case-control study. Associations with genetic variants were also investigated in the UK Biobank cohort [31].

2. Subjects and methods

2.1. Study populations

2.1.1. Case-Control study

The study population included persons enrolled in a case-control study of glioma risk factors (GliomaSE) [11]. In brief, cases were aged 18 years or older with a recently diagnosed (within 3 months of recruitment) primary intracranial glioma. Cases were recruited at neurosurgery and neuro-oncology clinics at major medical centers throughout the southeastern United States, which included: Moffitt Cancer Center in Tampa, Florida; Vanderbilt University Medical Center in Nashville, Tennessee; University of Alabama at Birmingham; Emory University in Atlanta, Georgia; and the Kentuckiana Cancer Institute in Louisville, Kentucky. Among eligible glioma patients, 87% were enrolled a median of 1 month following initial diagnosis (IQR: 2–7 weeks). Controls were recruited from friends and non-blood related associates of the cases in the study, as well as residents from the same communities as the cases identified in white page listings. Of eligible households contacted, approximately 50% yielded a participant for the study. For cases and controls, a structured interview was administered by a member of the research team to collect information on demographics, medical history, and potential risk factors of glioma. All subjects provided oral DNA as a basis for genetic investigations [32,33]. Subjects were also asked to provide toenail samples for studies of trace elements in glioma risk [11]. All subjects were genotyped using the Affymetrix 'UKBiobank' array (http://www.ukbiobank.ac.uk/scientists-3/uk-biobank-axiom-array/) that offers genome-wide coverage including the 25 selenoenzymes and other selenium pathway genes of interest. The study was approved by the institutional review board at each participating center.

2.1.2. Cohort study

The UKBiobank (UKB) cohort was employed to study associations of genes of interest with glioma incidence. The full UKB cohort consists of 502,619 subjects, ages 40 to 69, recruited from 2006 to 2010 [31]. All subjects were genotyped using the Affymetrix 'UKBiobank' array with anonymized genotype and descriptive data for each subject downloaded by investigators under an approved protocol (Application #16944). A diagnosis of glioma was determined based on ICD-9 and ICD-10 codes provided by the National Health Service (NHS) Central Registers, with follow up through November 30, 2014 for England and Wales residents and December 31, 2014 for Scotland residents [31]. The current study is based on 313,868 UKB nongenetically related cohort members with no history of cancer at baseline (other than non-melanoma skin), generating 322 incident glioma cases. Written consent was obtained at recruitment.

2.2. Toenail selenium measurement

The substudy of trace metals in glioma has been previously described [11]. Toenail samples were analyzed in a sample of 300 cases and 300 age, sex, and state matched controls from the case-control study. Toenail samples were harvested a median of 24 days and a maximum of 88 days following glioma diagnosis (10th-90th percentile range: 10–44 days). Toenail clippings were analyzed by instrumental neutron activation analysis (NAA) at the University of Missouri Reactor. The toenail samples were analyzed in 3 separate batches, each containing 100 cases and 100 matched controls. Matched case-control pairs were handled identically in each analytical run, with laboratory personnel blinded to case-control status. All toenail clippings prior to analysis by sonication in 10% v/v nitric acid and deionized water. To ensure quality control, samples were created in duplicate and analyzed to ensure consistency, as well as with 5 NIST SRM 1577 Bovine liver quality control samples. The Se concentration in the samples ranged from 0.60 μg/g to 4.6 μg/g, and the mean concentration of Se was 0.879 μg/g. The average coefficient of variation (CV) was 3.7% among sample pairs; if a duplicate pair had a CV of greater than 5%, both samples were re-analyzed (27 pairs total). Toenails were not available for Se measurement in the UKB cohort.

2.3. Toenail Se analyses

The association between Se levels in the toenail and glioma risk was estimated with odds ratios (OR) and 95% confidence intervals (CI) using logistic regression. We examined risk associated with increasing quartile of nail Se as defined in the controls, with the lowest quartile considered the referent group. To test for linear trend, an ordinal term reflecting increasing quartile of toenail Se was included in regression models. All regression models included terms for age (5 year age groups), state of residence at diagnosis, sex, and batch. As use of dandruff shampoo can result in abnormally high levels of Se in the nails