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ORIGINAL ARTICLE

Tofu, urinary phytoestrogens, and melanoma: An analysis of a national database in the United States

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ABSTRACT

Background/Objectives: Phytoestrogens are naturally occurring estrogen-like compounds commonly found in foods, especially soybeans and soy products. There have been recent interests as well as evidence in animal studies suggesting that phytoestrogens may protect against cancers, including skin cancers such as melanoma. To date, no human or epidemiological studies have been performed to evaluate this association with melanoma. The objective of this study was to investigate the relationship between tofu consumption, urinary phytoestrogen, and diagnosis of melanoma in a national epidemiologic database.

Methods: Data on the history of melanoma and measured urinary phytoestrogen levels (daidzein, O-desmethylangolensin, equol, enterodiol, genistein, and enterolactone) from the United States National Health and Nutrition Examination Survey database from 1999 to 2010 were obtained and analyzed with univariate and multivariate tests. Using information about tofu consumption and sun-protective behaviors, we analyzed the data for the period 2003–2006.

Results: Patients who were older or with higher body mass index (BMI) were significantly more likely to be diagnosed with melanoma in the past [odds ratio (OR) 1.06; 95% confidence interval (CI) 1.05–1.07; $p < 0.001$; and OR 1.04; 95% CI 1.02–1.06; $p < 0.001$, respectively]. Those with a history of melanoma had lower levels in five of the six measured creatinine-adjusted urinary phytoestrogens. However, this relationship was not statistically significant after adjusting for confounding factors such as age, sex, ethnic groups, and BMI. A diet with tofu had a significant positive correlation with the levels of measured urinary phytoestrogens. By contrast, the association between a history of melanoma and such diet did not achieve statistical significance.

Conclusion: In our study, patients with a history of melanoma tend not to consume tofu in their diet and have lower urinary phytoestrogens levels. The relationship was not statistically significant and more studies need to be carried out.

Introduction

Melanoma, though accounting for <2% of all skin cancer, is responsible for the majority of skin cancer mortality.[1] For the past three decades, the incidence of melanoma has been on the rise.[1] According to the American Cancer Society's estimates for 2015, approximately 73,870 new cases will be diagnosed and 9,940 deaths will be attributed to melanoma in the United States.[1] Based on the 2009–2011 data from the Surveillance, Epidemiology, and End Results program, the lifetime risk of developing melanoma is approximately 2.1%.[2]

Age, ethnicity, high level of exposure to sunlight, history of sunburn during childhood, and fair skin complexion are important risk factors for melanoma development.[3,4] Among these, exposure to ultraviolet light has been established as the only recognized modifiable risk factor.[5] Hence, chemoprevention of melanoma would be highly desirable, with exploration of a variety of dietary

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and medicinal chemicals attracting considerable interest.[6] The role of diet in the chemoprevention of melanoma has always been controversial and can be challenging for dermatologists during patient counseling. Antioxidants, in particular, have garnered interests in dermatology in recent years. Plant-derived antioxidants, such as green tea polyphenols, resveratrol, lycopene, curcumin, as well as phytoestrogen have been suggested to reduce the risk of skin cancer.[7,8]

Phytoestrogens are naturally occurring estrogen-like compounds commonly found in various foods, especially soybeans and soy products, flaxseed, and sesame seed.[9] Recently, phytoestrogen-containing products have become popular among health-conscious populations. There have been growing interests in the consumption of phytoestrogen-containing products as a form of cancer-preventive supplementation. Recent animal studies indicated that phytoestrogens can mitigate the oxidative stress and inflammation inherent in many chronic skin diseases and skin cancer.[10] Although there is enough evidence for the protective effects of phytoestrogens against skin tumorigenesis in animal models and cell culture studies,[10–15] human studies that evaluate these effects are lacking. In this study, we aim to investigate whether there is an association between tofu in the diet, urinary phytoestrogens, and diagnosis of melanoma using the data from United States (U.S.) National Health and Nutrition Examination Survey (NHANES) database.

Methods

Study population

The NHANES is a periodic annual population survey that targets the civilian, noninstitutionalized U.S. population.[16] The major objectives of the survey were to estimate the burden of various common diseases, trends in risk behaviors, and environmental exposures as well as to establish any possible relationship between diet, nutrition, and health. It has a stratified multistage probability sampling design.[16] In our analysis of interest, randomly selected individuals aged 20–85 years were interviewed about several variables of interest. A total of 59,205 participants subsequently completed laboratory examinations. Data on the history of melanoma diagnosis and urinary phytoestrogens levels in the cycle years from 1999 to 2010 were retrieved and analyzed retrospectively.

Outcome

Diagnoses of melanoma were identified from the 1999–2010 NHANES “Medical Condition” section of the questionnaire data. Study participants were asked to report if they were ever diagnosed with melanoma. Information on the age at which melanoma was first diagnosed was also recorded.

Laboratory and questionnaire data variables

The measured urinary phytoestrogens levels included genistein, daidzein, O-desmethylangolensin (O-DMA), equol, enterodiol, and enterolactone. Urine samples were processed using enzymatic deconjugation of the glucuronidated phytoestrogens, followed by solid-phase extraction.[17] Subsequently, the quantification of these phytoestrogens in the urine was performed using the high-performance liquid chromatography–electrospray ionization-tandem mass spectrometry method.[17] These urinary phytoestrogen metabolites were measured using random spot urine specimens, which were susceptible to intraindividual variability. To compensate for this variability, urinary phytoestrogen levels were divided by individuals' spot urinary creatinine level to yield creatinine-adjusted values. Variables such as age, sex, ethnic groups, and body mass index (BMI) were included for analysis as possible confounding factors.

To clearly define the relationship between dietary phytoestrogens and melanoma as well as to explore the impact of potential confounding factors, an analysis of the data from 2003 to 2006 was conducted. In NHANES, detailed dietary records documenting tofu consumption and questions regarding sun-protective behaviors were only available in the cycle years from 2003 to 2006. Data regarding tofu consumptions were collected by asking if participants had tofu, soy burgers, or soy meat substitutes in their usual diet for at least the past 12 months. Those who reported consumption for at least once a week were considered to have a significant intake of phytoestrogens in their diet.

All results were adjusted for melanoma-related confounding variables such as age, sex, ethnic groups, sun-protective behaviors, and BMI using multivariate logistic regression. Sun-protective behaviors investigated in the survey questionnaire included staying in the shade, wearing suitable hats, wearing long sleeves as well as applying sunscreens. In this analysis, participants who engaged in one of the aforementioned sun-protective behaviors most of the time were deemed to have regular sun-protective behaviors.

Data analysis

Using independent sample t test and Mann–Whitney U test, creatinine-adjusted urinary phytoestrogen levels were compared between those with melanoma and those without melanoma. Univariate and multivariate logistic regression analyses were performed to calculate the crude odds ratio (OR) as well as adjusted ORs of the relationship, taking into account the aforementioned confounding factors. Both independent sample t test and Mann–Whitney U test were performed to assess the relationship between tofu consumption and levels of creatinine-adjusted urinary phytoestrogens. Dietary patterns of tofu consumption between those with and without melanoma were analyzed using Chi-square test or Fisher's exact test.

SPSS (version 22; IBM, Armonk, NY, USA) was used for the analysis of the abovementioned variables to evaluate statistical significance. OR, 95% confidence interval (CI), and p values were calculated to test the null hypotheses of the association between tofu consumption/urinary phytoestrogens and melanoma. A two-sided $p < 0.05$ was considered statistically significant.

Clinical information and laboratory data on the 1999–2010 NHANES cycles were available from the publicly accessible U.S. Centers for Disease Control and Prevention database. The NHANES was approved by the U.S. National Center for Health Statistics Ethics Review Board and documented consent was obtained from all participants.

Results

A total of 59,205 participants from the NHANES database from 1999 to 2010 were included in the analysis. There were 172 reported cases of melanoma. The median age of diagnosis was 59 years. The median time of diagnosis was 8 years prior to the survey. Patients who had a history of melanoma were significantly older than those without (OR 1.06; 95% CI 1.05–1.07; $p < 0.001$). Of these 172 melanoma cases, 90 were men and 82 were women ($p = 0.402$). The median BMI of those who had a history of melanoma was 26.9 kg/m^2. Patients who had a history of melanoma had a significantly higher BMI compared with those without (OR 1.04; 95% CI 1.02–1.06; $p < 0.001$).

Urinary phytoestrogen data were available for 15,688 participants during the survey period from 1999 to 2010. Of these, there