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Original Communication

Visceral Adiposity Index and Cancer Prevalence in U.S. Adults: A Cross-Sectional Analysis of NHANES 1999–2020

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Abstract

Objective: Visceral adiposity has been implicated in carcinogenesis through chronic inflammation, insulin resistance, and lipid dysregulation, whereas body mass index (BMI) does not capture fat distribution. The Visceral Adiposity Index (VAI)—combining waist circumference, BMI, triglycerides, and high-density lipoprotein-cholesterol (HDL-C)—serves as a surrogate of visceral fat function, but its value for cancer risk prediction is unclear. We aimed to evaluate the association between VAI and cancer prevalence in U.S. adults using NHANES 1999–2020, assess independence from BMI, characterize subgroup and dose–response patterns, and conduct prespecified exploratory site-specific analyses. **Methods**: A total of 20,699 adults aged ≥20 years were included after excluding participants with missing data. The primary outcome was a self-reported history of physician-diagnosed cancer, with the exclusion of non-melanoma skin cancers—such as basal cell carcinoma and squamous cell carcinoma—due to their typically indolent behavior and minimal epidemiological impact. Importantly, melanoma cases were included in the analysis. VAI was analyzed both as a continuous variable and in quartile-based categories (<1.0, 1.0–<2.0, 2.0–<3.0, and ≥3.0). Weighted logistic regression models were constructed with progressive adjustment for demographic, lifestyle, and metabolic covariates (e.g., hypertension, diabetes). Restricted cubic spline (RCS) analyses were performed to assess the dose–response relationship between VAI and cancer, and interaction analyses were conducted across subgroups defined by sex, age, BMI, and hypertension status. **Results**: In the unadjusted model, each one-unit increase in VAI was associated with significantly higher odds of cancer (OR = 1.019; 95% CI: 1.003–1.035; $p = 0.019$). Participants in the highest VAI category (≥3.0) had approximately threefold increased odds of cancer compared to those in the lowest category (<1.0) (OR = 3.04; $p < 0.001$). After stepwise adjustment for demographic and lifestyle factors, the association attenuated; in our prespecified primary model that excluded BMI and hyperlipidemia to avoid overadjustment, the association remained statistically significant (OR = 1.024; 95% CI: 1.004–1.045; $p = 0.021$), indicating that higher VAI was independently associated with cancer prevalence. RCS analysis suggested a weak, approximately linear increase in cancer prevalence odds with increasing VAI, without a clear threshold effect; the overall association was statistically significant ($p = 0.0428$), and the test for nonlinearity showed borderline significance ($p = 0.0540$). Subgroup analyses showed a consistent pattern across most strata, except for a borderline significant interaction by hypertension status ($p = 0.044$), with a stronger association in individuals without hypertension. In pre-specified site-specific analyses, no individual cancer type demonstrated an independent positive association with VAI after full adjustment; intermediate VAI levels were inversely associated with cervical cancer, a counterintuitive finding that warrants cautious interpretation given limited case counts. **Conclusions**: Higher VAI levels were associated with increased cancer prevalence; however, the strength of the association diminished after controlling for traditional obesity metrics. These findings suggest that VAI may offer limited independent predictive value for cancer risk beyond BMI. Further prospective and mechanistic studies are warranted to establish causal relationships and evaluate the utility of VAI in identifying high-risk subpopulations.

Keywords: visceral adiposity index; VAI; cancer; NHANES; obesity; BMI; RCS; cross-sectional study

1. Introduction

Cancer has become one of the leading causes of death worldwide. Recent estimates indicated approximately 19.3 million new cancer cases globally in 2020, and the incidence is projected to increase to nearly 27.5 million by 2040 [1]. Overweight and obesity are well-established modifiable risk factors associated with increased risks of at least 12 types of cancer, including colorectal, pancreatic, liver, renal, gallbladder, ovarian, endometrial, esophageal adenocarcinoma, and postmenopausal breast cancers [2]. The underlying mechanisms linking obesity to carcinogenesis are closely related to metabolic dysfunction induced by excess adipose tissue accumulation, particularly visceral adipose tissue (VAT) [3]. Compared with subcutaneous adipose tissue, VAT—located around visceral organs—is more strongly associated with metabolic abnormalities such as insulin resistance and chronic low-grade inflammation, conditions widely recognized as key drivers of cancer development [4]. Previous studies have suggested that VAT accumulation not only induces direct metabolic disturbances but also promotes the secretion of pro-inflammatory cytokines (e.g., IL-6, TNF-α) and bioactive molecules such

as fatty acids. These substances can reshape the tumor microenvironment, subsequently facilitating cancer cell proliferation, metastasis, and therapeutic resistance [5,6]. Further evidence highlights the critical role of visceral fat relative to subcutaneous fat in systemic and local oncogenic mechanisms, mediated by its pronounced metabolic activity through insulin resistance, activation of the insulin-like growth factor (IGF) axis, chronic inflammation, dysregulation of sex hormones, and activation of HIF-1α and NF-κB pathways [7]. Additionally, VAT contributes to gastrointestinal cancer progression via disrupted insulin signaling, adipose-related inflammation, and altered sex hormone metabolism [8]. Moreover, central obesity-related hyperinsulinemia, increased pro-inflammatory cytokines (IL-6, TNF-α), and reduced anti-inflammatory adipokines (e.g., adiponectin) further promote a microenvironment conducive to tumor development [9,10]. Obesity is a heterogeneous condition, and recent studies have highlighted the existence of metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) phenotypes [11, 12]. Individuals with MHO exhibit favorable metabolic profiles, such as preserved insulin sensitivity and normal lipid levels, despite excess adiposity. In contrast, individuals with MUO show insulin resistance, elevated triglycerides, and systemic inflammation even at similar BMI levels. These phenotype differences imply that visceral adiposity, rather than general obesity alone, may be a stronger driver of metabolic complications and cancer risk. Therefore, fat distribution may provide greater predictive value for cancer risk assessment compared with general obesity measures.

The traditional measure of obesity, body mass index (BMI), reflects only overall adiposity without distinguishing between visceral and subcutaneous fat distribution. This limitation reduces its accuracy in assessing metabolic and disease risks. For example, individuals with elevated BMI predominantly due to subcutaneous fat accumulation might carry relatively low metabolic risk, whereas individuals with normal BMI but significant visceral fat deposition may suffer from severe insulin resistance and metabolic disorders [13]. To address these shortcomings, Amato et al. [14] introduced the Visceral Adiposity Index (VAI), a composite metric combining anthropometric indicators (waist circumference and BMI) with lipid parameters (triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)), designed to provide a more metabolically informative surrogate of visceral fat dysfunction [15]. Unlike BMI, which overlooks metabolic heterogeneity, VAI correlates more robustly with insulin resistance, low-grade systemic inflammation, and atherogenic lipid profiles—key intermediates in the obesity–cancer axis. Notably, VAI identifies metabolically unhealthy individuals even within the normal BMI range, a clinically relevant distinction not afforded by BMI. This advantage was empirically demonstrated by Romero-Corral et al. [16] and Yang et al. [17], who showed that VAI—but not BMI—was significantly associated with endothelial dysfunction and metabolic syndrome in obese men [14]. VAI has since been validated in diverse populations as a predictive tool for cardiometabolic disorders, including type 2 diabetes, chronic kidney disease, cardiovascular disease, and all-cause mortality [18]. A large-scale Chinese study further established that VAI outperforms both BMI and waist circumference in identifying individuals at risk for incident diabetes [19]. Despite these strengths, the role of VAI in oncologic epidemiology remains underexplored. While metabolic-based indices such as the lipid accumulation product (LAP) and triglyceride-glucose (TyG) index have demonstrated predictive superiority over BMI for certain gastrointestinal cancers, the position of VAI within this framework is not well-defined [20]. This knowledge gap underscores the need to evaluate whether VAI provides incremental value in cancer risk stratification beyond conventional obesity measures.

Currently, only a few studies have investigated associations between VAI and specific cancers. A prospective study among a Japanese population found significantly increased colorectal cancer risk among individuals with elevated VAI, with approximately a 78% higher risk in the highest VAI tertile compared to the lowest [21]. Similarly, a small-scale case-control study in women showed higher VAI among breast cancer patients than healthy controls, with VAI independently associated with breast cancer risk after multivariate adjustment [22]. Nonetheless, studies assessing other cancer types are sparse, and it remains unclear whether VAI has superior predictive utility for overall cancer risk compared to traditional obesity indicators such as BMI. Notably, some cancers exhibit complex relationships with obesity, exemplified by the obesity paradox observed in prostate cancer, wherein obese men paradoxically have lower incidence yet worse prognosis [23]. Such complexity underscores the need for comprehensive evaluation of associations between VAI and overall or site-specific cancer risks, as well as exploration of underlying biological mechanisms.

Therefore, this study utilized nationally representative data from the U.S. National Health and Nutrition Examination Survey (NHANES) from 1999 to 2020 to systematically investigate the association between VAI and cancer prevalence. Additionally, we examined whether VAI independently predicts cancer risk after thorough adjustment for BMI and relevant metabolic comorbidities. Multivariate weighted logistic regression models were constructed to incrementally include covariates and control for confounding biases. Restricted cubic spline (RCS) analyses were used to explore the dose–response relationship between VAI and cancer risk. Subgroup analyses were also conducted to assess consistency across different populations and to identify potential effect modifiers. By overcoming previous limitations related to sample size, variable adjustment, and analytical depth, this study aimed to clarify the predictive value

of VAI as an indicator of cancer risk and explore its potential clinical implications for cancer prevention, early screening, and public health interventions.

2. Methods

2.1 Data Source and Study Population

This study was based on publicly available data from the NHANES, a nationally representative survey conducted biennially by the U.S. Centers for Disease Control and Prevention (CDC). NHANES uses a complex, multistage, stratified probability sampling design to collect data from the civilian, non-institutionalized U.S. population. For this analysis, data from 11 continuous survey cycles between 1999–2000 and 2019–2020 were combined. All estimates incorporated sampling weights, strata, and primary sampling units (PSUs) as recommended by the CDC to account for the complex sampling design and ensure national representativeness.

Participants were included if they were aged $\geq$20 years and had complete data for cancer history, components required to calculate the VAI—including WC, BMI, TG, and HDL-C—as well as all prespecified covariates. Individuals were excluded if they were pregnant or had missing information on any key variables, such as cancer status, anthropometric measures, or lipid profiles. After applying inclusion and exclusion criteria, a final sample of 20,699 participants was retained for analysis (Fig. 1).

Cancer status was determined based on responses to the NHANES questionnaire item: "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" Participants answering "yes" were classified as having cancer. In accordance with NHANES guidelines, cases of non-melanoma skin cancer (e.g., basal cell or squamous cell carcinoma) were excluded due to their typically benign nature and limited epidemiological significance. The primary endpoint was overall cancer prevalence; non-melanoma skin cancer (NMSC) was excluded from the overall endpoint but retained for exploratory site-specific analyses (cervix, NMSC, breast, colon, melanoma, prostate).

2.2 Exposure Variable

The VAI, the primary exposure variable in this study, was calculated using sex-specific equations proposed by Amato et al. [14]. These formulas incorporate WC, BMI, TG, and HDL-C, and were defined as follows:

$$Male\ VAI = \frac{WC\ (cm)}{39.68 + (1.88 \times BMI)} \times \frac{TG\ (mmol/L)}{1.03} \times \frac{1.31}{HDL\ (mmol/L)}$$

$$Female\ VAI = \frac{WC\ (cm)}{36.58 + (1.89 \times BMI)} \times \frac{TG\ (mmol/L)}{0.81} \times \frac{1.52}{HDL\ (mmol/L)}$$

TG and HDL-C were converted from mg/dL to mmol/L before calculation (TG $\div$ 88.57; HDL-C $\div$ 38.67).

WC was measured in centimeters at the end of a normal expiration, with participants in a standing position and measurement taken at the top of the iliac crest. BMI was calculated as weight (kg) divided by the square of height in meters (kg/m^2). Both TG and HDL-C levels were obtained from fasting venous blood samples ($\geq$9 hours) and analyzed in NHANES-certified laboratories using enzymatic methods for TG and precipitation or direct methods for HDL-C.

VAI was treated as a continuous variable in the primary analyses. To further assess its potential nonlinear association with cancer risk, participants were also categorized into four groups based on the approximate quartile distribution and rounded cutoffs of VAI:

Group 1: (reference): VAI $<$1.0

Group 2: 1.0 $\leq$ VAI $<$ 2.0

Group 3: 2.0 $\leq$ VAI $<$ 3.0

Group 4: VAI $\geq$3.0

This classification approach ensured relatively balanced sample sizes across groups and facilitated the assessment of a dose–response trend in cancer risk across increasing VAI levels. The VAI cutoff values ($<$1.0, 1.0–$<$2.0, 2.0–$<$3.0, and $\geq$3.0) were derived from the approximate quartile distribution of VAI observed in this study population and were subsequently rounded to facilitate clinical interpretability. This classification strategy aligns with established methodologies in previous epidemiological studies examining VAI and disease risk [15,19].

2.3 Outcome Variable

The primary outcome of this study was cancer status, determined based on responses to the standardized medical conditions questionnaire from the NHANES. Specifically, participants were asked: "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" (MCQ220). Individuals who answered "yes" were classified as having a history of cancer, and those who answered "no" were categorized as non-cancer participants.

According to NHANES guidelines, this item captures physician-confirmed malignancies and explicitly excludes non-melanoma skin cancers (e.g., basal cell carcinoma and squamous cell carcinoma), which are typically indolent and commonly omitted from epidemiological cancer studies. Therefore, participants who reported only non-melanoma skin cancers were not considered cancer cases. In contrast, those reporting diagnoses such as breast, lung, prostate, liver, or colorectal cancers, or hematologic malignancies (e.g., leukemia), were included in the cancer-positive group.

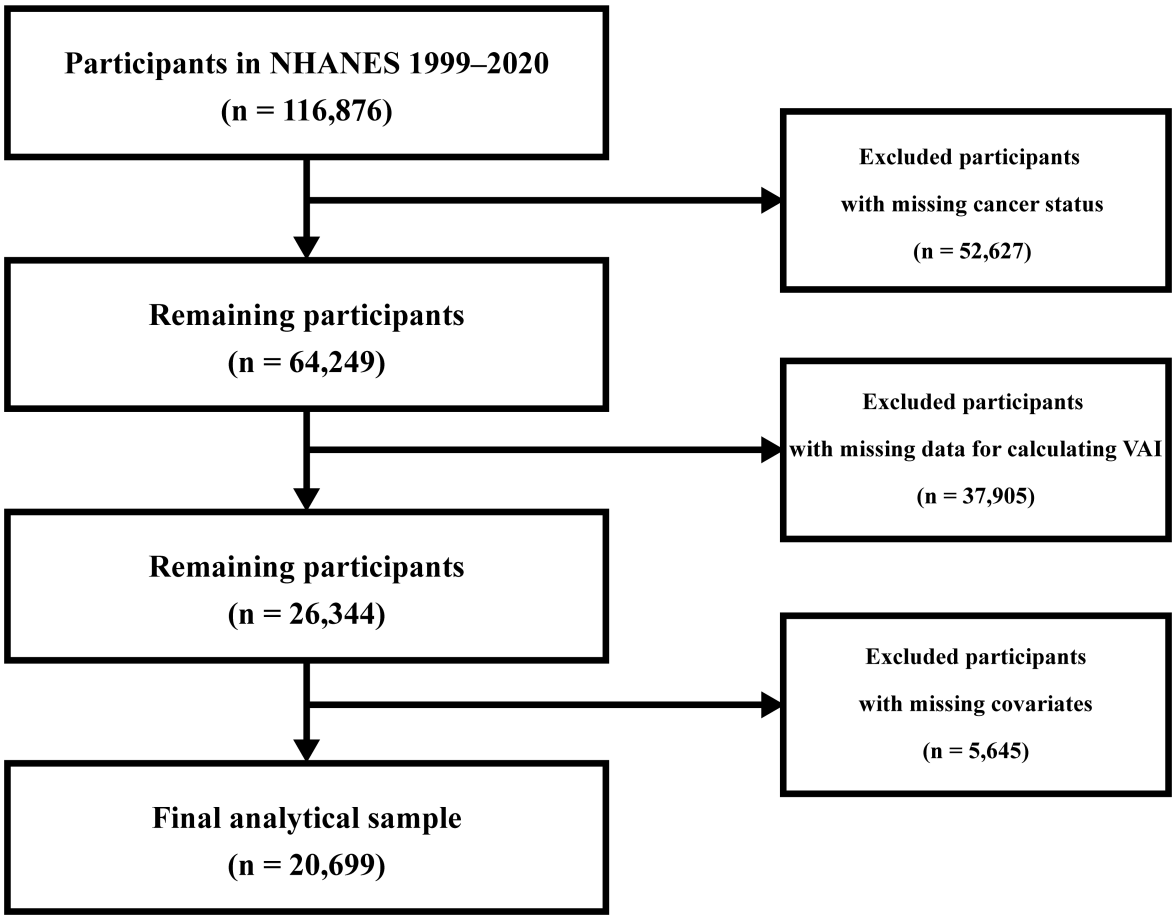

Fig. 1. Participant selection flowchart from the NHANES 1999–2020 cycles. From the initial sample of 116,876 individuals, we excluded those missing cancer status (n = 52,627), lacking sufficient data for Visceral Adiposity Index (VAI) calculation (n = 37,905), and those with incomplete covariates (n = 5645). A total of 20,699 eligible adults were included in the final analysis.

Although NHANES records cancer type and anatomical site, our prespecified primary endpoint was overall cancer prevalence. NMSC was excluded from the overall endpoint but retained for site-specific analyses. For the primary analyses, all qualifying malignancies were aggregated into a binary variable (yes/no), consistent with prior NHANES-based studies.

It should be noted that, given the cross-sectional nature of NHANES, cancer status represents point-prevalence—reflecting participants' self-reported history of ever having been diagnosed with cancer at the time of the survey. This differs from cancer incidence and should be interpreted as cumulative prevalence rather than newly diagnosed cases during a defined period.

2.4 Covariates and Model Adjustment

To control for potential confounding and accurately evaluate the association between the VAI and cancer prevalence, a range of covariates were included in the multivariable models. These covariates encompassed demographic characteristics, socioeconomic status, lifestyle behaviors, anthropometric measures, and metabolic comorbidities.

Demographic and socioeconomic factors included age (continuous, in years), sex (male/female), and ethnicity, classified according to NHANES definitions as non-Hispanic white, non-Hispanic black, Mexican American, and other ethnicity. Education level was categorized as <9 years, 9–11 years, high school graduate or equivalent (GED), and college or above. Marital status was dichotomized as married/cohabiting vs. unmarried, separated, divorced, or widowed. Socioeconomic status was assessed using the poverty income ratio (PIR), defined as the ratio of family income to the federal poverty threshold, and treated as a continuous variable.

Lifestyle variables included smoking status (never vs. current or former smoker) and alcohol consumption in the past 12 months (yes/no). Physical activity, where available, was assessed based on self-reported frequency and intensity and classified as meeting or not meeting recommended guidelines.

Anthropometric measures included BMI (kg/m^2) and WC (cm), both treated as continuous variables. As WC is a component of the VAI formula, it was excluded from primary regression models to avoid multicollinearity. Per

the prespecified plan, WC was evaluated in sensitivity analyses (mutual adjustment and sex-specific WC quartiles), and collinearity diagnostics (Pearson/Spearman correlations; variance-inflation factors) informed model building (**Supplementary Tables 1–3**).

Metabolic comorbidities included diabetes, hypertension, and dyslipidemia. Diabetes was defined as self-reported physician diagnosis, fasting plasma glucose (FPG) $\geq$7.0 mmol/L, or glycated hemoglobin (HbA1c) $\geq$6.5%. Hypertension was defined as self-reported physician diagnosis or measured blood pressure meeting clinical criteria. Dyslipidemia was defined as self-reported diagnosis or current use of lipid-lowering medications.

Model definitions and the dual-modeling strategy are detailed in the Statistical Analysis section.

2.5 Statistical Analysis

All analyses were performed in R (version 4.3.3, R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org/) using the NHANES complex survey design (weights, strata, and PSUs) to obtain nationally representative estimates. Baseline characteristics were summarized as survey-weighted means (95% CIs) or weighted percentages and compared using design-adjusted *t*-tests and the Rao–Scott χ^2 test. We fit three survey-weighted logistic models: Model 1 (unadjusted); Model 2 (age, sex, race/ethnicity, education, marital status, poverty-income ratio); and Model 3 (Model 2 plus smoking, alcohol use, diabetes, and hypertension; BMI and hyperlipidemia were excluded to avoid over-adjustment given the VAI construct). Prespecified sensitivity analyses comprised (i) mutual-adjustment models simultaneously entering VAI (per 1-unit) and waist circumference (per 5-cm); (ii) sex-specific WC-quartile models aligned with the primary specifications; and (iii) collinearity diagnostics using Pearson/Spearman correlations and variance-inflation factors (VIFs; $VIF_j = \frac{1}{(1-R_j^2)}$). To assess independence from general adiposity, we re-introduced BMI (and, in site-specific models, hyperlipidemia) and benchmarked results against a BMI-exposure model. Dose–response was examined with restricted cubic splines applied to the primary BMI-free Model 3 (three knots at the 25th, 50th, and 75th percentiles; median reference), with tests for overall association and nonlinearity. Subgroup analyses applied Model 3 within strata of sex, age (<60/$\geq$60 years), BMI (<30/$\geq$30 kg/m^2), hypertension, and diabetes; multiplicative interactions (e.g., VAI $\times$ hypertension) were tested in the full sample. Site-specific logistic regressions by VAI quartiles were exploratory; Model 3 additionally included BMI and hyperlipidemia; non-melanoma skin cancer was excluded from the overall endpoint but retained for site-specific analyses; *p* values were not adjusted for multiplicity. All tests were two-sided with $\alpha = 0.05$.

3. Results

3.1 Baseline Characteristics

A total of 20,699 participants aged $\geq$20 years from NHANES were included in the analysis, among whom 1900 participants reported a history of cancer. Table 1 summarizes the weighted baseline demographic, lifestyle, and clinical characteristics stratified by cancer status.

Participants with cancer were significantly older than those without cancer (mean age: 62.1 vs. 45.6 years; $p < 0.0001$), indicating that cancer was more prevalent among middle-aged and older adults. Sex distribution differed significantly, with a higher proportion of females in the cancer group (57.8% vs. 49.1%; $p < 0.0001$). Regarding ethnicity, non-Hispanic whites accounted for a much greater proportion in the cancer group (88.1%) compared to the non-cancer group (69.0%; $p < 0.0001$), whereas the proportions of non-Hispanic black and Mexican American individuals were relatively lower. These disparities may reflect differences in age distribution or cancer screening rates across racial/ethnic groups.

Marital status showed a modest difference, with a higher proportion of married or cohabiting individuals in the cancer group (68.3% vs. 64.8%; $p = 0.01$). Education levels were comparable between groups, with no statistically significant difference ($p = 0.09$). The PIR was higher among individuals with cancer (3.36 vs. 3.04; $p < 0.0001$), possibly reflecting greater access to healthcare or survivor bias.

Regarding anthropometric characteristics, mean BMI was similar between groups (28.7 vs. 28.8 kg/m^2; $p = 0.53$), suggesting no significant difference in general adiposity. However, the mean VAI was slightly higher in the cancer group than in the non-cancer group (2.26 vs. 2.08; $p = 0.03$), indicating a greater burden of visceral adiposity. Additionally, the prevalence of diabetes (23.4% vs. 13.1%) and hypertension (56.2% vs. 35.5%) was substantially higher in the cancer group (both $p < 0.0001$). The prevalence of hyperlipidemia was also moderately elevated in the cancer group (80.9% vs. 70.6%; $p < 0.0001$), supporting the notion that metabolic comorbidities are more common among cancer survivors.

Lifestyle behaviors differed as well. A lower proportion of participants in the cancer group were current or former smokers (16.6% vs. 21.4%; $p < 0.001$), which may reflect behavioral changes following diagnosis or survivor bias. Conversely, alcohol consumption in the past 12 months was reported less frequently among cancer participants (72.5% vs. 76.9%; $p < 0.001$), possibly due to lifestyle modifications or health-related restrictions.

In summary, individuals with cancer tended to be older, had a higher proportion of females (57.8% vs. 49.1%), and were more likely to be non-Hispanic white. They also exhibited higher socioeconomic status, a greater burden of metabolic comorbidities, and increased visceral adiposity. These baseline differences were considered po-

Table 1. Baseline characteristics of participants by cancer status (NHANES 1999–2020).

Variable	Total (weighted)	No cancer	Cancer	*p*-value
Age, years	47.16 (46.71–47.61)	45.63 (45.19–46.06)	62.08 (61.23–62.94)	<0.0001 ***
Family income-to-poverty ratio	3.07 (3.02–3.13)	3.04 (2.99–3.10)	3.36 (3.25–3.46)	<0.0001 ***
BMI, kg/m^2	28.79 (28.64–28.94)	28.80 (28.64–28.96)	28.68 (28.35–29.02)	0.53
Visceral adiposity index	2.10 (2.04–2.15)	2.08 (2.02–2.14)	2.26 (2.11–2.42)	0.03 *
Sex, n (%)				<0.0001 ***
Female	10,210 (49.90%)	9213 (49.08%)	997 (57.81%)	
Male	10,489 (50.10%)	9586 (50.92%)	903 (42.19%)	
Ethnicity, n (%)				<0.0001 ***
Non-Hispanic Black	4118 (9.84%)	3875 (10.37%)	243 (4.63%)	
Mexican American	3465 (7.84%)	3333 (8.42%)	132 (2.13%)	
Other ethnic group	3602 (11.56%)	3433 (12.22%)	169 (5.15%)	
Non-Hispanic White	9514 (70.77%)	8158 (68.99%)	1356 (88.09%)	
Education, n (%)				0.09
Less than 9th Grade	2144 (5.20%)	1976 (5.25%)	168 (4.67%)	
9–11th Grade	2887 (10.48%)	2657 (10.64%)	230 (8.89%)	
High school/GED	4792 (24.12%)	4345 (24.18%)	447 (23.51%)	
College or above	10,876 (60.20%)	9821 (59.92%)	1055 (62.93%)	
Marital status, n (%)				0.01 *
Married/cohabitating	12,675 (65.08%)	11,473 (64.75%)	1202 (68.33%)	
Other	8024 (34.92%)	7326 (35.25%)	698 (31.67%)	
Diabetes, n (%)				<0.0001 ***
No	16,756 (85.92%)	15,404 (86.87%)	1352 (76.64%)	
Yes	3943 (14.08%)	3395 (13.13%)	548 (23.36%)	
Smoking status, n (%)				<0.001 ***
Never	16,360 (79.07%)	14,763 (78.63%)	1597 (83.41%)	
Former/current	4339 (20.93%)	4036 (21.37%)	303 (16.59%)	
Alcohol use (past year), n (%)				<0.001 ***
No	5886 (23.51%)	5249 (23.09%)	637 (27.52%)	
Yes	14,813 (76.49%)	13,550 (76.91%)	1263 (72.48%)	
Hypertension, n (%)				<0.0001 ***
No	11,866 (62.62%)	11,163 (64.55%)	703 (43.80%)	
Yes	8833 (37.38%)	7636 (35.45%)	1197 (56.20%)	
Hyperlipidemia, n (%)				<0.0001 ***
No	5656 (28.41%)	5294 (29.37%)	362 (19.08%)	
Yes	15,043 (71.59%)	13,505 (70.63%)	1538 (80.92%)	

Weighted means (95% CIs) and weighted proportions (%) are reported. *p*-values for continuous and categorical variables were derived from survey-weighted linear regression and Rao–Scott χ^2 tests, respectively. Estimates account for the complex NHANES sampling design. *$p < 0.05$; ***$p < 0.001$.

tential confounders and were adjusted for in subsequent regression analyses.

3.2 Regression Results

Table 2 summarizes the results of weighted logistic regression models assessing the association between VAI and cancer prevalence. In the unadjusted Model 1, VAI was significantly associated with cancer prevalence (OR = 1.019, 95% CI: 1.003–1.035; $p = 0.019$), indicating ~1.9% higher odds of cancer per one-unit increase in VAI. After adjusting for demographic and socioeconomic factors (Model 2), the association was slightly attenuated and became marginally significant (OR = 1.017, 95% CI: 0.998–1.037; $p = 0.072$). In the primary BMI-free Model 3, the association remained statistically significant (OR = 1.024; 95% CI: 1.004–1.045; $p = 0.021$); by contrast, re-introducing BMI and hyperlipidemia in a sensitivity model attenuated the association to non-significance (OR = 1.016; 95% CI: 0.996–1.036; $p = 0.119$). These results suggest that the initially observed association between VAI and cancer prevalence may be largely explained by BMI and related metabolic abnormalities, indicating possible residual confounding or mediation effects.

To further examine potential dose–response relationships, participants were stratified into four VAI categories based on approximate quartiles: <1.0, 1.0–<2.0, 2.0–<3.0,

Table 2. Multivariable weighted logistic regression models evaluating associations of VAI with cancer prevalence among U.S. adults (NHANES 1999–2020).

VAI	Model 1	Model 2	Model 3
Continuous (per 1-unit increase)			
OR (95% CI)	1.019 (1.003, 1.035)	1.017 (0.998, 1.037)	1.024 (1.004, 1.045)
p-value	0.019	0.072	0.021*
Quartiles (Ref = Q1, VAI <1.0)			
Q2 (1.0–<2.0)	1.15 (0.85, 1.55)	1.12 (0.81, 1.55)	1.19 (0.87, 1.63)
Q3 (2.0–<3.0)	1.40 (1.05, 1.90)	1.25 (0.90, 1.74)	1.38 (0.99, 1.94)
Q4 (≥3.0)	3.04 (1.53, 6.01)	2.02 (0.95, 4.32)	2.19 (1.00, 4.80)
p for trend	<0.001***	0.069	0.039*

Abbreviations: OR, odds ratio; CI, confidence interval; VAI, visceral adiposity index.

Note. Estimates are derived from survey-weighted logistic regression models.

Model 1: Unadjusted;

Model 2: Adjusted for age, sex, ethnicity, education, marital status, and poverty-income ratio;

Model 3: Further adjusted for smoking, alcohol use, diabetes, and hypertension.

*$p < 0.05$; ***$p < 0.001$.

and ≥3.0. Using the lowest VAI group (<1.0) as the reference, odds ratios progressively increased in unadjusted analyses (Model 1), with ORs of approximately 1.15 (1.0–<2.0 group), 1.40 (2.0–<3.0 group), and 3.04 (≥3.0 group; 95% CI: 1.53–6.01; p for trend < 0.001; **Supplementary Fig. 1**). However, after comprehensive adjustment (in sensitivity models re-introducing BMI and hyperlipidemia), these estimates notably decreased, and the OR for the highest VAI group declined to approximately 1.50, with the 95% CI overlapping 1.0, indicating no statistically significant association. This substantial attenuation supports the interpretation that the observed association between elevated VAI and cancer prevalence (odds) primarily reflects underlying general adiposity and metabolic dysfunction rather than an independent effect of visceral adiposity alone.

Collectively, these findings indicate a weak positive association between VAI and cancer prevalence in the unadjusted analysis. However, this association was substantially reduced and became nonsignificant after controlling for major confounders, particularly BMI and metabolic comorbidities. In the primary BMI-free model (Model 3), which excluded BMI and hyperlipidemia to avoid potential overadjustment, the association remained statistically significant (OR = 1.024, 95% CI: 1.004–1.045; p = 0.021), suggesting that elevated VAI is independently associated with increased cancer prevalence. To assess whether the attenuation observed in the VAI–cancer association was specific to composite indices or reflective of broader adiposity-related confounding, we constructed a fully adjusted logistic regression model with BMI as the primary exposure. As presented in Table 3, BMI was likewise not significantly associated with cancer prevalence (OR = 1.00; 95% CI: 0.99–1.01; p = 0.65), thereby closely paralleling the null findings observed with VAI (Table 2). This convergence reinforces the interpretation that neither general nor visceral adiposity confers meaningful independent predictive value for cancer once key metabolic comorbidities are accounted for. The complete model specification and covariate-level estimates are provided in **Supplementary Table 1**. In sensitivity analyses that added WC to the fully adjusted model, estimates for VAI remained directionally consistent and our inferences were unchanged (**Supplementary Tables 2,3**).

Table 3. Association between BMI and cancer prevalence in a separate BMI-exposure comparator model.

Variable	OR (95% CI)	*p*-value
BMI (per 1-unit increase)	1.00 (0.99–1.01)	0.65

Note. This separate BMI-exposure comparator model was adjusted for age, sex, ethnicity, education level, marital status, poverty-income ratio, diabetes, hypertension, hyperlipidemia, smoking status, and alcohol use; VAI was not included. This model is distinct from the primary VAI Model 3.

3.3 Subgroup and Interaction Analyses

To evaluate the robustness of the association between VAI and cancer prevalence, as well as explore potential effect modifiers, stratified subgroup analyses were conducted. Results are summarized in Table 4. In prespecified site-specific analyses, no individual cancer site showed an independent positive association with VAI after multivariable adjustment; unadjusted signals for colon and melanoma did not persist, whereas intermediate VAI levels were inversely associated with cervical cancer and warrant cautious interpretation (Table 5). Overall, the direction of association between VAI and cancer prevalence remained consistent across subgroups, though effect sizes were modest. Among the examined subgroups, only hypertension × VAI demonstrated a borderline significant interaction (p = 0.044), whereas sex, age, BMI, and diabetes had no significant interactions (all $p > 0.05$). This finding suggests that

Table 4. Stratified subgroup analyses of the association between VAI and cancer prevalence per 1-unit increase in VAI (Model 3).

Subgroup	OR (95% CI)	*p*-value	Interaction *p*-value
Sex			0.067
Male	0.982 (0.938, 1.027)	0.419	
Female	1.021 (0.996, 1.046)	0.094	
Age group (years)			0.702
<60	1.020 (1.000, 1.042)	0.053	
≥60	1.023 (0.985, 1.062)	0.231	
BMI (kg/m^2)			0.976
<30	1.007 (0.977, 1.037)	0.660	
≥30	1.011 (0.989, 1.033)	0.340	
Hypertension			0.044*
Yes	0.973 (0.936, 1.011)	0.159	
No	1.024 (0.998, 1.049)	0.067	
Diabetes			0.264
No	1.002 (0.968, 1.038)	0.907	
Yes	0.993 (0.970, 1.015)	0.516	

VAI, visceral adiposity index; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Adjusted ORs and 95% CIs were estimated from survey-weighted logistic regression models using the primary BMI-free Model 3, adjusting for age, sex, race/ethnicity, education, marital status, poverty-income ratio, smoking, alcohol use, diabetes, and hypertension; within each stratum, the stratifying variable was omitted from covariate adjustment. BMI was used only for subgroup stratification and was not included as an adjustment covariate. Hyperlipidemia was not included in the primary Model 3. Interaction *p* values reflect multiplicative interaction terms. *$p < 0.05$ considered statistically significant.

hypertension status might modestly modify the VAI–cancer association.

In sex-stratified analyses, no significant association was observed among males (OR = 0.982; 95% CI: 0.938–1.027; $p = 0.419$). However, among females, a marginally significant positive association emerged (OR = 1.021; 95% CI: 0.996–1.046; $p = 0.094$). Although the interaction term for sex × VAI approached statistical significance ($p = 0.067$), it did not reach conventional thresholds, suggesting only a weak potential effect modification by sex.

Age-stratified analyses yielded similar estimates between younger (<60 years: OR = 1.020; $p = 0.053$) and older (≥60 years: OR = 1.023; $p = 0.231$) individuals. The age × VAI interaction was non-significant ($p = 0.702$), indicating no age-related effect modification. Similarly, stratification by BMI showed no significant associations in either the BMI <30 kg/m^2 group (OR = 1.007; $p = 0.660$) or the BMI ≥30 kg/m^2 group (OR = 1.011; $p = 0.340$), with a non-significant interaction ($p = 0.976$). Diabetes status also did not significantly modify the VAI–cancer relationship (non-diabetic: OR = 1.002; diabetic: OR = 0.993; interaction $p = 0.264$).

Notably, hypertension status showed contrasting results. Among hypertensive individuals, VAI was inversely but non-significantly associated with cancer prevalence (OR = 0.973; 95% CI: 0.936–1.011; $p = 0.159$), while a marginally positive association was noted among normotensive participants (OR = 1.024; 95% CI: 0.998–1.049; $p = 0.067$). The interaction term for hypertension × VAI approached statistical significance ($p = 0.044$), suggesting that hypertension status might modestly influence the direction and magnitude of the VAI–cancer association. This may be attributed to hypertension-related mechanisms such as chronic inflammation and insulin resistance or to differential healthcare utilization causing detection bias. To better visualize these subgroup differences, we present a forest plot (Fig. 2) illustrating adjusted odds ratios and confidence intervals across different strata. However, given the lack of independently significant associations within each subgroup and the modest interaction effect size, these findings should be interpreted cautiously. To further assess potential synergistic modification, a three-way interaction model (VAI × sex × hypertension) was constructed. As shown in **Supplementary Fig. 2**, a statistically significant association was observed only among females without hypertension (OR = 1.034; 95% CI: 1.004–1.065), while estimates for other subgroups remained non-significant. These findings suggest that combined stratification may reveal interaction effects that are not apparent in single-variable subgroup analyses.

Table 5. Site-specific association of VAI quartiles with cancer prevalence (NHANES 1999–2020).

Cancer site	VAI quartile (vs Q1 <1.0)	Model 1 OR (95% CI)	*p*-value	Model 2 OR (95% CI)	*p*-value	Model 3 OR (95% CI)	*p*-value
Cervix (cervical)	Q1	Ref	—	Ref	—	Ref	—
	Q2 (1.0–<2.0)	0.78 (0.46–1.32)	0.350	0.67 (0.38–1.16)	0.150	0.53 (0.29–0.95)	0.033*
	Q3 (2.0–<3.0)	0.51 (0.25–1.03)	0.061	0.45 (0.22–0.94)	0.033*	0.30 (0.13–0.67)	0.003**
	Q4 (≥3.0)	1.69 (0.96–2.95)	0.067	1.36 (0.72–2.55)	0.343	0.81 (0.40–1.65)	0.566
Skin (non-melanoma)†	Q1	Ref	—	Ref	—	Ref	—
	Q2 (1.0–<2.0)	0.82 (0.59–1.14)	0.231	0.73 (0.51–1.03)	0.071	0.77 (0.54–1.10)	0.152
	Q3 (2.0–<3.0)	0.80 (0.51–1.25)	0.325	0.69 (0.44–1.11)	0.123	0.78 (0.47–1.28)	0.317
	Q4 (≥3.0)	0.99 (0.67–1.46)	0.960	0.91 (0.60–1.37)	0.641	1.03 (0.65–1.63)	0.899
Breast	Q1	Ref	—	Ref	—	Ref	—
	Q2 (1.0–<2.0)	1.08 (0.71–1.64)	0.727	0.84 (0.54–1.31)	0.441	0.89 (0.57–1.38)	0.597
	Q3 (2.0–<3.0)	1.29 (0.76–2.19)	0.337	0.96 (0.56–1.64)	0.867	1.06 (0.60–1.88)	0.840
	Q4 (≥3.0)	1.08 (0.66–1.78)	0.760	0.77 (0.45–1.30)	0.326	0.85 (0.50–1.47)	0.563
Colon	Q1	Ref	—	Ref	—	Ref	—
	Q2 (1.0–<2.0)	1.86 (0.87–3.97)	0.109	1.47 (0.69–3.13)	0.320	1.35 (0.62–2.91)	0.450
	Q3 (2.0–<3.0)	1.75 (0.81–3.82)	0.156	1.33 (0.58–3.05)	0.499	1.15 (0.51–2.61)	0.735
	Q4 (≥3.0)	2.24 (1.05–4.75)	0.036*	1.73 (0.75–3.96)	0.195	1.41 (0.61–3.23)	0.421
Melanoma	Q1	Ref	—	Ref	—	Ref	—
	Q2 (1.0–<2.0)	1.33 (0.76–2.35)	0.320	1.18 (0.66–2.12)	0.577	1.11 (0.61–2.01)	0.741
	Q3 (2.0–<3.0)	1.86 (1.01–3.40)	0.045*	1.61 (0.86–3.02)	0.133	1.44 (0.74–2.79)	0.284
	Q4 (≥3.0)	1.58 (0.79–3.15)	0.192	1.41 (0.68–2.94)	0.356	1.21 (0.55–2.67)	0.639
Prostate‡	Q1	Ref	—	Ref	—	Ref	—
	Q2 (1.0–<2.0)	1.10 (0.72–1.69)	0.660	1.09 (0.69–1.74)	0.704	1.04 (0.66–1.62)	0.879
	Q3 (2.0–<3.0)	1.00 (0.62–1.60)	0.992	1.16 (0.69–1.93)	0.580	0.99 (0.58–1.68)	0.964
	Q4 (≥3.0)	0.90 (0.56–1.45)	0.658	1.17 (0.70–1.95)	0.551	1.01 (0.60–1.73)	0.961

Model definitions. Model 1: unadjusted. Model 2: adjusted for age, sex (omitted in sex-restricted models), race/ethnicity, education, marital status, and poverty-income ratio. Model 3 (site-specific): Model 2 plus smoking, alcohol use, diabetes, and hypertension, and—to assess independence—additionally included BMI and hyperlipidemia. All models used the NHANES complex survey design (weights, strata, PSUs).

VAI quartiles. Q1 <1.0 (reference), Q2 1.0–<2.0, Q3 2.0–<3.0, Q4 ≥3.0.

Population restrictions. Breast cancer analyses were restricted to women; prostate cancer analyses were restricted to men (sex was not entered as a covariate in these models).

Multiplicity. Two-sided *p* values are reported; no multiplicity adjustment was applied in these exploratory site-specific analyses.

NMSC. Non-melanoma skin cancer (NMSC) was excluded from the primary overall endpoint but is shown here for site-specific exploration.

Abbreviations. VAI, Visceral Adiposity Index; OR, odds ratio; CI, confidence interval. Survey-weighted logistic regression; values are OR (95% CI) and *p* value.

† NMSC, non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma); excluded from the primary overall endpoint but shown here for site-specific exploration.

‡ Prostate cancer analyses are restricted to men (sex was not entered as a covariate in these models).

Significance codes. *$p < 0.05$; **$p < 0.01$.

In summary, the association between VAI and cancer prevalence was directionally consistent yet weak across subgroups. A borderline significant interaction ($p = 0.044$) was detected with hypertension, indicating a stronger positive association among normotensive individuals, whereas no significant interactions were observed with sex, age, BMI, or diabetes. Future research should explore this differential effect further.

3.4 Dose–Response Relationship and Restricted Cubic Spline Analysis

To further characterize the potential nonlinear dose–response relationship between VAI and cancer prevalence, we incorporated RCS functions into the primary BMI-free Model 3. A third-degree spline was constructed using three knots placed at the 25th, 50th (median, 1.464), and 75th percentiles of VAI distribution.

The analysis showed a statistically significant overall association between VAI and cancer prevalence (p =

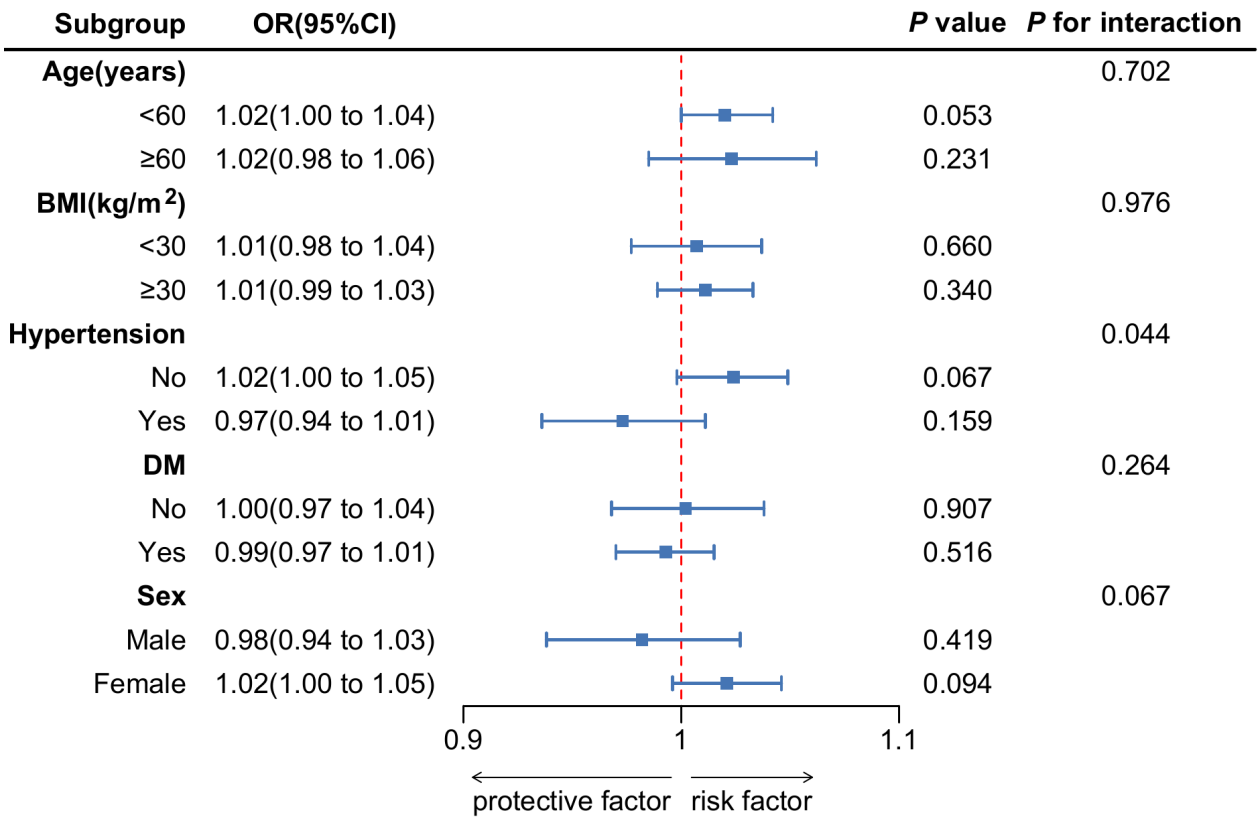

Fig. 2. Stratified analysis of associations between VAI and cancer prevalence across subgroups. Estimates were derived from survey-weighted logistic regression models using the primary BMI-free Model 3, adjusting for age, sex, race/ethnicity, education, marital status, poverty-income ratio, smoking, alcohol use, diabetes, and hypertension; within each stratum, the stratifying variable was omitted from covariate adjustment. Each square represents the OR (per 1-unit increase in VAI) with 95% CIs. The vertical dashed line denotes the null (OR = 1). Interaction *p* values test multiplicative interaction.

0.0428), with borderline evidence of nonlinearity (p = 0.054). As shown in Fig. 3, the RCS curve suggested a weak, approximately linear increase in the odds of cancer with increasing VAI, without a clearly identifiable threshold or sharp inflection point. The confidence intervals widened substantially at the upper range of VAI values, indicating greater uncertainty and warranting cautious interpretation of estimates in this range.

Overall, the RCS analysis supports a positive, approximately linear association between VAI and cancer prevalence. Although the strength of the association was not substantial after full covariate adjustment, VAI levels in the moderate-to-high range may still carry predictive relevance.

It is important to note that, given the cross-sectional nature of the data, cancer status reflects prior or current diagnosis, and reverse causation cannot be ruled out. For instance, metabolic alterations following cancer diagnosis could influence VAI values. Therefore, the dose–response findings should be interpreted as suggestive rather than confirmatory. Longitudinal studies are needed to validate the observed trends and clarify the clinical utility of VAI as a risk marker across its distribution.

3.5 Supplementary Analyses and Robustness Checks

To further verify the robustness of our main findings, we performed several supplementary analyses. First, we constructed an alternative model excluding BMI to evaluate potential collinearity effects, given that BMI is a component of the VAI calculation. After removing BMI, the OR for VAI slightly increased to 1.022 (p = 0.08). Although the association remained non-significant, this minor change indicates that the attenuation observed after controlling for BMI was modest, and that the diminished association between VAI and cancer was unlikely due to BMI adjustment alone. Other metabolic comorbidities might also have played critical roles.

Second, we conducted sex-specific RCS analyses to investigate potential nonlinearities separately among males and females. The dose–response curves were similar across both sexes, consistently indicating an approximately linear trend without significant nonlinear inflection points. This finding further supports the linearity assumption adopted in the primary analysis.

Additionally, we explored the potential association between VAI and obesity-related cancer types (e.g., colorectal, liver, pancreatic, and female reproductive system can-

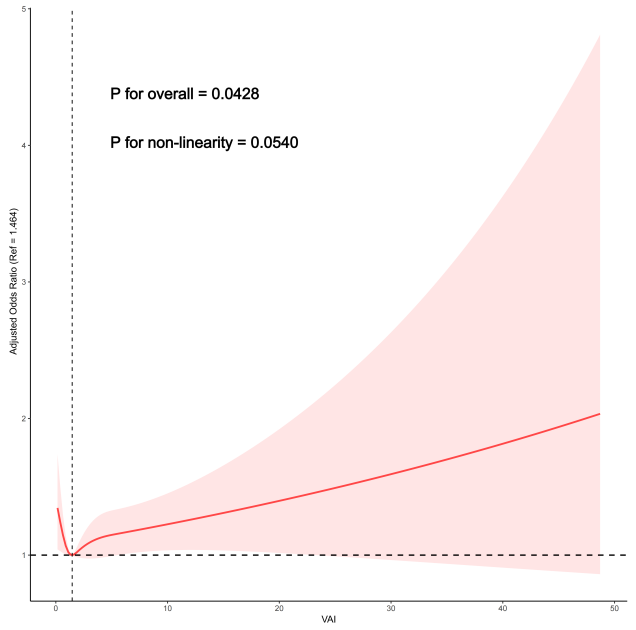

Fig. 3. Dose–response relationship between VAI and cancer prevalence based on restricted cubic spline (Model 3). The solid line indicates the adjusted OR of cancer across VAI values. The model was adjusted for age, sex, ethnicity, education, marital status, poverty-income ratio, diabetes, smoking, alcohol use, and hypertension. The shaded area represents 95% confidence intervals. The reference value was set at VAI = 1.464 (median). *p* for overall association = 0.0428; *p* for non-linearity = 0.054.

cers) as a restricted endpoint, comprising 346 cancer cases. In the unadjusted model, the OR of VAI associated with these cancers was 1.030 ($p = 0.005$). However, after full covariate adjustment, the OR attenuated to 1.018 ($p = 0.11$), a trend consistent with the overall cancer analysis. Given the limited cancer type-specific data provided by NHANES, these results should be interpreted cautiously.

Collectively, these sensitivity and exploratory analyses produced consistent results aligned with our primary findings, with no contradictory evidence observed. The statistical trends between VAI and cancer remained robust across various model specifications and population subsets.

4. Discussion

This nationally representative cross-sectional study based on NHANES 1999–2020 comprehensively examined the relationship between VAI and cancer prevalence in U.S. adults. While the unadjusted analysis suggested a modest positive association between VAI and cancer prevalence, this relationship became substantially attenuated after progressive adjustment for sociodemographic factors, metabolic comorbidities, and overall adiposity. In the primary BMI-free Model 3, the VAI–cancer association was statistically significant (OR = 1.024; 95% CI: 1.004–1.045); by contrast, in sensitivity models re-introducing BMI and hyperlipidemia, it attenuated to 1.016 (0.996–1.036) and lost significance—a pattern most consistent with confounding/mediation by general adiposity and lipid pathways rather than a VAI-specific effect; BMI itself was null (Table 3), the direction for VAI persisted in mutually adjusted models with WC (**Supplementary Table 2**), and WC–BMI collinearity was substantial (**Supplementary Table 3**). Given that VAI incorporates components closely tied to insulin resistance, lipid abnormalities, and inflammation, its predictive capacity may overlap with these metabolic pathways. Accordingly, the attenuation observed in BMI/hyperlipidemia-adjusted sensitivity models is most consistent with partial confounding/mediation and over-adjustment from overlapping biology and should be interpreted cautiously, rather than as evidence against any VAI-related pathway. These findings underscore the distinction between a raw statistical correlation and an independent clinical predictor. Although VAI captures key facets of visceral adiposity and lipid dysfunction, its incremental value beyond established measures such as BMI appears limited in this population-based context. Additionally, restricted cubic spline analysis revealed an approximately linear dose–response, with borderline evidence of nonlinearity ($p = 0.0540$) and a statistically significant overall trend ($p = 0.0428$). Notably, a borderline interaction with hypertension ($p = 0.044$) indicated a slightly stronger VAI–cancer association among normotensive individuals; given the small effects and exploratory nature, this finding is hypothesis-generating and should be interpreted with caution. Attenuation emerged only when BMI and hyperlipidemia were added in sensitivity analyses; thus, partial over-adjustment for components/consequences of the VAI construct is a plausible explanation and findings should be interpreted cautiously. This occurs when variables used to construct a composite index are also adjusted for as covariates, potentially introducing multicollinearity and attenuating true associations. In this study, the concurrent inclusion of BMI, triglycerides, and HDL-C as covariates may have partially masked the relationship between VAI and cancer by adjusting away overlapping biological mechanisms. To address this, we conducted a supplementary model excluding BMI, which yielded a slightly elevated but still non-significant association (OR = 1.022; $p = 0.08$), suggesting that BMI adjustment only partially explained the attenuation. These findings imply a shared pathophysiological basis between general and visceral adiposity, rather than simple statistical redundancy. Overadjustment is a recognized limitation in models involving composite indices and has been previously discussed in the context of VAI [15,24]. Future studies employing mediation analysis, structural equation modeling, or multicollinearity diagnostics may help isolate the independent effects of VAI and guide optimal model design.

These findings align well with previous literature. In a Japanese prospective cohort, Okamura et al. [21] reported a 98% higher risk of colorectal cancer among individuals in

the highest versus lowest VAI tertile, a relationship remaining robust even after BMI adjustment. Using Mendelian randomization, Karlsson et al. [25] identified a causal relationship between VAT and disease-specific cancer mortality independent of BMI, with stronger associations observed in women. Similarly, Godinho-Mota et al. [22] demonstrated elevated VAI levels in breast cancer patients compared with controls (OR $\approx$ 1.91), which persisted after adjusting for BMI. Additionally, Parra-Soto et al. [26], analyzing UK Biobank data from over 380,000 middle-aged adults followed for approximately 8 years, found that elevated VAI was associated with increased risks of liver, gallbladder, colorectal, and breast cancers. Unlike these studies that focused on specific cancer sites or metabolically susceptible groups, our cross-sectional design assessed the overall cancer prevalence, thus possibly diluting stronger site-specific associations. Nevertheless, the borderline positive relationship observed in women in our study suggests a potential role of VAI as a predictive marker in specific populations, such as postmenopausal breast cancer patients. Supporting this, Lee et al. [27] showed through PET/CT imaging that the combination of VAT metabolic activity (SUV) and relative VAT volume (rVAT) significantly predicted overall survival in colorectal cancer patients, particularly among females. Another imaging-based study also reported that each standard deviation increase in abdominal VAT volume was associated with approximately a 20% higher breast cancer risk in postmenopausal women, consistent with our findings [28]. Furthermore, Yoshida et al. [29] found that VAT percentage (VAT%) was superior to BMI in predicting intraoperative blood loss and surgical complexity among obese endometrial cancer patients, particularly those undergoing pelvic lymphadenectomy, highlighting the broader clinical implications of VAT beyond carcinogenesis. These findings indicate that VAT not only contributes to tumor development but also significantly affects surgical accessibility and perioperative safety, reinforcing its role as a valuable clinical risk indicator in oncologic and operative decision-making.

VAI integrates waist circumference, BMI, triglycerides, and HDL-C, reflecting both central adiposity and lipid dysfunction. From a pathophysiological perspective, elevated VAI signifies increased visceral fat accumulation, insulin resistance, decreased adiponectin, elevated leptin, and heightened inflammation through activation of cytokines such as IL-6 and TNF-α—processes strongly implicated in carcinogenesis [4,9]. Recent studies have reported that VAT-derived secretions from advanced esophageal cancer patients can downregulate IFN-γ production in T cells and enhance immune checkpoint expression in regulatory T cells, fostering systemic immunosuppression and tumor progression [30]. Mongan et al. [31] demonstrated that conditioned media from VAT in esophageal adenocarcinoma patients enhanced radiation sensitivity in therapy-resistant cells, suggesting VAT directly modulates tumor microenvironment responses. Chaplin et al. [32] further summarized evidence that VAT contributes directly to colorectal cancer progression via metabolic reprogramming, immune evasion, and microenvironment remodeling, supporting VAI's mechanistic relevance in cancer risk prediction. Indeed, VAT functions as a highly active endocrine organ, promoting tumorigenesis via hypoxia-driven inflammation, NF-κB-mediated pathways, and IGF-axis activation, collectively enhancing proliferation, inhibiting apoptosis, and stimulating angiogenesis [7]. Dysfunctional VAT induces macrophage infiltration and chronic local inflammation, facilitating tumor cell proliferation, invasion, and metastasis. VAT-induced systemic inflammation, mediated by insulin resistance and pro-inflammatory factors (TNF-α, IL-6, PGE2), further amplifies cancer progression risks [33]. A recent investigation of postmenopausal women revealed associations between elevated VAT and gut dysbiosis, including increased pro-inflammatory Proteobacteria, lower Firmicutes/Bacteroidetes ratios, and elevated systemic endotoxemia markers, suggesting that VAT-related dysbiosis contributes to chronic inflammation and carcinogenesis [34]. These inflammatory pathways further activate oncogenic signaling cascades such as PI3K/Akt, IGF-1, and mTOR, potentiating tumor cell proliferation, survival, and angiogenesis [9,10,33]. Furthermore, the positive correlation between VAI and inflammatory biomarkers such as CRP—a marker associated with worse prognosis in breast and tongue cancers—reinforces the potential utility of VAI as an indirect indicator of cancer-promoting systemic inflammation [35,36].

Nonetheless, the inclusion of both BMI and VAI in regression models introduces multicollinearity, which may obscure the independent contribution of VAI. Previous studies have advised caution in such modeling strategies to prevent unstable parameter estimation [24]. Despite this, several studies have demonstrated that VAI is associated with type 2 diabetes [20,24] and colorectal cancer [21], even after adjustment for BMI. The Women's Health Initiative (WHI) further reported that both VAT and the VAT-to-subcutaneous fat (VAT/SAT) ratio were significantly associated with postmenopausal breast cancer risk, independent of BMI [26]. Notably, Okamura et al. [21] observed a 1.98-fold increase in colorectal cancer risk in individuals within the highest VAI tertile, a relationship that remained significant following BMI adjustment. However, the cross-sectional design of NHANES limits causal inference. VAI and BMI were measured concurrently, and their components are interdependent. Moreover, cancer-related weight loss or metabolic alterations may reverse-influence VAI levels. Cancer therapies could also affect lipid metabolism, further confounding the observed associations.

Importantly, cancer types differ in their sensitivity to adiposity and metabolic dysregulation. Visceral obesity is more strongly linked to colorectal, liver, endometrial, and

postmenopausal breast cancers [2,37], whereas lung and certain prostate cancers—driven by smoking or hormonal factors—often show weak or inverse associations [2]. Analyzing all cancers as a single group may dilute associations in metabolically sensitive subtypes. Mendelian randomization studies from the UK Biobank have shown that central adiposity indicators (e.g., waist-to-hip ratio, abdominal fat) exhibit stronger genetic correlations with lipid-sensitive cancers than BMI [38]. A dual-sample MR study further demonstrated that genetically predicted VAT was significantly associated with hepatocellular carcinoma risk (OR per SD $\approx$ 5.7, p = 0.020), whereas BMI showed no significant association (p = 0.058) [39]. Several imaging and pathology-based studies support the prognostic role of VAT. Clark et al. [40] reported that higher VAT area and VAT/SAT ratio independently predicted recurrence risk in rectal cancer (HR $\approx$ 5.0), while BMI was not predictive. Ravensbergen et al. [41] found that elevated VAI was associated with aggressive tumor histology, such as low tumor–stroma ratio (TSR), and higher postoperative recurrence rates. A dose–response meta-analysis involving six observational studies confirmed that every 25 cm^2 increase in VAT area corresponded to a 13% increase in colorectal adenoma risk, reinforcing VAT's mediating role in early carcinogenesis [6]. Some researchers have speculated that certain antihypertensive medications, such as ACE inhibitors or ARBs, may indirectly affect tumor development through mechanisms involving visceral fat or adipose-related factors. However, there is currently a lack of direct mechanistic evidence, and further research is needed [42].

From a public health perspective, although VAI did not exhibit independent predictive power for cancer in the general population, it may serve as a supplementary screening tool for metabolically unhealthy normal-weight (MUNW) individuals—those with normal BMI but underlying metabolic abnormalities. Prior studies have shown that targeted interventions reducing abdominal fat, particularly bariatric surgeries such as Roux-en-Y gastric bypass and sleeve gastrectomy, are associated with significantly lower risks of obesity-related cancers. For example, the SPLENDID cohort reported a 32% reduction in overall cancer incidence (HR = 0.68) and a 48% reduction in cancer-specific mortality (HR = 0.52) among surgical patients compared to non-surgical controls [43]. Moreover, increasing evidence suggests that the pattern of fat distribution is more informative than total adiposity in cancer prognosis. In particular, low levels of subcutaneous adiposity have been independently linked to higher cancer-specific mortality across several malignancies, highlighting fat storage patterns as potential prognostic biomarkers [44]. Even in individuals who do not meet diagnostic criteria for metabolic syndrome, elevated VAI is frequently associated with insulin resistance, dyslipidemia, and reduced HDL-C—indicating a metabolically at-risk phenotype. These features suggest that VAI could aid in the early identification of high-risk individuals, supporting timely lifestyle interventions and targeted cancer screening strategies [45]. From a clinical perspective, individuals with significantly elevated VAI should be closely monitored for their overall metabolic health status. Tailored lifestyle interventions and early cancer screening strategies are recommended to mitigate potential oncologic risk in this population.

This study has several strengths, including a large sample size, nationally representative data, rigorous statistical methodology, and comprehensive multivariable adjustment. However, several limitations must be acknowledged. First, the cross-sectional design precludes causal inference regarding whether elevated VAI precedes or results from cancer. Second, cancer diagnoses were self-reported, potentially introducing misclassification or recall bias. Third, site-specific analyses were exploratory, covered six cancer sites with modest case counts, and p values were not adjusted for multiple comparisons; estimates should be interpreted cautiously. Fourth, as an indirect index, VAI is susceptible to fluctuations in lipid profiles, dietary patterns, and medication use. Finally, residual confounding may exist due to unmeasured variables such as diet, physical activity, and inflammatory biomarkers (e.g., CRP).

From a cancer prevention standpoint, future research should evaluate whether targeted interventions aimed at reducing VAI—such as lifestyle modifications, pharmacologic therapies, or bariatric procedures—can effectively lower cancer risk. Given that VAI encapsulates key metabolic and inflammatory dysregulations involved in tumorigenesis, interventions specifically attenuating visceral adiposity and improving lipid profiles may offer superior risk mitigation compared to general weight loss alone. Randomized controlled trials assessing changes in VAI as a surrogate endpoint for cancer incidence, especially in metabolically unhealthy individuals with normal BMI, could establish its clinical relevance as a modifiable risk marker. Furthermore, integrating VAI into precision prevention frameworks may enable more efficient identification and stratification of high-risk individuals for early screening and behavioral counseling.

In conclusion, our findings indicate a weak positive association between VAI and cancer prevalence, which diminished after adjustment for BMI and metabolic comorbidities. While VAI does not appear to have substantial independent predictive value in the general population, it may still be clinically relevant for identifying individuals at elevated risk, particularly within high-risk subgroups such as metabolically abnormal individuals or postmenopausal women. Future studies should incorporate large-scale prospective cohorts, site-specific cancer analyses, inflammatory biomarkers, and genetic causal inference approaches to validate the prognostic utility of VAI. Ultimately, a better understanding of the mechanistic links between visceral adiposity and cancer may support the integration of VAI into comprehensive cancer risk stratification

frameworks and inform preventive strategies targeting abdominal fat accumulation.

5. Conclusions

This cross-sectional study based on NHANES data revealed a modest positive association between the VAI and cancer prevalence among U.S. adults. However, this association was largely attenuated after adjusting for BMI and metabolic comorbidities, suggesting the relationship was predominantly explained by traditional obesity measures rather than the independent predictive capacity of VAI. Dose–response analyses indicated a weak, approximately linear increase in cancer prevalence odds with higher VAI, without a clear threshold effect. Subgroup analyses demonstrated consistent associations across populations, with no substantial effect modification observed, except for a borderline interaction by hypertension status ($p = 0.044$), indicating a stronger association among individuals without hypertension. Collectively, our data do not provide strong evidence for an advantage of VAI over BMI in predicting overall cancer risk. Nonetheless, given the established role of visceral adiposity in metabolic dysfunction and carcinogenesis, further studies are warranted. Large-scale prospective cohort studies incorporating inflammatory biomarkers, genetic causal inference, and cancer subtype-specific analyses are essential to better define the potential role of VAI in cancer prediction among selected high-risk populations. If future evidence confirms its independent predictive value, VAI could be integrated into clinical cancer risk assessment tools. Additionally, mechanistic research elucidating how visceral fat-derived adipokines and cytokines promote cancer development could identify promising intervention targets. In conclusion, this study emphasizes the importance of visceral adiposity in understanding obesity-related cancer risk and highlights the necessity of evaluating any single metabolic indicator, including VAI, within a broader, multifactorial, and life-course-based framework to enhance cancer prevention strategies.

Availability of Data and Materials

All relevant data are publicly available from the NHANES repository maintained by the U.S. Centers for Disease Control and Prevention (CDC). Data used in this study were extracted from NHANES 1999–2020 survey cycles and are accessible at: https://www.cdc.gov/nchs/nhanes/index.htm. We confirm that no restrictions apply to the availability or reuse of the data analyzed in this manuscript.

Author Contributions

XC, MY, and WZ conducted the research. XC led the conceptualization, methodology, and writing of the original draft. MY was responsible for investigation and data curation. WZ contributed to software development and formal analysis. JT supervised the project, provided project administration, and participated in validation and manuscript reviewing. XY contributed to conceptualization, supervision, and funding acquisition, and participated in manuscript reviewing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study utilized publicly available, de-identified data from the NHANES database. NHANES protocols were approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all participants provided written informed consent. No additional ethical approval was required for this secondary analysis of anonymized public-use data.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR39830.

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