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DATABASE ANALYSIS

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Association of Thiamine Intake with Human Papillomavirus (HPV) Infection in American Women: A Secondary Data Analysis Based on the National Health and Nutrition Examination Survey from 2003 to 2016

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCE 1 Yue-xi Zhou
BE 1 Fang-fang Zhu
C 2 Chi Chen
D 1 Ying-xuan Zhang
F 1 Xiao-li Lv
F 1 Jing-wei Li
AG 3 Song-ping Luo*
AG 3 Jie Gao*

1 First Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, P.R. China
2 Department of Immunology and Microbiology, Guiyang College of Traditional Chinese Medicine, Guiyang, Guizhou, P.R. China
3 Department of Obstetrics and Gynecology, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, P.R. China

* Jie Gao and Song-ping Luo contributed equally to this research

Corresponding Authors: Jie Gao, e-mail: gjfkts@qq.com, Song-ping Luo, e-mail: songpingluo@hotmail.com

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Background: Studies have shown that thiamine intake is associated with cervical cancer, but the relationship between thiamine and HPV infection remains unclear. In the present study, we used the National Health and Nutrition Examination Survey (NHANES) database to investigate whether HPV infection was associated with thiamine intake.

Material/Methods: A total of 13 471 women ages 18-59 years were selected from the NHANES database from 2003 to 2016. Using thiamine intake as the independent variable, HPV infection as the dependent variable, and sociodemographic data and other data as the covariates, we analyzed the relationship between thiamine and HPV infection by conducting a weighted logistic regression model in a cross-sectional research design.

Results: The two-piecewise linear model indicated the inflection point of thiamine intake was 2.07 mg. On the left side of the inflection point, the difference in the thiamine intake of log2 conversion was related to the difference of 0.82 in HPV infection, which means that the increase of every 1 unit increase in thiamine intake is associated with the decrease of the HPV infection by 18%. On the right side of the inflection point, we did not observe a correlation between HPV infection and thiamine intake.

Conclusions: Thiamine intake is negatively correlated with HPV infection. Intake of an appropriate amount of thiamine can prevent HPV infection. The best preventive effect can be achieved when the intake is about 2 mg, and excessive intake will not increase the preventive effect.

MeSH Keywords: Cross-Sectional Studies • Human Papillomavirus DNA Tests • National Center for Health Statistics (U.S.) • Thiamine

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Background

Previous research indicated the prevalence of human papillomavirus (HPV) infection in the cervix was 42.7% [1]. HPV infection is transmitted through sexual behavior, with high-risk areas being North America, Europe, and Africa, where the populations have relatively more sexual activity and more sexual partners [2]. It is estimated that 291 million women carry HPV DNA worldwide, and about one-third of them carry the most common HPV infection, type 16 or 18, which can develop into precancerous lesions and cervical cancer [3]. The infection is temporary and does not need intervention. About 90% of the infections will be eliminated by the immune system within a few months to 2 years and cannot be detected [4]. But if HPV enters the latent state in the basal cells of the cervical epithelium, it may lead an undetectable amount of virus and cause a false-negative result [5,6]. When the body is infected by HPV, it will cause the immune response and produce the serum antibody of the corresponding HPV type. Unfortunately, the antibody may disappear with increasing age or decreasing immunity, which cannot provide protection against reinfection. However, there is a risk of reinfection after elimination of HPV infection [6–8]. Acquired HPV infection lasts for more than 1 year, and the probability of developing cervical squamous intraepithelial lesions is greatly increased. If untreated, it can cause cancer [9]. In developing countries and regions, knowledge about cervical cancer and HPV infection is poor; as a result, HPV vaccination rates are lower than in developed regions [10,11]. Serious adverse events after HPV vaccination have been reported and its safety still cannot be completely confirmed [12]. Finding another way to prevent HPV infection is a good complement to the above deficiencies. Given the risk of HPV reinfection, the inevitable misdiagnosis rate of HPV screening, the risks of vaccine use, and other issues, it is essential to strengthen the prevention of HPV infection by modification of daily diet.

There are a growing number of reports on dietary nutrients and HPV infection. Studies have found that HPV infection is associated with nutrients in the diet [13–15], which have different abilities to prevent and combat the development of diseases caused by HPV infection [16]. High circulating levels of micronutrients seem to enhance time to clearance, and can rapidly resolve HPV infections [17]. Moreover, micronutrients in plasma can prevent premalignant lesions of the cervix and cervical cancer [14,18]. B vitamins, such as folate (vitamin B9), riboflavin (vitamin B2), and vitamin B12 intake, are inversely associated with HPV infection and persistence [13,19]. These B vitamins participate in one-carbon metabolism and DNA methylation [20], which affect epigenetic changes of the HPV virus [21]. Thiamine (vitamin B1) is also involved in the process of one-carbon metabolism [20]. One-carbon metabolism is a complex biochemical process that provides methyl for DNA methylation. Under the catalysis of thiamine pyrophosphate kinase (TPK), thiamine is phosphorylated in cytoplasm and converted into thiamine pyrophosphate (TPP) with enzyme activity. As an important cofactor involved in one-carbon metabolism, TPP can reversibly cleave carbon-carbon bonds [22]. In addition, thiamine is closely related to riboflavin and vitamin B12. They are the coenzymes that are necessary for aerobic respiration of mitochondria and energy production of cells, coordinate metabolism of glucose, fatty acids, and amino acid of mitochondria [23]. A case-control study that explored the relationship between diet and cervical dysplasia suggested that thiamine plays a protective role in cervical carcinogenesis caused by persistent HPV infection [24]. Therefore, we hypothesized that thiamine may be associated with HPV infection. In this study, we used the NHANES dataset to evaluate the association between thiamine and HPV infection.

Material and Methods

Study samples

The National Health and Nutrition Examination Survey (NHANES) uses studies combining interviews and physical examinations, and was designed to assess the health and nutritional status of adults and children in the United States. It was conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control (CDC). Female participants aged 18 to 59 years were selected as the study population from the 2003–2004 survey cycle to the 2015–2016 survey cycle from the NHANES database. Self-collected cervicovaginal swabs were obtained at mobile examination centers. Detailed dietary intake information obtained from NHANES participants was used to estimate the types and amounts of foods and beverages consumed during the 24 h before the interviews, and to estimate intakes of thiamine from those foods and beverages. The information of participants was collected by self-administered questionnaire and household interviews. The present study selected 13 471 participants after excluding missing samples (Figure 1). The NHANES protocol was reviewed and approved by the NCHS Research Ethics Board, and all participants provided signed informed consent. Data used in this study are de-identified and publicly available. More details about the study samples can be found on the NHANES website (*https://wwwn.cdc.gov/Nchs/Nhanes*).

Variables

The dependent variable was HPV infection, which is a binary variable, including HPV-negative and HPV-positive. Self-collected cervicovaginal swabs were collected and tested with the Linear Array HPV genotyping assay. Based on the description of NHANES in other studies [25], a total of 37 HPV

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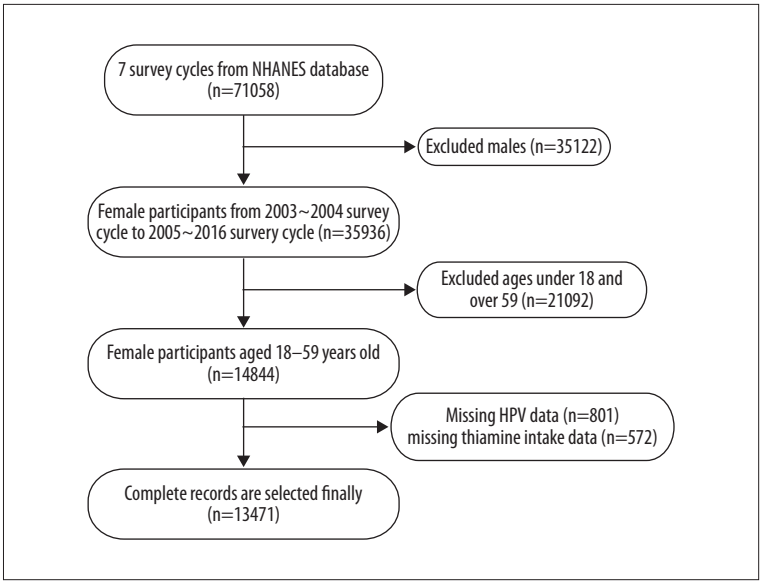

Figure 1. Flowchart of the study. This study selected 13 471 participants after excluding those with missing samples.

genotypes were detected and included for the participants detected with HPV-positivity. High-risk HPV genotypes (cancer-associated HPV types) include types 16, 18, 31, 33, 35, 39, 45 51, 52, 56, 58, 59, and 68, and other HPV genotypes are regarded as low-risk HPV.

The targeted independent variable was thiamine intake (mg). These data were collected and calculated at the Mobile Examination Center by household interviews. Participants were asked to complete a 24-h recall that included all food and drinks consumed from midnight to midnight on the previous day, but dietary supplements were excluded [26,27].

Covariates were based on social demographic data and previous studies of HPV related factors [28–30]. Social demographic data included age (years), race/ethnicity (Mexican-American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), education (less than 9th grade, Grades 9–11, high school graduation, college, more than college), marital status (married or living with partner, widowed, divorced, or separated), and body mass index (BMI, kg/m^2). Other suspected confounding factors include alcohol drinking frequency, sexual partner number, age of first sexual activity, smoking over 100 cigarettes per year, vaginal or anal intercourse times, use of contraceptives, and use of female sex hormones.

Statistical analysis

In the first step, we presented the baseline data for the participants who were included in this study in Table 1. Due to the skewed distribution of thiamine in the population, we performed a log2 transformation to conform to normal distribution. To calculate the different outcomes among each covariate, a weighted chi-square test was used for the categorical variables and a weighted linear regression model was used for continuous variables in the baseline data. The results of continuous variables were expressed as mean±standard deviation, and the results of categorical variables were expressed as frequency and percentage.

In the second step, we used weighted univariate and multivariate logistic regression models according to the recommendations of the STROBE statement [31]. No variables were adjusted in Model 1. Model 2 only adjusted social demographic variables, including body mass index, age, education, marital status, and ethnicity. Model 3 is a fully adjusted model that adjusted all the covariates shown in Table 1.

In the third step, the targeted independent variable thiamine intake was converted into a categorical variable according to quartile, and we assessed whether the OR value changes between different groups were equidistant. A smooth curve fitting and a generalized additive model (GAM) were used to assess the nonlinear relationship between thiamine intake and HPV infection. Since a nonlinear relationship was detected, a recursive algorithm was used to calculate the inflection point, and a weighted two-piecewise linear model was constructed on both sides of the inflection point. The best-fitting model was determined based on the *P* value of the log-likelihood ratio test. If the *P* value of the log-likelihood ratio test was greater than 0.05, we considered that there was a linear relationship between thiamine intake and HPV infection, otherwise, there was a nonlinear relationship.

We used the statistical packages R (The R Foundation; *http://www.r-project.org*; version 3.4.3) and Empower Stats (www.empowerstats.com; X&Y Solutions, Inc.) to perform the whole process of data analysis.

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Table 1. Baseline characteristics of participants.

Thiamine intake (log2 transform)	Q1	Q2	Q3	Q4	P value
N	3828	3581	3385	2677	
Age	37.27±12.65	37.31±12.41	37.26±12.02	35.19±12.04	<0.001
BMI	29.31±7.67	29.09±7.60	29.13±7.66	28.99±8.01	0.407
Frequency of drinking in the past 12 months	3.27±12.89	3.17±7.94	3.40±11.84	3.14±9.83	0.847
Number of sexual partners in the past year	1.45±3.02	1.20±1.49	1.53±5.16	1.28±1.87	0.019
Age of first sexual activity	17.22±3.41	17.54±3.75	17.75±3.73	17.57±3.78	<0.001
Race/ethnicity					<0.001
Mexican American	687 (17.95%)	652 (18.21%)	664 (19.62%)	567 (21.18%)	
Other Hispanic	346 (9.04%)	328 (9.16%)	327 (9.66%)	205 (7.66%)	
Non-Hispanic White	1427 (37.28%)	1494 (41.72%)	1386 (40.95%)	1114 (41.61%)	
Non-Hispanic Black	1069 (27.93%)	807 (22.54%)	685 (20.24%)	551 (20.58%)	
Other race/ethnicity	299 (7.81%)	300 (8.38%)	323 (9.54%)	240 (8.97%)	
Education					<0.001
Less than 9th grade	289 (8.44%)	224 (6.91%)	194 (6.25%)	174 (7.33%)	
Grades 9-11	519 (15.16%)	458 (14.12%)	385 (12.41%)	312 (13.14%)	
High school graduation	819 (23.93%)	653 (20.13%)	649 (20.92%)	460 (19.38%)	
College	1154 (33.71%)	1128 (34.77%)	991 (31.94%)	782 (32.94%)	
More than college	642 (18.76%)	781 (24.08%)	884 (28.49%)	646 (27.21%)	
Marital status					<0.001
Married or living with partner	1877 (51.58%)	1966 (57.42%)	1952 (60.02%)	1520 (59.44%)	
Widowed, divorced or separated	1762 (48.42%)	1458 (42.58%)	1300 (39.98%)	1037 (40.56%)	
Smoking over 100					<0.001
No	2089 (59.72%)	2131 (64.36%)	2093 (66.07%)	1587 (65.47%)	
Yes	1409 (40.28%)	1180 (35.64%)	1075 (33.93%)	837 (34.53%)	
Vaginal or anal intercourse times					<0.001
0	33 (1.53%)	25 (1.22%)	15 (0.76%)	19 (1.31%)	
1–11	188 (8.74%)	119 (5.83%)	146 (7.38%)	102 (7.02%)	
12–51	544 (25.30%)	462 (22.64%)	445 (22.49%)	314 (21.64%)	
52–103	681 (31.67%)	717 (35.13%)	703 (35.52%)	497 (34.25%)	
104–364	418 (19.44%)	418 (20.48%)	429 (21.68%)	297 (20.47%)	
≥365	286 (13.30%)	300 (14.70%)	241 (12.18%)	222 (15.30%)	
Used contraceptives					0.003
No	1097 (30.73%)	921 (27.35%)	867 (27.45%)	747 (29.94%)	
Yes	2473 (69.27%)	2446 (72.65%)	2292 (72.55%)	1748 (70.06%)	

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Table 1 continued. Baseline characteristics of participants.

Thiamine intake (log2 transform)	Q1	Q2	Q3	Q4	P value
Used sex hormones					0.022
No	2782 (87.65%)	2713 (89.18%)	2551 (88.45%)	1989 (90.25%)	
Yes	392 (12.35%)	6329 (10.82%)	333 (11.55%)	215 (9.75%)	
HPV infection					<0.001
No	1936 (50.57%)	2047 (57.16%)	2034 (60.09%)	1590 (59.39%)	
Yes	1892 (49.43%)	1534 (42.84%)	1351 (39.91%)	1087 (40.61%)	

Mean±SD for continuous variables: *P* value was calculated by weighted linear regression model. % for Categorical variables: *P* value was calculated by weighted chi-square test.

Table 2. The linear and nonlinear relationship between thiamine intake and HPV infection assessed by weighted univariate and multivariate logistic regression models.

Exposure	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	GAM model β (95% CI)
HN *vs.* HP	n=13471	n=12089	n=4170	n=4170
thiamine intake (mg) (log2 transform)	0.83 (0.79, 0.86)	0.87 (0.83, 0.91)	0.87 (0.80, 0.95)	0.87 (0.80, 0.95)
Thiamine intake (mg) (log2 transform) (quartile)				
Q1	Ref	Ref	Ref	Ref
Q2	0.77 (0.70, 0.84)	0.83 (0.75, 0.91)	0.83 (0.69, 0.99)	0.83 (0.70, 0.99)
Q3	0.68 (0.62, 0.75)	0.76 (0.68, 0.84)	0.73 (0.61, 0.87)	0.74 (0.62, 0.88)
Q4	0.70 (0.63, 0.77)	0.77 (0.69, 0.86)	0.75 (0.62, 0.92)	0.75 (0.62, 0.92)
P for trend	<0.0001	<0.0001	0.0007	0.0009

Model 1 – no covariates were adjusted; Model 2 – only sociodemographic variables were adjusted (body mass index, age, education, marital status, and ethnicity); Model 3 – all covariates presented in Table 1 were adjusted; GAM Model – all continuous variables in the covariates were adjusted as smooth.

Results

Baseline characteristics of participants

The weighted distribution of the covariates of the participants selected from NHANES 2003-2016 is shown in Table 1. There was no significant difference among groups in BMI, frequency of drinking, or number of sexual partners. For continuous variables, people who ingested more thiamine were younger and the age of first sexual activity was older. For categorical variables, there were differences in race/ethnicity, education, marital status, smoking, sexual intercourse or anal sex, use of contraceptives and sex hormones, and HPV infection. In detail, non-Hispanic whites, other Hispanic, other races, education more than college, married or living with partner, never smoking, use of sex hormones, and HPV infection were negative for those who ingested more thiamine.

Association of thiamine intake with HPV infection

Effect sizes of the association of thiamine intake with HPV infection are listed in Table 2. The results of the unadjusted model (model 1) indicated that thiamine intake was negatively correlated with HPV infection (β=0.83, 95% CI: 0.79, 0.86), which means that the increase of every 1 unit (log2 transformed) in thiamine is associated a 17% decrease in risk of HPV infection. Model 2 showed the same trend as model 3, in which the risk of HPV infection was reduced by 13% for each unit of log2 transformed thiamine intake (mg) increase. Interestingly, after adjusting all of the variables in Table 1, model 3 showed the same reduction rate as model 2 with the increase of thiamine per unit, showing that thiamine intake was still a protective factor for HPV infection. Assuming that there was a curved relationship between continuous variables and thiamine intake, we applied the GAM model to fit all continuous variables as

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Table 3. Nonlinear relationship detecting by weighted two-piecewise linear model.

	HPV infection	
Model I		
Regression coefficients	0.87	(0.80, 0.95)
Model II		
Inflection point of thiamine intake (log2 transform)	1.05	
Regression coefficients (≤inflection point)	0.82	(0.74, 0.90)
Regression coefficients (>inflection point)	1.40	(0.93, 2.10)
Regression coefficient difference	1.71	(1.09, 2.68)
predicted value of thiamine intake (Y) at inflection point	–0.37	(–0.48, –0.27)
P for log likelihood ratio test	0.019	

smooth, producing exactly the same results (β=0.87, 95% CI: 0.80, 0.95). After the thiamine intake was converted from a continuous variable to a categorical variable by quartile, and Q1 group was used as a reference, the effect values of all the above models were less than 1. In addition, the effective values of the Q3 and Q4 groups were smaller than those in the Q2 group. This clearly demonstrated that the protective effect against HPV infection was more obvious with the increase of thiamine intake dose.

As shown in Table 3 and described in Figure 2, there was a nonlinear relationship between thiamine intake and HPV infection. We constructed a weighted two-segment linear regression model using smooth curve fitting, and found that the *P* value of the log-likelihood ratio test was less than 0.05, indicating that the two-piecewise linear model was the best-fitting model. The inflection point of thiamine intake was 2.07 mg. On the left side of the inflection point (thiamine intake ≤2.07 mg), the difference in thiamine intake of log2 transform was related to the 0.82 difference in HPV infection. On the right side of the inflection point, we did not observe a correlation between HPV infection and thiamine intake (β=1.40, 95% CI: 0.93, 2.10).

We also performed a sensitivity analysis to make the research more rigorous. HPV infection was divided into high-risk infection and low-risk infection. Supplementary Table 1 compares the association between different types of HPV infections (high-risk type or low-risk type) with thiamine intake. When thiamine intake was treated as a continuous variable, it was a protective factor for high-risk HPV infection if the covariates were not adjusted or if only social demographic variables were adjusted (β= 0.83,95% CI: 0.79, 0.88; β=0.89, 95% CI: 0.84, 0.94). In model 3 and the GAM model, thiamine tended to reduce the incidence of high-risk HPV infection (β=0.91, 95% CI: 0.82, 1.01; β=0.92, 95% CI: 0.83, 1.03), but the results were not statistically significant. For low-risk HPV infections, thiamine intake was inversely associated with HPV infection

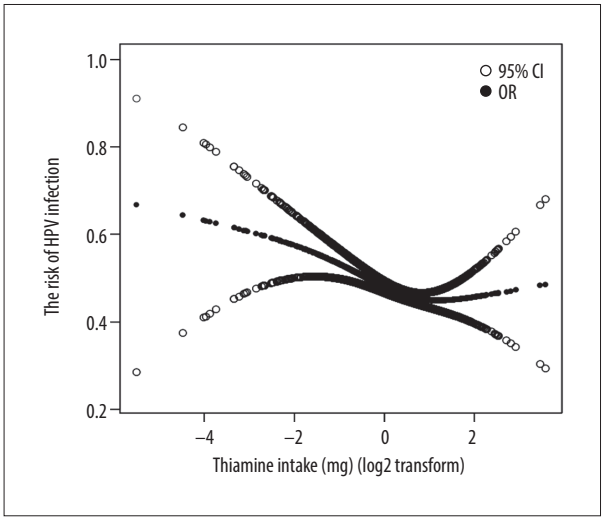

Figure 2. Correlation between the risk of HPV infection and thiamine intake. The inflection point of thiamine intake was 2.07 mg. On the left side of the inflection point (thiamine intake ≤2.07 mg), the difference in thiamine intake of log2 transform is related to the 0.82 difference in HPV infection. On the right side of the inflection point, we did not observe a correlation between HPV infection and thiamine intake (β=1.40, 95% CI: 0.93, 2.10).

in model 1, model 2, model 3, and the GAM model. This means that increased thiamine intake always protected against low-risk HPV infection.

Discussion

The purpose of this study was to determine whether there is a correlation between HPV infection and thiamine intake. The results illustrated that thiamine intake was not only associated with HPV infection, but also reduced the risk of HPV infection. However, this protective effect has a saturating effect, that is,

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once more than a certain amount of thiamine was ingested, the protective effect is no longer enhanced. According to the calculated inflection point of our study, 2 mg is recommended as the optimal thiamine intake to prevent HPV infection.

According to the Institute of Medicine (US) Standing Committee on the scientific evaluation of dietary reference intakes for thiamine [32], the recommended dietary allowance (RDA) for adult women (19–70 years) is 1.1 mg/d. The median intake by young women was approximately 1.2 mg daily. Frank et al. [33] reported that several special clinical conditions increased the risk for thiamine deficiency and provided supplementary dose recommendations. There are no reports available on preventing HPV infection by consumption of thiamine in food. Our study shows that the risk of HPV infection is lowest when thiamine intake is around 2 mg. This is an important reference for clinical protection against HPV infection. For some areas where HPV vaccine penetration is limited or where HPV screening rates are low, adjusting dietary intake of appropriate thiamine may ameliorate this situation.

Nutrient-gene interactions occur with a variety of B vitamins, including folate, thiamine, and vitamin B12 [34], and they can regulate gene expression at the mRNA transcription level and translation level. Through the actions of phosphorylated forms, thiamine is transformed to TPP, directly interacts with mRNA in the body, induces a structural alteration in mRNA that reduces the binding of ribosome, and blocks the translation of mRNA [35,36]. As a widely investigated vitamin, thiamine deficiency is known to be involved in sepsis [37], neurological diseases [38], and cardiovascular diseases [39]. However, little is known about the relationship between thiamine and HPV infection. Previous research on diet and premalignant lesions of the cervix show that thiamine is a protective factor for squamous intraepithelial lesions of the cervix (SIL), especially for high-grade SIL [24]. Viral loads of HPV DNA infection were reported to be associated with the severity of premalignant lesions of the cervix [40]. There is no direct evidence that HPV infection is associated with thiamine intake, but many basic molecular mechanism experiments suggest this possibility. Hypoxia-inducible factor 1-α (HIF-1α) is stabilized in the absence of thiamine, and expression and activation of its target gene, vascular endothelial growth factor (VEGF), is correspondingly increased [41]. The expression of VEGF-C is associated with high-risk HPV infection of cervical lesions, with linearly increasing expression starting from low-grade CIN, which can be used as an early marker of cervical cancer [42]. The literature on the role of thiamine in HIV infection suggests that thiamine affects HIV through matrix metalloproteinase (MMP), vascular endothelial growth factor (VEGF), and cyclooxygenase 2(COX-2), and thiamine supplementation may be beneficial to AIDS patients [43]. Interestingly, HIV seropositivity is closely related to the high incidence rate of HPV and the high prevalence of HPV polygenic infection [44]. Studies have shown that these 2 viruses share a common mechanism in susceptible cells, including epithelial destruction or dysplasia, and decreased protein secretion involved in proinflammatory cytokine production or immune response [45]. The above research results indicate that there may be some connection between thiamine and HPV infection.

According to our review, a higher intake of nutrients with antiviral function may prevent HPV infection from progressing to high cervical intraepithelial neoplasia [46]. The results of this study showed that thiamine has potential preventive and intervention effects on HPV-infected patients. Progression of cervical cancer takes decades due to persistent HPV infection. Therefore, this long window provides a golden opportunity for clinical intervention. To conserve limited medical resources, it is more appropriate to obtain the correct nutrients from daily diet to protect against HPV infection. We speculate that thiamine has potent antiviral effects, but this speculation requires more prospective studies to verify.

Our research may provide a reference for building predictive models and developing dietary guidelines. One of the main strengths of the study was the large sample size from the NHANES database. However, we used a cross-sectional study design, so we were unable to show a causal relationship between thiamine intake and HPV infection. In addition, our study only included women aged 18-59, so our results may not apply to women who are younger than 18 or older than 59 or to males.

Conclusions

In conclusion, thiamine intake is negatively correlated with HPV infection. Dietary intake of an appropriate amount of thiamine can prevent HPV infection. The best preventive effect can be achieved when the intake is about 2 mg, and excessive intake will not increase the preventive effect.

Conflict of interests

None.

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Supplementary Data

Supplementary Table 1. Association of thiamine intake with different types of HPV infection.

Exposure	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 3 β (95% CI)	GAM model β (95% CI)
High-risk HPV infection	n=10565	n=9410	n=3187	n=3187
Thiamine intake (mg) (log2 transform)	0.83 (0.79, 0.88)	0.89 (0.84, 0.94)	0.91 (0.82, 1.01)	0.92 (0.83, 1.03)
Low-risk HPV infection	n=10495	n=9537	n=3174	n=3174
Thiamine intake(mg) (log2 transform)	0.82 (0.78, 0.86)	0.86 (0.81, 0.91)	0.84 (0.76, 0.93)	0.85 (0.76, 0.94)

Model 1 – no covariates were adjusted; Model 2 – only sociodemographic variables were adjusted (body mass index, age, education, marital status, and ethnicity); Model 3 – all covariates presented in Table 1 were adjusted; GAM Model – all continuous variables in the covariates were adjusted as smooth.

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