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The Association Between Melanoma and Exposure to Arsenic Among U.S. Adults Using the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2016

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Abstract

Background: Melanoma is a deadly skin cancer at late stages, and its incidence has been increasing significantly over the last ten years in the United States. Chronic exposure to arsenic has been associated in many studies as a risk factor for non-melanoma skin cancer, notably squamous cell carcinoma. However, current knowledge is limited regarding melanoma and long-term arsenic exposure.

Methods: We conducted a cross-sectional study using the 2003-2016 cycles of the National Health and Nutrition Examination Survey (NHANES), to investigate the association between arsenic exposure and self-reported melanoma and non-melanoma skin cancer diagnoses. Univariate and multivariate logistic regression were conducted. To evaluate the association with source of tap water, an odds ratio was calculated across melanoma and non-melanoma compared to controls with no cancer diagnoses.

Results: White people, higher education, higher socioeconomic status (SES), and smokers were more likely to be diagnosed with melanoma or non-melanoma skin cancer. After adjusting for age and race/ethnicity, the crude odds ratio of people with > 50 ug/L of arsenic in their urine and having melanoma or non-melanoma was 1.87 (95%Cl: 0.58-6.05) and 2.23 (95% Cl: 1.12-4.45), respectively. Individuals with non-melanoma skin cancer diagnoses were 2.06 more likely to report drinking water from a non-municipal source.

Conclusion: A relationship between the incidence of melanoma and exposure to arsenic (measured in urine) among U.S. adults was not found using NHANES from 2003-2016. Non-municipal water sources were associated with non-melanoma and should be further investigated.

Key Words: Melanoma, Skin Cancer, Arsenic, NHANES

Introduction

Skin cancer is malignant growths of skin tissue and is one of the most common cancer diagnoses in the United States (U.S.) (1,2). It is estimated that 1 in 5 Americans will develop skin cancer by the age of 70 years. The annual cost of treating skin cancer is estimated to be $8.1 billion (3). The major categories include melanoma and non-melanoma skin cancers. Non-melanoma skin cancers, basal and squamous cell carcinoma (BCC and SCC), are the most common forms of skin cancer. They are highly treatable and have lower rates of metastasis and mortality (1). Melanoma, also known as malignant or cutaneous melanoma, is a less common but far more dangerous skin cancer due to its ability to spread if not managed early (4).

Arsenic is naturally occurring in the environmental. Short and long terms exposures to arsenic contribute to several health problems, such as the increased risk of cardiovascular diseases, diabetes, and pulmonary diseases. Arsenic is classified as a human carcinogen and has been found to be associated with lung, bladder, kidney, prostate, liver, and non-melanoma skin cancer (5-8). While studies have provided evidence of the occurrence of non-melanoma skin cancers with increasing arsenic exposure, the association between melanoma and arsenic exposure is not fully understood.

The purpose of this study is to measure the association between total arsenic levels in the urine and melanoma. The specific aims are:

Aim #1: Describe the study population that includes people with melanoma, non-melanoma, and no cancer

Aim #2: Describe the total urinary arsenic levels across all groups: melanoma, non-melanoma, and no cancer

Aim #3: Explore the association between the source of tap water and skin cancer compared to no cancer

Aim #4: Measure for a possible association between the development of melanoma and total urinary arsenic levels among U.S. adults

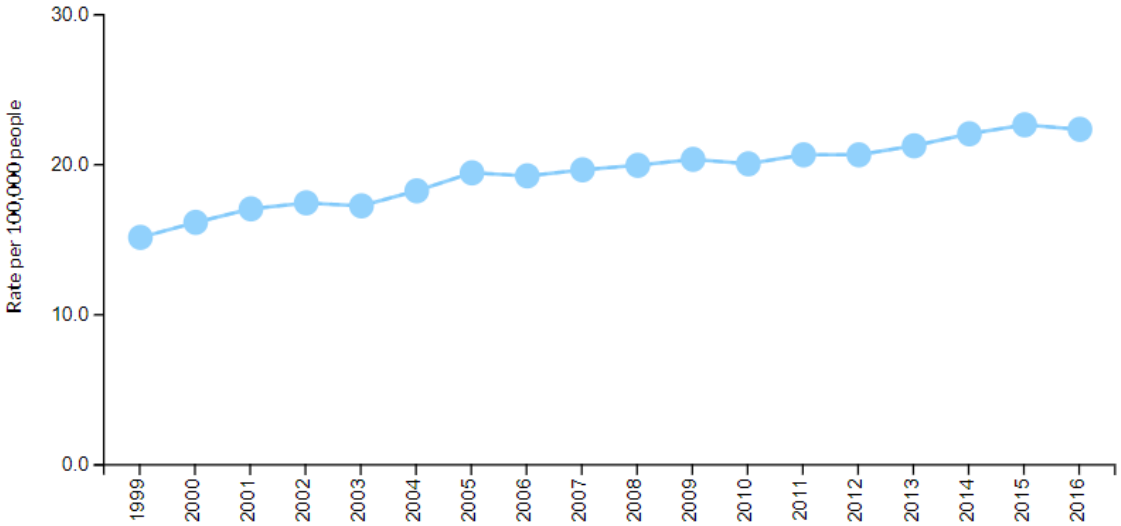
We collected data from the National Health and Nutrition Examination Survey (NHANES) cycles from 2003 to 2016 to address the specific aims.

Background and Significance

The Epidemiology of Melanoma

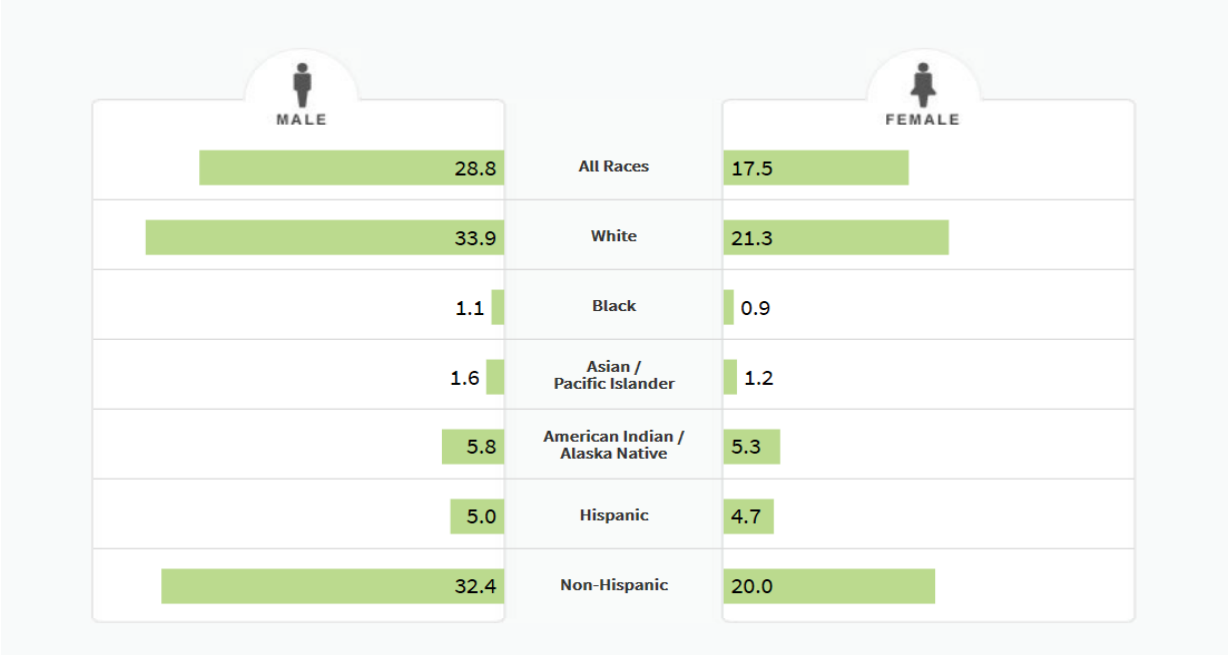
Melanoma is a serious public health concern. From 2006-2016, its age-adjusted rate had increased from 19.3 to 22.3 per 100,000 (Figure 1), and the number of new melanoma cases is expected to increase by 7.7% in 2019 (3,9). In 2019, Melanoma is the 5th diagnosed cancer in the U.S. Men have a higher incidence of melanoma compared to women (28.8 and 17.5 per 100.000, respectively). White and non-Hispanic men (33.9 and 32.4 per 100,000, respectively) have a higher incidence of melanoma than women (21.3 and 20.0 per 100,000, respectively) from the same race/ethnicity (Figure 2) (10). Melanoma is the most diagnosed cancer among young adults, particularly women (11). Based on the American Cancer Society, the incidence of melanoma in women (1 in 150) is higher in men (1 in 215) before age 50 (11-13).

Figure 1. The Incidence of Melanoma per 100,000 in the U.S., from 1999-2016



Centers for Disease Control and Prevention https://gis.cdc.gov/Cancer/USCS/DataViz.html

Figure 2. The Incidence of Melanoma per 100,000 by Sex, and Race/Ethnicity in the U.S.

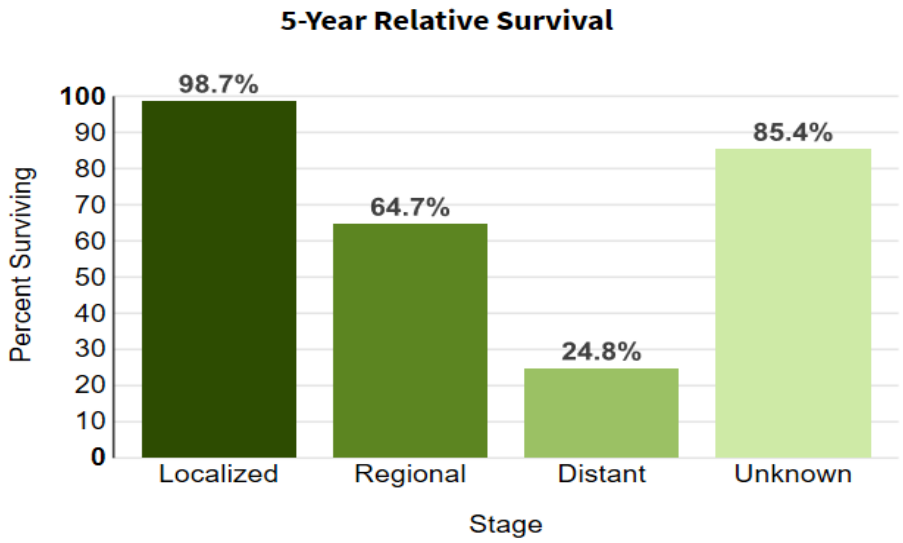


National Cancer Institute, Surveillance, Epidemiology, and End Results Program https://seer.cancer.gov/statfacts/html/melan.html

While melanoma only comprises about 1% of skin cancer diagnoses, it accounts for a large majority of skin cancer deaths (11). This is due in part to its potential for local and

metastatic spread. The 5-year survival rates of melanoma are different based on its stage. When melanoma is diagnosed at early stages, the 5-year survival reaches 98%. This percent decreases to 24.8% when metastatic (Figure 3) (10). Early detection and treatment of melanoma, as well as a better understanding of risk factors, are critical to improving patient survival rate.

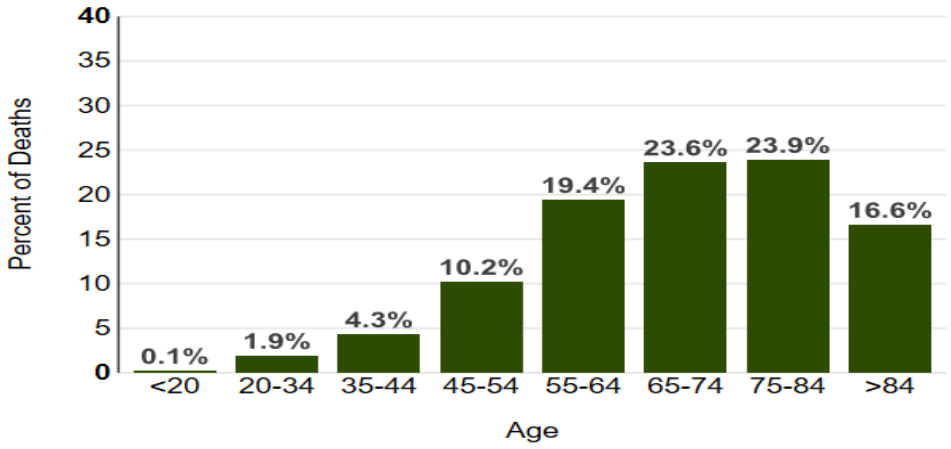
Figure 3. The 5-Year Relative Survival of Melanoma by Stage at Diagnosis in the U.S.



National Cancer Institute, Surveillance, Epidemiology, and End Results Program https://seer.cancer.gov/statfacts/html/melan.html

In terms of mortality, individuals with melanoma die mostly after the age of 55, and the highest mortality percent happens in individuals in the 75-84 age range (23.9%) (Figure 4). The mortality rate for men compared to women from all races is more than twice as high (3.7 and 1.5 per 100,000, respectively). Additionally, white and non-Hispanic men have a mortality rate of 4.3 and 4.0 per 100,000, respectively, which is higher in comparison to women from the same race/ethnicity (10).

Figure 4. The Percent of the Mortality of Melanoma by Age Group in the U.S.



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Risk Factors for Melanoma

The main risk factor of skin cancer is ultraviolet (UV) radiation, which can be preventable. Phenotypic characteristics, including white skin with red or blonde hair, blue or green eyes, or fair skin, are considered risk factors. Furthermore, a family history of melanoma and advanced age with excessive sun exposure during childhood increases the risk of melanoma (14). Environmental exposures, such as pesticides, play an essential role in increasing the risk of melanoma and non-melanoma skin cancer (15,16).

Prevention and Control Measure for Melanoma

Arsenic Exposure

Arsenic is considered one of the most toxic metals, and arsenic poisoning is a global public health problem. Over 140 million people located in 50 countries consume water that contains arsenic with a level of over 10 ug/L (7). In Bangladesh alone, over 40% of the population consumes water with levels of arsenic higher than that recommended by the country's standards of 50 ug/L (50 ppb) (7,17).

Arsenic has two chemical forms: organic and inorganic. Inorganic arsenic is carcinogenic (7). Exposure to inorganic arsenic comes mainly through contaminated drinking water and food, such as fish, grain, and dairy products, which are found in contaminated water and irrigation of food crops. Arsenic is used as a component of pesticides and can be found in soil and water (5,18,19). In addition, tobacco is a potential source of exposure to inorganic arsenic (7).

In the U.S., the Environmental Protection Agency (EPA) has lowered the maximum contaminant level (MCL) of arsenic allowable in public water systems from 50 to 10 parts per billion (ppb) in 2001 to ensure safe drinking water. Public water systems were required to come into compliance with the EPA regulation by 2006. However, private wells are not monitored by the EPA, and approximately 10% of the people in the United States drink water from an unregulated source (19,20). Private wells in areas that utilize fertilizers or contain industrial waste may be contaminated with high arsenic levels (21).

Association Between Arsenic and Health Conditions

Arsenic exposure has been linked to an increased risk of several health conditions. In one study, individuals with arsenic exposure had their urine arsenic measured with a 5 year follow up. Urinary dilution was accounted for by dividing total arsenic by urine creatinine. The study found that left ventricular hypertrophy was associated with a 2-fold increase in arsenic (baseline 4.24 ug/g creatinine) by odds of: 1.47 (95 % Cl: 1.05-2.08) in all participants, and 1.58 (95 % Cl: 1.04-2.40) among pre-hypertensive or hypertensive people (6). Occupational exposure to arsenic has been proven to be associated with pulmonary disorders over time and lung cancer (8,22). A correlation has been shown between the level of arsenic in water and increases in mortality due to respiratory diseases. The hazard ratio of people with >178 ug/L of water arsenic and having a chronic cough was 1.60 (95 % Cl: 1.27-2.01) compared to those with ≤ 7 ug/L (23). The

elimination process of arsenic through the kidney may lead to cytotoxicity in the renal system (8,24). Arsenic also has been associated with bladder cancer in New England. Participants with the highest cumulative arsenic exposure (97.5% percentile) from drinking water had twice the risk of developing bladder cancer compared to the lowest percentile (25%) (25).

Association Between Arsenic Exposure and Skin Cancer

The distribution of arsenic in the body is primarily in keratin-rich tissues such as skin, hair, and nails (26). The effect of acute arsenic poisoning has been shown to have carcinogenic qualities that inhibit the completion of DNA repair. Arsenic could harm the skin by causing lesions, hyperpigmentation, and hyperkeratosis, especially on the palms and soles (7,26,27). With long-term exposure to arsenic, there may be an increase in the risk of developing non-melanoma skin cancer. Additionally, the synergistic effect with UV exposure may happen (27-30). Arsenic exposure might play another role with cancer, such as pro-metastatic carcinogens, which could increase the mortality rate of cancers (31).

A link between arsenic and non-melanoma skin cancer has been established. A study in Wisconsin found an increased odds ratio (OR= 1.81, 95% Cl: 1.10 – 3.14) of having non-melanoma skin cancer with chronic water arsenic exposure of arsenic levels between 1.0 ug/L to 9.9 ug/L. The highest odds ratio was for cases with water arsenic concentration ≥ 10 ug/L (OR= 1.92, 95% Cl: 1.01 – 3.68) (32). Arsenic concentration was measured in the subjects' urine [metabolism products: monomethylarsonic acid (MMA), dimethylarsinic acid (DMA)] and toenails. It was found that a higher concentration of arsenic increased the association of being diagnosed with BCC and SCC (33-35).

A prospective study in Denmark estimated approximately 40 years of arsenic exposure in drinking water for participants from 50 to 64 years of age. They found a decrease in the

incidence of non-melanoma skin cancer in areas with low levels of arsenic in drinking water (36). Another prospective study from 2004-2015 was conducted in Bangladesh to look at the association between skin cancers and the ingestion of arsenic-contaminated groundwater. This study found that areas with a high level of arsenic in the groundwater had higher incidences of BCC and SCC compared to other locations (37).

A case-control study in Iowa (U.S.) investigated the association between the concentration of arsenic in subjects' toenails with the incidence of melanoma compared to colorectal cancer (control group). They found that individuals with the highest arsenic levels in toenails ($\geq$ 0.084 ug/g) were 2 times more likely to develop melanoma compared to those with the lowest levels ($\leq$ 0.020 ug/g). In addition, the odds approximately doubled when people had a history of skin cancer (38). In contrast, a retrospective study (adjusted for UV radiation) conducted in New Mexico in a non-Hispanic white population found no association of arsenic concentration in toenails and urine with melanoma cases (0.09 ± 0.06 ug/g, and 6.33 ± 7.33 ug/L, respectively) compared to controls (0.11 ± 0.06 ug/g, and 6.14 ± 4.40 ug/L, respectively,) (39). The Denmark study also showed no significant difference between an increased level of arsenic in drinking water and melanoma risk (36).

Methods

Data source, National Health and Nutrition Examination Survey (NHANES)

NHANES is a national mobile health survey designed to assess adults' and children's health and nutritional status in the US. This survey is a major program of the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). It began in the 1960s, focusing on different health topics, and in 1999 it became a continuous survey to assess the health and nutritional status of adults and children in the U.S.

Every year, the NHANES database is nationally representative of the general noninstitutionalized US citizens. NHANES contains interview questionnaires and examination components. The data utilizes a complex, multistage, and stratified design with oversampling. Its protocols were approved by the National Center for Health Statistics Institutional Review Board, and consents were obtained from all participants (40).

Study design, study sample, and data collection

A cross-sectional study was conducted using NHANES data from 2003 to 2016 to address the specific aims. All participants in NHANES were included except participants less than 20 years of age and persons with cancer other than skin cancer. Participants missing data in urinary total arsenic levels or water sources were excluded from those analyses. Cancer data in NHANES is self-reported. Participants with skin cancer were identified using codes MCQ230A, MCQ230B, MCQ230C, and MCQ230D from the medical condition questionnaire survey. The total urinary arsenic levels were measured using inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS) (41). Total urinary arsenic levels were measured on a subsample of the total population, approximately one-third of the NHANES population. Arsenic data in urine was extracted for the first 5 NHANES cycles (2003-2012) from the laboratory data using "Arsenic – Total & Speciated– Urine" or "Arsenic – Total & Speciated– Urine- Special Sample." For the last two cycles (2013-2016), arsenic was extracted from the laboratory data from "Arsenic -Total– Urine" or "Arsenic -Total– Urine-Special Sample" (42). The urinary arsenic total level was categorized into two groups ($\leq$ 50 ug/L or > 50 ug/L) based on the previous data of arsenic toxicity in urine from the Minnesota Department of Health (43).

Covariates

Demographic variables from 2003- 2016 included: age in years, gender (male/female), race/ethnicity (whites/non-whites), the ratio of family income to poverty (0.00-1.30, >1.30-3.50, and >3.50 and 5.00), and education level (high schools or less, some college or the associate of art (AA) degree, and college graduate or above). Race/ethnicity was further categorized into white and non-white due to the limited sample size of non-whites. The ratio of family income to poverty was based on the Supplemental Nutrition Assistance Program (SNAP) (44).

Dermatology data was collected for people from 20 to 59 years of age; additionally, the NHANES cycle from 2007-2008 has limited access. For this study population, dermatology data was not available for 2007- 2008 participants and, therefore, was not used. The number of sunburns in the past year was available for most participants and used as a measure for UV exposure and categorized into never and ever.

Smoking status was also categorized into two groups (never, ever) based on questions regarding cigarette use: “Smoked at least 100 cigarettes in life” and “Do you now smoke cigarettes?”. The tap water source was accessed from the dietary survey and categorized as municipal (community supplies), non-municipal (well/rain cistern and springs), and does not drink from tap water.

Statistical Methods

The purpose of the National Health and Nutrition Examination Survey (NHANES) is to produce national estimates representative of the total noninstitutionalized U.S. population, and the sample is selected using a complex, four stages sample design. NHANES guidelines were followed to combine survey cycles and generate sample weights for subsamples and use the strata and primary sampling unit information (variance) units provided on public-use files for

variance estimation. Representational variables were extracted from NHANES 2003-2016 demographic, and laboratory data include masked variance pseudo-stratum (SDMVSTRA), masked variance pseudo-cluster (SDMVPSU), and subsample A weight for arsenic data (WTSA2YR from 2003-2010 and WTFSM from 2011-2016). These variables would estimate the real statistical results if the entire sampling frame was surveyed. The weight variables (WTSA2YR and WTFSM) were divided by 7 to ensure the national representation for the 7 cycles. All data were merged into one data set by a sequence number (SEQN).

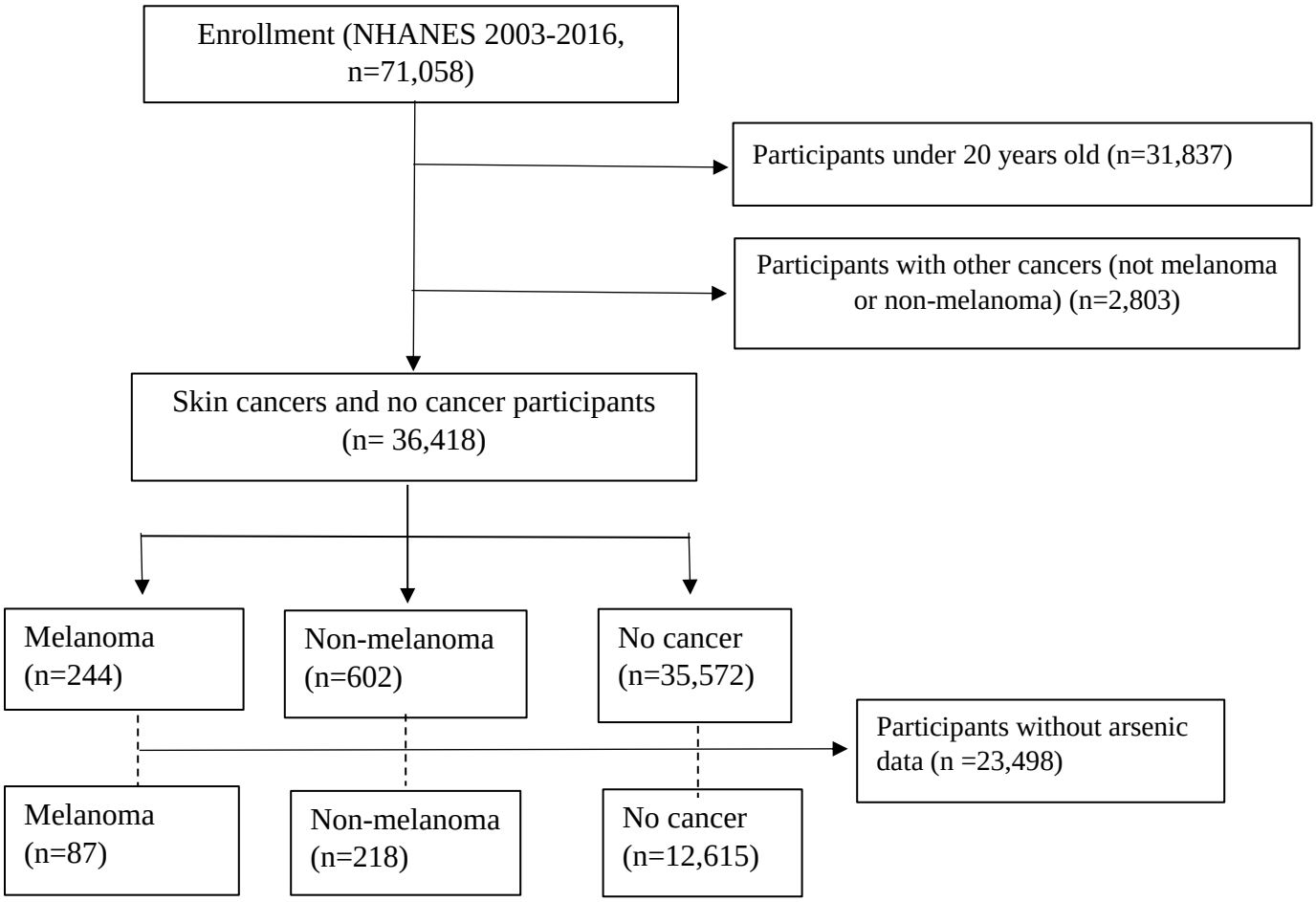
The dependent variables were melanoma skin cancer and non-melanoma skin cancer to participants with no cancer. The independent variable was total urinary arsenic levels. The chi-square test for categorical variables and t-test for continuous variables were used to compare participants with melanoma and participants with non-melanoma to participants with no cancer. P-values less than 0.05 were considered significant. Univariate and multivariate logistic regression analyses were conducted to detect the variables that had a significant effect on melanoma and non-melanoma. Odds ratios and 95% confidence interval were reported for univariate analysis and multivariate models. The Breslow-Day test (0.1 significance level) was used to identify effect modifiers with total urinary arsenic levels. If no interaction, testing for confounders was calculated based on a 10% difference from crude and adjusted odds ratios. For the third aim of the study, the tap water source was investigated in the context of skin cancers using univariate logistic regression. SAS statistical software (version 9.4, SAS Inc., Cary, NC, USA) was used.

Results

Study sample

The NHANES cycles from 2003-2016 had a total of 71,058 participants. Cancer status was measured using the NHANES-medical condition (MCQ) questionnaire, which is only given to subjects who are 20 years of age or older; therefore, 31,837 participants under 20 years of age were excluded from the study. Participants who had other types of cancers (not melanoma or non-melanoma) were excluded (n=2,803). The total population with cancer data in NHANES was 36,418 participants. Arsenic testing was conducted on approximately one-third of the NHANES study population, and only 12,920 participants had information about the total urinary arsenic (ug/L). Participants with arsenic data were divided into three groups: melanoma skin cancer (n=87), non-melanoma skin cancer (n=218), and no cancer (n=12,615) (Figure 5).

Figure 5. A flow diagram of participant inclusion.



Description of the study population

The general characteristics of the total sample size (n=36,418) with skin cancer to healthy participants with no cancer was analyzed. The mean age and standard error (SE) for melanoma and non-melanoma were similar at 62.73 years (0.77) and 63.49 years (0.74), respectively. Participants without cancer were significantly younger (mean: 45.44 (0.21), $p < 0.0001$). A larger proportion of males were identified in the melanoma and non-melanoma diagnoses groups. However, the association was not significant (Table 1).

Participants with melanoma and non-melanoma skin cancer were significantly more likely to be white ($p < 0.0001$), similar to what has been previously reported in the literature (11,14). Participants with higher education (college graduate or above) level were more likely to have melanoma ($p < 0.05$) and non-melanoma ($p < 0.0001$) compared to no cancer. The ratio of family income to poverty showed a significant increase in the percent of participants with a ratio >1.30 (higher SES) as having skin cancer ($p < 0.0001$). There was no difference between participants with skin cancer who had a sunburn compared to never had a sunburn, but data for dermatology questionnaire in NHANES was missing, particularly individuals aged 60 or older, to draw a conclusion. Ever smokers were significantly more likely to be diagnosed melanoma ($p < 0.01$) and non-melanoma ($p < 0.001$) skin cancers compared to never smokers (Table1).

The association between the tap water source and skin cancer

The third aim of the study was to explore the association between water sources and skin cancer. The total population with data on tap water source was 30,253 participants. Participants with non-melanoma skin cancer diagnoses were 2.06 (95% Cl: 1.25-3.41) times more likely to report a non-municipal water source compared to participants without cancer. There was no

significant difference in water source between participants with melanoma and participants with no cancer, although the odds ratio was elevated (OR=1.87, 95 Cl: 0.87-4.04) (Table2).

Table 1. Characteristics of the study participants (age =>20) by skin cancer, NHANES 2003-2016 (n=36,418)

	Cancer Types				
	No cancer (n=35,572)	**Melanoma (n=244)**	**P-Value**	**Non-melanoma (n=602)**	**P-Value**
Participants characteristics	No. (column %)	No. (column %)		No. (column %)	
Age (in years) [a]	45.44 (0.21) [a]	62.78 (0.77) [a]	<0.0001 [b]	63.49 (0.74) [a]	<0.0001 [b]
Sex			0.3397 [c]		0.0550 [c]
Male	17,256 (48.51)	135 (55.33)		341 (56.64)	
Female	18,316 (51.49)	109 (44.67)		261 (43.67)	
Race/Ethnicity			<0.0001 [c]		<0.0001 [c]
White	14,750 (41.47)	221 (90.57)		570 (94.68)	
Non-White	20,822 (58.53)	23 (9.43)		32 (5.32)	
Education Level			0.0239 [c]		<0.0001 [c]
High school or less	17,817 (50.17)	90 (36.89)		192 (31.89)	
Some college or AA degree	10,103 (28.45)	81 (33.20)		184 (30.56)	
College graduate or above	7,594 (21.38)	73 (29.92)		226 (37.54)	
Missing	58	0		0	
Ratio of Family Income to Poverty			<0.0001 [c]		<0.0001 [c]
≤1.30	10,669 (32.79)	38 (17.12)		78 (13.93)	
>1.30-3.50	12,150 (37.34)	93 (41.89)		206 (36.79)	
> 3.50-5.00	9,723 (29.88)	91 (40.99)		276 (49.29)	
Missing	3,030	22		42	
Had a Sunburn			0.6052 [c]		0.0793 [c]
Never	13,668 (64.13)	31 (51.67)		60 (48.39)	
Ever	7,646 (35.87)	29 (48.33)		64 (51.61)	
Missing	14,258	184		478	
Smoking Status			0.0024 [c]		0.0006 [c]
Never smokers	19,774 (55.64)	102 (41.80)		262 (43.52)	
Ever smokers	15,764 (44.36)	142 (58.20)		340 (56.48)	
Missing	34	0		0	

[a] Column percent. [b] Estimated by mean and standard error (SE) based on weight. [c] T-test based on weight. [d] Chi-square goodness of Fit tests or Fisher test based on weight. [e] Non-white includes black, Hispanic, and other races. AA= Associate of Ar

Table 2. Characteristics of the study participants (age=>20) by source of drinking water, NHANES 2003-2016 (n=30,253)

	Source of tap water				
	Municipal (n=21,294)	**Non-municipal (n=3,180)**	**OR (95% Cl)**	**Does not drink tap water (n=5,779)**	**OR (95% Cl)**
	No. (column %)	No. (column %)		No. (column %)	
Skin Cancer Types					
Melanoma	149 (0.70)	49 (1.54)	1.87 (0.87-4.04)	16 (0.28)	0.50 (0.20-1.22)
Non-melanoma	399 (1.87)	102 (3.21)	2.06 (1.25-3.41)	36 (0.62)	0.59 (0.30-1.15)
No cancer	20,746 (97.43)	3,029 (95.25)	1.00	5,727 (99.10)	1.00

Municipal group (Ref.), OR = odds ratio, Cl = confidence interval.

Description of the study population with Arsenic data

The study population with arsenic data was 12,920 participants. Less than 10% of the population had urinary total arsenic levels >50 ug/L. Similar to the full population, there were significant differences seen in age and race/ethnicity. Skin cancer cases were seen significantly more often in individuals who were white and were elderly. Education levels and the ratio of family income to poverty were no longer significant for the melanoma group but remained significant for the non-melanoma group when compared to participants with no cancer. The history of sunburn was not statistically significant for association with melanoma or non-melanoma diagnoses. The association for the non-melanoma diagnoses with smoking status remained significant but not for the melanoma participants (Table 3).

No significant association had seen between melanoma and high urinary arsenic levels (>50 ug/L) compared to those with low urinary arsenic levels (OR=1.45, (95% Cl: 0.46-4.62). As well for non-melanoma, no significant odds had shown with urinary arsenic levels (OR=1.65, (95% Cl: 0.91-3.16). As expected, there was a significant association between skin cancer and age, with one year increase in age, the crude odds ratio increased by 1.08 (95% Cl: 1.07-1.10) for melanoma, and 1.07 (95% Cl: 1.06-1.08) for non-melanoma (Table 4).

Table 3. Characteristics of the eligible participants (age =>20) by skin cancer with arsenic data, NHANES 2003-2016 (n=12,920)

	Cancer Types				
	No cancer (n=12,615)	**Melanoma (n=87)**	**P-Value**	**Non-melanoma (n=218)**	**P-Value**
Participants characteristics	No. (column %)	No. (column %)		No. (column %)	
Arsenic			0.4106 [c]		0.0910 [c]
≤50 ug/L	11,698 (92.73)	82 (94.25)		199 (91.28)	
>50 ug/L	917 (7.27)	5 (5.75)		19 (8.72)	
Age (in years) [a]	45.35 (0.27)	64.58 (0.67)	<0.0001 [b]	63.30 (0.97)	<0.0001 [b]
Sex			0.5902 [c]		0.1928 [c]
Male	6,314 (50.05)	45 (51.72)		124 (56.88)	
Female	6,301 (49.95)	42 (48.28)		94 (43.12)	
Race/Ethnicity			<0.0001 [c]		<0.0001 [c]
White	5,283 (41.88)	79 (90.80)		205 (94.04)	
Non-White	7,332 (58.12)	8 (9.20)		13 (5.96)	
Education Level			0.2450 [c]		0.0031 [c]
High school or less	6,435 (51.04)	33 (37.93)		69 (31.65)	
Some college or AA degree	3,495 (29.31)	31 (35.63)		79 (36.24)	
College graduate or above	2,477 (19.65)	23 (26.44)		70 (32.11)	
Missing	8	0		0	
Ratio of Family Income to Poverty			0.0733 [c]		0.0031 [c]
≤1.30	4,000 (33.44)	13 (15.66)		37 (18.05)	
>1.30-3.50	4,367 (37.60)	40 (48.19)		79 (38.54)	
> 3.50-5.00	3,248 (27.96)	30 (36.14)		89 (43.41)	
Missing	1,000	4		13	
Had a Sunburn			0.0730 [c]		0.4301 [c]
Never	5,059 (64.00)	7 (29.17)		27 (54.00)	
Ever	2,846 (36.00)	17 (70.83)		23 (46.00)	
Missing	4,710	63		168	
Smoking Status			0.0803 [c]		0.0050 [c]
Never smokers	6,200 (49.16)	31 (35.63)		83 (38.07)	
Ever smokers	6,411 (50.84)	56 (64.37)		135 (61.93)	
Missing	4	0		0	

[a] Column percent. [b] Estimated by mean and standard error (SE) based on weight. [c] T-test based on weight. [d] Chi-square goodness of Fit tests or Fisher test based on weight. [e] Non-white includes black, Hispanic, and other races. AA= Associate of Art

Participants with melanoma were more likely to be white (OR=18.13; 95% Cl: 8.24 – 39.90). Participants with melanoma were also more likely to be wealthier. The ratio of family income to poverty was 1.91 (95% Cl: 1.01-3.62) for individuals (>1.30-3.50) and 2.37 (95% Cl:1.11-5.04) for individuals (>3.50-5.00) compared to participants ≤1.30. Other covariates measured showed no association with melanoma (Table 4).

For non-melanoma, the crude odds ratio among white people compared to non-white was 27.71 (95% Cl: 12.74 – 60.28). Higher levels of education and ratio of poverty to family income were associated with non-melanoma. The crude odds ratio of having non-melanoma for smoker was 1.57 times higher compared to never smokers (95% Cl:1.14-2.15) (Table 4).

Multivariate Models for skin cancers and urinary total arsenic levels

There was no interaction among covariates, but race/ethnicity had more than a 10% difference in odds when included in the model; race/ethnicity was identified as a confounder. Age also was included in the model due to clinical interest. Two models were built for each skin cancer group. The models for melanoma and non-melanoma groups were with all available participants after adjusting for age and race/ethnicity. The sunburn variable was not added to the multivariate analysis because of low statistical power (Table 5).

For melanoma, after adjusting for age and race/ethnicity (model 1), the adjusted odds ratio of having total urinary arsenic above the toxicity level (>50 ug/L) was 1.87 compared to those with ≤50 ug/L of urinary total arsenic level (%95 Cl: 0.58-6.05). This was not statistically significant ($p < 0.1$). For non-melanoma, after adjusting for age and race/ethnicity (model 1), the adjusted odds ratio of exposure to high levels of total urinary arsenic was 2.23 in participants with non-melanoma skin cancer diagnoses compared to participants without cancer (%95 Cl: 1.12-4.45, p-value <0.05).

Table 4. Univariate logistic regression of the study participants (age =>20) by skin cancer with arsenic data, NHANES 2003-2016 (n=12,920)

	Cancer Types	
	Melanoma	**Non-melanoma**
Participants characteristics	OR (95% Cl)	OR (95% Cl)
Arsenic		
≤50 ug/L	1.00	1.00
>50 ug/L	1.45 (0.46-4.62)	1.69 (0.91-3.16)
Age (in years)	1.08 (1.07-1.10)	1.07 (1.06-1.08)
Sex		
Male	1.15 (0.68-1.94)	1.26 (0.89-1.79)
Female	1.00	1.00
Race / Hispanic origin		
White	18.13 (8.24-39.90)	27.71 (12.74-60.28)
Non-White	1.00	1.00
Education Level		
High school or less	1.00	1.00
Some college or AA degree	0.96 (0.54-1.73)	1.70 (1.13-2.56)
College graduate or above	1.53 (0.81-2.89)	2.06 (1.34-3.18)
Ratio of Family Income to Poverty		
≤1.30	1.00	1.00
>1.30 – 3.50	1.91 (1.01-3.62)	2.23 (1.29-3.86)
> 3.50	2.37 (1.11-5.04)	2.74 (1.55-4.85)
Had a Sunburn		
Never	1.00	1.00
Ever	2.93 (0.84-10.21)	1.29 (0.84-10.21)
Smoking Status		
Never smokers	1.00	1.00
Ever smokers	1.57 (0.94-2.63)	1.57 (1.14-2.15)

No cancer group (Ref.). OR= Odds ratio. Cl= Confidence Interval.

Table 5. Multivariate logistic regression models for skin cancer vs. no cancer

Predictors	Models	
	Melanoma (n=87)	Non-melanoma (n=218)
	Model (AOR, 95% CI)	Model (AOR, 95% CI)
Arsenic		
>50 ug/L vs. ≤50 ug/L	1.87 (0.58-6.05)	2.23 (1.12-4.45) *
Age (in years)	1.07 (1.06-1.09) **	1.07 (1.05-1.08) **
Race/Ethnicity		
White vs. Non-white	13.43 (5.98-30.18) **	21.42 (9.82-46.75) **

No cancer group (Ref.). AOR = adjusted odds ratio, CL = confidence interval. * p-value<0.05, ** p-value<0.0001.

Discussion

Our results are in agreement with previous studies that have found an association between non-melanoma skin cancer diagnoses and arsenic exposure (24,30,31). We did not find an association between melanoma and total urinary arsenic levels. To our knowledge, the association between melanoma and exposure to arsenic has been reported in two studies that measured arsenic levels in toenails and the drinking water system in Iowa (U.S.) and Denmark (36,38). Both studies measured urine in different measurements, and the Denmark study was an ecological study, which might lead to ecological fallacy. A case-control study conducted in New Mexico, which measured exposure to arsenic in urine, found results consistent with our study on the association between melanoma and arsenic (39). Both our study and the New Mexico case-control study had a small sample size. In our study, we had only 5 participants reported melanoma with a high level of arsenic in urine (>50 ug/L).

A study conducted in Canada showed an increase in the risk of melanoma in those with higher socioeconomic status (SES). It was hypothesized that the association with higher SES might be due to improved access to screening and economic security, which allowed leisure times that could be spent in sunny areas (45). Our results with total melanoma participants

supported the association with socioeconomic status using education level and income to poverty ratio as a marker of SES. This relationship was not seen in the population with arsenic data, but it was seen with the total participants.

We did not have adequate data to estimate UV light exposure in melanoma participants. As previously reported, people with multiple sunburns are more likely to develop melanoma compared to persons who do not have a history of sunburn (36,39). We could not explore this relationship because of the limited data available on sunburn history. if we had enough statistical power, we might have different crude and adjusted odds ratios.

We also investigated the association between melanoma and the source of tap water. In some reports, ecological studies noted an increased odds ratio between the level of arsenic in drinking water and the incidence of skin cancer (melanoma and non-melanoma) (32,37). We found an association between non-melanoma skin cancer and drinking from non-municipal water sources. For melanoma, the crude odds ratio was not statistically significant but was elevated (1.87). No relationship was found between total urinary arsenic levels and water sources. We hypothesize there may be another component in non-municipal water, leading to the association with non-melanoma. These results emphasize how important it is to have a drinking water system that passes-through a filtering process.

This study had several limitations. The cross-sectional design does not allow us to establish a temporal relationship between the exposure to arsenic and outcomes of melanoma and non-melanoma skin cancer. Data on sun exposure and the response was incomplete. We were unable to include those variables, which have been included in other papers in our analysis. Arsenic measured in urine corresponded to a three-day exposure history. We cannot determine if acute exposure to arsenic is indicative of chronic exposure. Age at and length of chronic

exposure may also be important factors that we were unable to be measured. NHANES is a national survey that is designed to be representative of the noninstitutionalized U.S. population. We followed the analysis guidelines so our data can be generalized to the U.S. population. The data was collected based on a highly valid and reliable survey. Further research with improved study design and complete variable information is warranted to determine if there is an association between arsenic and melanoma.

Conclusion

A relationship between the incidence of melanoma and exposure to arsenic (measured in urine) among U.S. adults was not found using NHANES data from 2003-2016. After adjusting for age, race/ethnicity, people with non-melanoma skin cancer diagnoses were more likely to have a high total urinary arsenic level. Non-municipal water sources may be associated with skin cancer and should be further investigated.

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Public Health Competencies

- **Epidemiological Competencies**

1. **Analyze dataset using computer software:** My capstone project needs to use a publicly available database called NHANES from 2003-2016 to answer the research question. In order to do the analysis, I downloaded this data and combined it into one dataset. I performed several statistical tests to analyze the data based on what I learned in my biostatistics classes and applied epidemiology class. All analyses were conducted with SAS statistical software (version 9.4).
2. **Utilize analytical approaches to describe, summarize, and interpret epidemiologic data:** After conducting the analysis portion of my capstone, I described my study population from the NHANES 2003-2016 dataset using tables and a flow chart. I summarized and interpreted the findings from the analysis based on what I learned from epidemiology classes. Finally, I concluded my study results in an epidemiological manner.

- **Foundational Competency**

1. **Assess population needs, assets and capacities that affect communities' health:** Based on my capstone, the results might agree or disagree with some studies' findings that assessed the relationship between exposure to arsenic and melanoma. Therefore, the findings could help in the application of public health interventions to restrict or reduce the exposure of arsenic in drinking water, particularly in private wells, and other sources of arsenic. This may decrease the incidence and mortality of melanoma.

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