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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

were 50 cases with a history of melanoma. Increasing levels in five of the six measured creatinine-adjusted urinary phytoestrogens (daidzein, O-DMA, equol, enterodiol, and genistein) were associated with lower odds, albeit not statistically significant, of being diagnosed with melanoma (Table 1). Multivariate logistic regression analysis with confounding variables such as age, sex, ethnic groups, and BMI also failed to yield any significant relationship.

As shown in Table 2, compared with those without melanoma, study participants with a history of melanoma had lower levels in five of the six creatinine-adjusted urinary phytoestrogens. However, none of the results reached statistical significance under both two-sample *t* test and Mann–Whitney *U* test.

In the analysis of data from 2003 to 2006, there were 19,467 study participants and 57 cases of melanoma. The underlying demographics characteristics were comparable to the overall study population. Detailed dietary patterns were available for 4225 study participants, and among them 884 had tofu in their diet. Of the 19,467 study participants who responded to the questions on sun-protective behaviors, 28.5% reported engaging in at least one of the four sun-protective behaviors listed in the questionnaire (staying in the shade, wearing suitable hats, wearing long sleeves, and applying sunscreens).

Dietary records documenting tofu consumption were analyzed to evaluate whether they correlated with the six measured creatinine-adjusted urinary phytoestrogens levels. As shown in Table 3, those who consumed tofu in their diet had significantly higher creatinine-adjusted urinary phytoestrogens, compared with those who did not consume any soy products. Although those who consumed tofu had decreased odds of being diagnosed with melanoma, the results did not reach statistical significance, even after adjusting for potential confounding factors such as age, sex, ethnic groups, BMI, and sun-protective behaviors (Table 4).

Discussion

Phytoestrogens are plant-based compounds that structurally resemble endogenous estrogens.[9] There are three major types of phytoestrogens, namely, lignans, isoflavones, and coumestans.[9] Among these, lignans (enterolactone and enterodiol) and isoflavones (genistein and daidzein) are frequently found in human diets.[18] The main site of phytoestrogen metabolism is the gastrointestinal tract, which results in the formation of heterocyclic phenols.[19] After ingestion, daidzein is further metabolized by intestinal bacteria to equol and O-DMA. In addition, absorbed phytoestrogens undergo enterohepatic circulation and are mostly excreted in the urine.[19]

Because of the presence of a phenolic ring that allows for binding to the estrogen receptor, phytoestrogens can either act as weak agonists, partial agonists, or as antagonists at estrogen receptors.[20] It is interesting to note that equol, but not O-DMA, has estrogenic activity.[19] As a result of their estrogenic activities, there have been concerns that exposure to phytoestrogen may induce or exacerbate hormone-related cancers. A systemic review of current literature, however, had demonstrated that soy consumption may be associated with decreased risk of breast cancer.[21] A recent meta-analysis demonstrated that, in men at risk, phytoestrogens resulted in significant reduction in the diagnosis of prostate cancer.[22] Other epidemiological studies, though inconclusive, also suggested that phytoestrogens may decrease the risks of lung, gastric, pancreatic, colorectal, and ovarian cancers.[9] This might be due to the anti-proliferative and antiangiogenic effects of phytoestrogens.[9] Thus far, there have only been animal studies investigating localized effect of topical phytoestrogens on skin tumorigenesis. It is still unclear how the systemic levels of phytoestrogens would translate into the local effect on the skin. Although knowledge on the most ideal method to measure phytoestrogen levels in the body is lacking, urinary levels of daidzein, genistein, and enterolactone have been shown to be good biomarkers of dietary intake.[23]

In our study, the creatinine-adjusted levels of urinary phytoestrogens seemed to be inversely associated with the history of melanoma. Although this relationship does not reach statistical significance, it suggests that there might be an association between intake of phytoestrogens and a decrease in development of melanoma. Multivariate analysis with known confounding factors such as age, sex, ethnic groups, and BMI yielded a similar relationship. Those with higher levels of urinary phytoestrogens have up to 1.2 times the odds of not having a history of melanoma. Other potential confounding factors such as family history of melanoma, skin types, or sun-protective behaviors were not available for the period 1999–2010 for multivariate analysis.

The analysis from 2003 to 2006 specifically examined the relationship between tofu consumption and melanoma. The creatinine-adjusted urinary phytoestrogens levels correlated significantly with consumption of phytoestrogen-containing products such as tofu.

Table 1 Univariate and multivariate logistic regression analyses of variables and history of melanoma in NHANES from 1999 to 2010.

Variables	Univariate		*p*	Multivariate		*p*
	Crude OR	OR 95% CI		Adjusted OR[a]	OR 95% CI	
Creatinine-adjusted urinary phytoestrogens (μg/gCr)						
Genistein (n = 15,688)	0.971	0.881–1.069	0.546	0.965	0.867–1.073	0.508
Daidzein (n = 15,684)	0.986	0.941–1.032	0.538	0.990	0.947–1.035	0.656
ODMA (n = 15,389)	0.926	0.737–1.165	0.513	0.923	0.739–1.153	0.480
Equol (n = 15,308)	0.783	0.367–1.674	0.528	0.690	0.239–1.998	0.690
Enterodiol (n = 15,658)	0.999	0.949–1.052	0.976	0.985	0.899–1.078	0.741
Enterolactone (n = 15,679)	1.002	0.994–1.010	0.621	0.995	0.973–1.017	0.653
Age (n = 59,205), y	1.063	1.054–1.072	<0.001	—	—	—
Sex (n = 59,205)						
Male	1.139	0.844–1.537	0.395	—	—	—
Female	1.000	—	—	—	—	—
Ethnic groups (n = 59,205)				—	—	—
Mexican American	0.038	0.014–0.104	<0.001	—	—	—
Other Hispanic	0.037	0.005–0.263	0.001	—	—	—
Non-Hispanic black	0.031	0.010–0.097	<0.001	—	—	—
Other race	0.052	0.007–0.373	0.003	—	—	—
Non-Hispanic white	1.000					
BMI (n = 53,381), kg/m^2	1.038	1.020–1.056	<0.001	—	—	—

BMI = body mass index; CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; ODMA = O-desmethylangolensin; OR = odds ratio.
[a] Adjusted for age, sex ethnic groups, and BMI.

Table 2 Correlation of creatinine-adjusted urinary phytoestrogens with a history of melanoma in NHANES from 1999 to 2010.

Mean creatinine-adjusted urinary phytoestrogens (μg/gCr)	History of melanoma		*t* statistic	*p**
	Yes	No		
Genistein ($n = 15,688$)	97.63	148.11	−0.554	0.579
Daidzein ($n = 15,684$)	214.47	329.44	−0.558	0.577
ODMA ($n = 15,389$)	32.65	72.09	−0.534	0.593
Equol ($n = 15,308$)	13.61	46.62	−0.507	0.612
Enterodiol ($n = 15,658$)	101.89	104.38	−0.030	0.976
Enterolactone ($n = 15,679$)	790.85	664.89	0.506	0.613

* Two-sample independent *t* test.
NHANES = National Health and Nutrition Examination Survey; ODMA = O-desmethylangolensin.

Table 3 Correlation of creatinine-adjusted urinary phytoestrogens and their relationship with dietary soy milk and tofu in NHANES from 2003 to 2006.

Mean creatinine-adjusted urinary phytoestrogens (μg/gCr)	Tofu in the diet		*t* statistic	*p**
	Yes	No		
Genistein ($n = 1422$)	238.61	92.07	−2.919	0.004
Daidzein ($n = 1422$)	459.90	199.92	−2.979	0.003
ODMA ($n = 1412$)	135.49	42.91	−2.778	0.006
Equol ($n = 1420$)	148.08	34.34	−1.604	0.110
Enterodiol ($n = 1422$)	179.02	110.42	−2.812	0.005
Enterolactone ($n = 1422$)	1267.79	698.45	−2.699	0.007

* Two-sample independent *t* test.
NHANES = National Health and Nutrition Examination Survey; ODMA = O-desmethylangolensin.

Table 4 Univariate and multivariate logistic regression analyses of variables and a history of melanoma in NHANES from 2003 to 2006.

Characteristics	History of melanoma?		Univariate analysis	*p*	Multivariate analysis	*p*
	Yes	No	Crude OR		Adjusted OR[a]	
Tofu in diet ($n = 4225$)						
Yes	2	882	0.686	0.625	0.667	0.615
No	11	3330	1.000		1.000	
Age ($n = 6549$), y	35.71	37.58	0.985	0.493	1.001	0.980
Sex ($n = 6549$)						
Male	4	3078	0.345	0.063	0.114	0.038
Female	13	3454	1.000		1.000	
Ethnic groups ($n = 6549$)						
Mexican American	5	1372	1.862	0.305	1.982	0.378
Other Hispanic	1	250	2.043	0.509	3.177	0.305
Non-Hispanic black	4	1542	1.343	0.648	1.916	0.404
Other race	1	324	1.577	0.674	2.609	0.400
Non-Hispanic white	6	3065	1.000	–	1.000	–
Sun-protective behaviors ($n = 6549$)						
Yes	14	5538	0.838	0.735	0.723	0.679
No	3	994	1.000		1.000	
BMI ($n = 6195$), kg/m^2	27.07	28.71	0.959	0.349	0.949	0.277

BMI = body mass index; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio.
[a] Adjusted for age, sex, ethnic groups, sun-protective behaviors, and BMI.

This is anticipated because individuals consuming more tofu would be expected to have higher phytoestrogen metabolites in their urine. However, no significant association was observed between the consumption of tofu and history of melanoma, even after adjusting for known risk factors for melanoma such as age, sex, BMI, ethnic groups, and Sun-protective behaviors. Although soy products such as tofu contained the highest concentration of phytoestrogens in the forms of genistein and daidzein, the relationship between phytoestrogens and melanoma might be underestimated because information on the intake of other well-recognized phytoestrogen-containing foods such as flaxseeds or sesame seeds was not available. Binary analysis of dietary phytoestrogens might also be too simplified to describe the relationship.

Studies utilizing different animal models have elucidated various potential pathways through which phytoestrogens may exert their photoprotective and antitumor effects. Genistein is postulated to protect against the development of melanoma by inhibiting UVB-induced epidermal growth factor and mitogen-activated protein kinase phosphorylation, which promote cell proliferation and photocarcinogenesis.[24] It also increases melanin production and tyrosinase activity to protect melanocytes from UVB radiation.[25]

The common food groups in Western diet that are rich in phytoestrogen include nuts and oilseeds, soy products, cereals and breads, legumes, meat products, and other processed foods that may contain soy, vegetables, or fruits.[26] The highest concentration of total isoflavones is found in soy products, followed by legumes, meat products, cereals and breads, nuts and oilseeds, vegetables, and finally fruits.[26] Soybeans, flaxseed, sesame seed, and any products that contain them have the highest amount of total phytoestrogens.[27] Most of these foods provide an important source of proteins and are generally healthy. Therefore, such food can be encouraged as part of a general healthy diet regime in patients with risk factors for melanoma or nonmelanoma skin cancers.

In this study, it is interesting to note that tofu consumption is significantly less prevalent among non-Hispanic whites, who were also significantly more likely to have a history of melanoma. Although this could be related to their Fitzpatrick skin types, which predisposed them to frequent sunburns, other biological factors[28] and different dietary/lifestyle habits among the various ethnic groups might also play a role. However, because fair skin complexion and a history of sunburns are well-established risk factors for melanoma, a focus on lifestyle modifications such as sun avoidance and sun-protective practices should still remain as the primary preventive strategy for reducing the incidence of melanoma.

One of the strengths of this study was that it conglomerated data from a comprehensive database collected over a decade. In addition, corrected urinary phytoestrogen levels based on urinary creatinine levels were used to account for interindividual/intra-individual variability in the absorption and metabolism of phytoestrogen. The main limitation was the potential inaccuracy in dietary data collection. Dietary habits were also likely to fluctuate throughout a person's life. Furthermore, it was difficult to quantify the exact amount of phytoestrogens in a person's diet. Another limitation was that urinary phytoestrogens levels were measured during the study, while the diagnosis melanoma was made prior to the study, with a median time of 8 years. As a result, a causal relationship between phytoestrogens and the occurrence of melanoma cannot be established. In addition, a comprehensive documentation of foods rich in lignans, such as flaxseeds and sesame seeds, was not available in the dietary questionnaire, precluding evaluation of the association between lignans and melanoma. Data on family history of melanoma and Fitzpatrick skin types were also not available. Only the data from 2003 to 2006 included information about certain phytoestrogen-containing foods and important melanoma risk factors such as sun-protective behavior.

In conclusion, those with a history of melanoma in our study had a consistently lower amount of phytoestrogen in their diet and urine. However, given the limitations of our study design and a lack of significant results, there is still insufficient evidence to support the protective effect of phytoestrogens. With animal studies providing increasing evidence for phytoestrogens as important agents in mitigating skin tumorigenesis, more epidemiological studies would be needed. A prospective cohort study would be ideal to further evaluate the association between phytoestrogen intake and melanoma incidence.

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