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Glycemic index, Glycemic load, Genetic Susceptibility and their interactions with Lung and Upper Aerodigestive Tract Cancers

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Glycemic index, Glycemic load, Genetic Susceptibility and their interactions with Lung and Upper Aerodigestive Tract Cancers

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy in Epidemiology

by

Chun-Pin Chang

2018

ABSTRACT OF THE DISSERTATION

Glycemic index, Glycemic load, Genetic Susceptibility and their interactions with Lung and Upper Aerodigestive Tract Cancers

by

Chun-Pin Chang

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2018

Professor Zuo-Feng Zhang, Chair

Background: Although some evidence suggests a link between high dietary sugar, glycemic index (GI), and glycemic load (GL) with increased cancer risk, the relationship with the risk of lung and UADT cancers and their interactions with glucose metabolism-related genetic variants remains largely unexplored. In addition, the contributions of GI and GL from different food sources have not yet been studied. **Objective and Methods**: We aimed to evaluate the associations of GI, GL and glucose metabolism-related genetic variants with lung cancer and UADT cancer susceptibility in a Los Angeles (LA) population-based case-control study. In this study population, we also evaluated novel interactions between glucose metabolism-related genetic variants, GI, GL, tobacco smoking and alcohol drinking for the susceptibility of lung

cancer and UADT cancers. At the global level, we conducted a pooled analysis using the dataset from the International Head and Neck Cancer Epidemiology (INHANCE) consortium to assess the associations by gender, tobacco smoking, alcohol drinking intensity and histological types of head and neck cancer (HNC), specifically for oral cavity and pharyngeal cancer (OPC) and laryngeal cancer (LC). **Results**: In the LA population-based case-control study, an increased odds of lung cancer with high GI diet and a reduced odds of UADT cancer with high sugar diet were observed. Furthermore, the effect of GI, GL and sugar might be source-dependent and modulated by smoking status. In addition, genetic variants in the pathway of glucose metabolism may modify the susceptibility of lung and UADT cancers. In the pooled analysis of eight case–control studies within the INHANCE consortium, we found elevated odds of HNC and laryngeal cancer with a high GI diet, and decreased odds of oral and pharyngeal cancer with a high GL diet. **Conclusion**: These results confirm the associations between a high GI diet and increased susceptibility of lung and laryngeal cancer. In addition, the associations could be varied by food sources, tobacco smoking and alcohol drinking. Furthermore, the associations between polymorphisms in the genes involved in the glucose metabolism and lung and UADT cancer susceptibility were observed, with the interaction of SNPs and tobacco smoking for lung cancer on both additive and multiplicative scale.

The dissertation of Chun-Pin Chang is approved.

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2018

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2. Yang TC, **Chang CP**, Lan YC, Liu CL, Shih MC, Wu FY, et al. Recombinant ORF66 and ORFK12 antigens for the detection of human herpesvirus 8 antibodies in HIV-positive and -negative patients. Biotechnology letters. 2009;31(5):629-37.

3. Lin CW, **Chang CP**, Wu FY, Liu CL. Comparative prevalence of plasma human herpesvirus 8 DNA in sexual contact and intravenous injection routes of HIV transmission. FEMS immunology and medical microbiology. 2008;52(3):428-30.

PRESENTATIONS AND POSTERS

1. Society for Epidemiologic Research 50th Annual Meeting, Poster, Seattle, USA (June 2017): "Dietary glycemic index and glycemic load and the risk of lung cancer: Clues from LA case-control study", poster.

2. UCLA Epidemiology Student Poster Session, Poster, Los Angeles, USA (Oct 2014): "Effects of CXCR5/CXCL13 genetic variation on CXCR5 B cell receptor levels in HIV-infected population".

3. The 39th Annual Meeting of the Chinese Society of Microbiology, Oral Presentation, Taipei, Taiwan (Dec 2005): "Prevalence of Human Herpesvirus 8 infection in leukemia patients by nested PCR".

CHAPTER 1. INTRODUCTION AND BACKGROUND

1.1 Epidemiology of Lung cancer

Lung cancer has been the most common cancer in the world for several decades. According to data from GLOBOCAN 2012 (1), there are estimated to be 1.8 million new cases of lung cancer in 2012 and it remains as the most common cancer in the world; lung cancer is also the most common cause of death among cancer patients worldwide, estimated to be responsible for nearly 20% of cancer deaths (1.6 million deaths). In the United States, lung cancer is the second most common cancer and the leading cause of cancer death for both men and women. According to data from Cancer Facts & Figure 2018(2), there are estimated 0.23 million new lung cancer cases and 0.15 million lung cancer deaths in 2018.

The major histological types of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung carcinoma (SCLC). SCLC tends to be more aggressive clinically than NSCLC and have a strong association with tobacco smoking (3). Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma are all subtypes of NSCLC. The trend of incidences for squamous, large and small cell lung carcinoma continue to decrease, while adenocarcinoma rates remain relatively constant in males and increasing in females in the United State from 1973 to 2010 (4).

Tobacco smoking is the best established risk factor for lung cancer, and contributes to

approximately 80% of lung cancer deaths in the US (5). Male current smokers had higher susceptibility for smoking attributable lung cancer than female current smokers with ratio of relative risk (RRR) of 1.61 (95% CI: 1.37－1.89) (6). People who were exposed to secondhand smoke also increased lung cancer risk with small magnitude. In a pooled analysis of the International Lung Cancer Consortium (ILCCO), never smokers who were ever exposed to secondhand smoke had 1.31 times odds of lung cancer (95% CI: 1.17–1.45) compared with never smokers who were never exposed (7).

Other environmental factors can also increase lung cancer risk, such as fine particulate matter or radon. Increased lung cancer risk was observed for each 10-$\mu g/m^3$ increment in ambient fine particulate matter $\leq 2.5\mu m$ ($PM_{2.5}$) concentration (HR, 95% CI: 1.43, 1.11－1.84) using the Adventist Health and Smog Study-2 (AHSMOG-2) (8). A nonlinear dose-response relationship ($P_{nonlinearity} < 0.014$) was observed between environmental radon exposure and lung cancer risk in a meta-analysis study (9) . Occupational exposures, such as workplace exposure to asbestos, arsenic, beryllium, cadmium, chromium, and nickel, also increased lung cancer incidence and mortality(10). Genome-wide association (GWA) studies identified several susceptibility loci in the 15q25, 5p15 and 6p21 regions, especially in 15q25.1 (11).

Tobacco smoking is the most important cause of lung cancer, however, around 10-25% of lung cancer cases were never smokers who smoke less than 100 cigarettes in their lifetime(12). Other

potential factors should be identified in order to prevent the disease and decrease the burden of lung cancer. In a meta-analysis study, protective effects on lung cancer risk were observed on people with highest vegetable diets (RR, 95% CI :0.92, 0.87－0.97) and with highest fruit diet (RR, 95% CI :0.82, 0.76－0.89)(13).

1.2 Epidemiology of UADT Cancer

Upper aero-digestive tract (UADT) cancers comprise several cancer sites, including oral cavity, pharynx, larynx and esophagus. Squamous cell carcinoma is the major histological cell type of the UADT cancers. According to the data from GLOBCAN 2012(1), UADT cancers rank 4th in incidence with estimated 1.14 million new cases and rank 2th in mortality with estimated 0.78 million deaths worldwide in 2012, that accounts for 8.12% of all cancer cases and 9.46% of all cancer deaths respectively in the world. In the United Sates(2), there is estimated to be 81,980 new cases of UADT cancer (4.74% of total cancer new cases) and 29,59 deaths (4.83% of total cancer deaths) in 2018.

Tobacco smoking and alcoholic beverage consumption remain the most established modifiable risk factors for UADT cancers (14-16). In a meta-analysis, the pooled relative risk of tobacco smoking on UADT cancer was 3.57 (95% CI: 2.63, 4.84) among current smokers compared with never smokers (17). For alcohol drinking, attributable fraction (AF) of oral cavity and pharynx, larynx and esophagus squamous cell carcinoma (ESCC) were 36.7%, 26.1% and 44.7%

worldwide, respectively(18). Tobacco smoking and alcohol drinking together explained 85% of hypopharyngeal/laryngeal cancer cases, 74% of oropharyngeal cancer cases, 67% of esophageal cancer cases and 61% of oral cancer cases in Europe (19). Human papillomaviruses (HPV) infection has been recognized to cause a subgroup of head and neck cancer (HNC). In the Canada HeNCe Life case-control study, HPV infection was associated with increased risk of HNC overall (aOR, 95% CI: 4.18, 2.94 – 5.95) and oropharyngeal cancer only (aOR, 95% CI: 10.3, 6.8 – 15.7) (20), especially for HPV 16 infection (21). Carcinogenic agents for UADT cancer also include betel quid, chewing tobacco, radiation, asbestos, acid mists, etc.(10). In contract, the protective effect of a high fruits and vegetables diet on HNC risk has been reported (22).

1.3 Glycemic index (GI) and glycemic load (GL)

GI and GL were developed to classify foods based on the postprandial blood glucose response. GI measures the immediate impact on blood glucose levels after consuming carbohydrates (23). GL incorporates the effects of both carbohydrate quality and quantity consumed and is calculated by multiplying the available carbohydrate content of food (in gram) by its GI and dividing the total by 100. The higher the GI and GL, the greater the elevation in blood glucose level (24). High dietary sugar, GI and GL consumption could contribute to carcinogenesis by altering insulin-like growth factor-I (IGF-I) pathway, generating oxidative stress or cell proliferation (25-

28). A number of epidemiological studies have reported associations between high sugar, GI and GL diets to higher risk for cancers, including colorectal (29, 30), pancreatic (31), endometrial (32), esophageal (33) and breast (30, 34, 35), prompting the American Cancer Society to recommend limiting added sugar consumption as a preventive measure against cancer (36). Other studies, however, found little evidence of the high sugar diet connection to a range of cancers (37, 38). More studies are needed to elucidate the role of GI and GL on cancer risk.

It has been suggested that dietary factors influence the risk of lung cancer (39) and head and neck cancer (HNC) (40). For lung cancer, De Stefani et. al.(41) published the first paper linking GI diet with lung cancer in 1998 using a hospital-based case-control study design in Uruguay (OR 4^{th} vs 1^{st} quartile, 95% CI: 2.77, 1.28－5.97). Later, George et. al. (42) analyzed the associations between GI/GL intake and several cancer sites using NIH–AARP Diet and Health Study data and found a null associations between GI/GL and lung cancer risk. The same lack of association was found by Hu et. al. in the Canadian population-based case-control study (43). However, the conflict result was found in the hospital-based case-control study, which concluded that GI was associated with increased risk of lung cancer (OR 5^{th} vs 1^{st} quintile, 95% CI: 1.48, 1.20－1.81) with a significant trend among non-Hispanic whites (44). For UADT cancer, Augustin et al. firstly reported the odds ratios (ORs) of GI and GL for cancers of the oral cavity, pharynx, larynx and esophagus (45); also George et al. estimated the associations of GI and GL

for head and neck cancer (42). The association between esophageal cancer and GI/GL diet was reported by another three epidemiological studies with inconclusive results (33, 46, 47). Although the association between GI, GL and cancer could be explained by an increasing bioavailability and bioactivity of IGFs, which can promote tumor development and stimulate cell proliferation (48), more research is required to further elucidate specific mechanisms underlying a putative role of GI and GL on lung and UADT cancers.

1.4 INHANCE Consortium

Since 2004, the International Head and Neck Cancer Epidemiology (INHANCE) consortium has provided opportunities to elucidate the etiology of head and neck cancer through large-scale pooled analyses of individual-level data from several case-control studies worldwide (49). Dietary habits have been previously investigated within the consortium considering intakes of food groups (50), nutrients (51, 52), and dietary patterns (40). We conducted a pooled analysis using the dataset from INHANCE consortium. The large sample size of the pooled analysis study allowed us to assess the associations by gender, tobacco smoking, alcohol drinking intensity and histological types of head and neck cancer, specifically for oral cavity and pharyngeal cancer (OPC) and laryngeal cancer (LC).

1.5 Gaps in the literature

A few studies have been published on the relationship between glycemic index (GI) and

glycemic load (GL) with lung and UADT cancers (33, 41, 43-47) with inconclusive results which highlight the need for additional investigations of GI and GL for cancers of lung and UADT. Moreover, to our knowledge in the published literature, the relationship between GI and GL from different food sources and cancer risks is not been evaluated. How genetic variation, GI and GL consumption influence lung and UADT cancer risk is still unknown. High GI and GL diet stimulate insulin release and increase glucose uptake, and has been hypothesized to link with cancer development. To address these questions, data from a population-based case-control study in Los Angeles County was analyzed to test the hypothesis that dietary GI and GL may be positive associated with susceptibility of lung and UADT cancers; in addition, how GI and GL from different food sources differentially modulate the development of lung and UADT cancers were estimated. Associations between dietary GI and GL and sub-sites of HNC were tested using INHANCE consortium data to ascertain the association in the global level.

CHAPTER 2. RESEARCH OBJECTIVES AND METHODS

2.1 Research Objectives

The overall objective of this study was to examine the relationships between GI, GL and risk of lung and UADT cancers. We estimated the magnitude of associations between GI, GL and sugar with each major histological type of lung and UADT cancers. We also explored potential gene-environment interactions between GI/GL, tobacco smoking, alcohol drinking and single nucleotide polymorphisms (SNPs) on the susceptibility of lung and UADT cancers.

2.2 Specific Aims and Hypotheses

Specific Aim 1. To estimate the associations of GI, GL and sugar intake from different food sources with lung and UADT cancers in the Los Angeles population-based case-control study.

Hypothesis 1. High GI and GL diet are associated with the susceptibility of lung and UADT cancers. In addition, GI and GL from different food sources are hypothesized to differentially modulate the development of lung and UADT cancers.

Specific Aim 2. To evaluate the associations between genetic variants and cancers of lung and UADT and to test for potential gene- environment (GxE) interactions with GI, GL, tobacco smoking and alcohol drinking in the Los Angeles population-based case-control study.

Hypothesis 2. Polymorphisms of glucose metabolism-related genes could influence the risk of lung and UADT cancers with potential interactions with environmental factors.

Specific Aim 3. To investigate the associations between GI, GL and cancers of the oral cavity and pharynx and larynx; and to explore the potential interactions of GI and GL with several variables, including tobacco smoking and alcohol drinking, on head and neck cancer, in a large pooled analysis based on a subset of eight case-control studies participating in the INHANCE consortium.

Hypothesis 3. GI and GL are positively associated with cancers of the oral cavity and pharynx and larynx.

2.3 Study Population, Design and Methods

2.3.1 LA study: Aim 1 and 2

The newly diagnosed lung and UADT cancer cases and population controls were recruited from Los Angeles County between 1999 and 2004. Detailed descriptions of the participant recruitment and data collection for the study can be found in previous publications (53, 54). Histologically confirmed lung and UADT cancer cases were recruited through the rapid ascertainment system of the University of Southern California (USC) Cancer Surveillance Program for Los Angeles County. Controls were originally matched to cases of lung and UADT cancers by age (within 10-year intervals), sex, and neighborhood of residence. In these data analyses, the matches were broken and all controls recruited from this study were used in order to increase power.

All participants were residents of Los Angeles County at the time of diagnosis for cases or recruitment for controls, ranged in age from 18 to 65 years during the enrollment period, and spoke English, Spanish, or had translators available at home. In-person interviews were conducted by trained study staff using standardized questionnaires to collect information on demographic factors, detailed dietary history, as well as histories of tobacco smoking and alcohol consumption, occupational and environmental exposures, medical history, and family history of cancer. Buccal cells were collected after interviews for genotyping. Participants were asked to brush their inside cheeks with a toothbrush and then rinse with mouthwash. All biological specimens were stored at -70°C until use in the Molecular Epidemiology Laboratory, located in Fielding School of Public Health, University of California at Los Angeles. The participation rates were 39% (611 of 1,556) for lung and 46% (601 of 1,301) for UADT cancer cases and 79% (1,040 of 1,321) for controls (53). The study was approved by the Institutional Review Boards (IRBs) of the University of California at Los Angeles and USC; all participants provided written informed consent.

The original study population included 611 lung cancer cases, 601 UADT cancer cases and 1,040 cancer-free controls. A total of 589 lung cancer cases, 570 UADT cancer cases and 1,026 controls were included in the aim 1 analyses after excluding the participants by the following criteria: 1) missing food frequency questionnaire (9 lung cancer cases, 7 UADT cancer cases and 6 controls); 2) daily energy intake less than 500 Kcal or larger than 5000 Kcal (13 lung cancer cases, 24 UADT

cancer cases and 8 controls). A total of 550 lung cancer cases, 489 UADT cancer cases and 949 controls were included in the aim 2 analyses after excluding the participants without genotype information.

2.3.2 Pooled data from INHANCE Consortium: Aim 3

Four case-control studies from the INHANCE pooled dataset (version 1.5) were extracted, where information on GL intakes were originally calculated and provided to the INHANCE Coordinator Center. GI value was calculated for the North Carolina (2002-2006), Italy Multicenter, Milan (2006-2009) and Switzerland studies (55-58). In addition, GI and GL intakes were calculated from study-specific food items and comparable food composition databases for the Boston (59), Seattle (1985-1995) (60), and Memorial Sloan Kettering Cancer Center (MSKCC) studies (61). GI and GL intakes from LA study were calculated in specific aim 1. At the end, eight case-control studies with information on GI and GL values were included in the aim 3 analyses. Three studies were conducted in Europe and five in the United States. Other details on the individual studies, harmonization of data, and data pooling methods have been previously described (62) and are summarized in Table 2-1. Informed consent was obtained from all subjects within the framework of the original studies. The investigations were approved by the relevant institutional review boards, according to the rules specific to each country at the time of data collection.

Cases were included if their cancer had been originally classified as an invasive cancer of oral

cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx, or HNC unspecified. Cases with cancers of the salivary glands or of the nasal cavity/ear/paranasal sinuses were excluded (63).

Here were the exclusion criteria for the pooled analyses: 1) cases without information on the cancer site of origin; 2) subjects with missing or implausible (<500 or >5,500 kcal) values of daily non-alcohol energy intake; 3) subjects with missing information on GI and GL. Thus, the aim 3 analyses included a total of 11,403 subjects, with 4,058 HNC cases and 7,345 controls.

2.4 Processing of Dietary Data

2.4.1 Dietary data in LA study

Measures of dietary intake were derived from a 78-item semi-quantitative FFQ based on the validated Brief Block FFQ (64). Participants were queried about their usual frequency of consumption over the previous year – rarely, never, per year, month, week, or day. Portion sizes were measured in teaspoons, tablespoons, ounces, pounds, cups, pieces, handfuls, pats, burritos, patties, bowls, and slices for solid food items and as number of cups, ounces, or glasses consumed for drinks. The reference period of the dietary intake was 1 year before diagnosis for cases and 1 year before interview for controls.

Food frequency was converted to daily intake in grams for each food item by linking portion size

and frequency in our FFQ with data from the USDA Nutrient Database Standard Reference, version 16 (SR16-1)(65). This document provides the grams per portion size as well as the nutritional composition for each food item.

The GI value (using a scale in which the glycemic index for pure glucose is 100) for each food item was derived from the international tables of glycemic index and glycemic load values (66-68). The daily GI for each participant was calculated by summing the products of the GI value and available carbohydrates of each food item consumed per day, then divided by the total amount of available carbohydrates consumed per day. Daily GI was calculated as below:

$$Daily\ GI = \frac{\sum(GI\ \ of\ each\ food\ item * available\ carbohydrates\ of\ each\ food\ item)}{total\ available\ carbohydrates} \quad (1)$$

This method also applied for calculating GI from certain food sources as below:

$$Source - specific\ GI = \frac{\sum(GI * available\ carbs\ from\ the\ certain\ food\ source)}{available\ carbohydrates\ from\ the\ certain\ food\ source} \quad (2)$$

Available carbohydrates were equal to total carbohydrates, including sugar and starch, minus the fiber content. The daily GL was calculated by summing the products of the GI value and available carbohydrates of each food item consumed per day divided by 100.

$$Daily\ GL = \frac{\sum(GI\ \ of\ each\ food\ item * available\ carbohydrates\ of\ each\ food\ item)}{100} \quad (3)$$

Similarly, GL from each food source was calculated by summing the products of the GI value and

available carbohydrates of each food item in that source divided by total daily GL intake:

$$Source - specific\ GL = \frac{\sum(GI * available\ carbs\ from\ certain\ food\ source)}{Daily\ GL} * 100 \quad (4)$$

Each GL unit represents the effect of consuming one gram of carbohydrate from glucose. The sources of GI/GL included: foods with high carbohydrates and sugar, fruits, vegetables, meat and mixed dishes, starches and salty snacks, breakfast foods, sweets and dairy products. Food items in the each food source were presented in Table 2-2.

Daily intake of calories, total sugars, carbohydrates and fiber were derived from each subject in the study. The carbohydrate intake was calculated as the sum of sugar, starch and fiber. Total sugar was the sum of individual monosaccharides (galactose, glucose, and fructose) and disaccharides (sucrose, lactose, and maltose). The distribution of GI, GL and sugar in the control group was used to determine the cut-off points for categorizing the continuous quantity into tertile. The daily nutrient intake for each food item was calculated by multiplying its daily food intake (in grams) by its nutrient composition. The total daily nutrient intake for each study participant was then calculated by summing the daily nutrient intake values across all food items. Participants with total energy intake less than 500 or more than 5,000 calories per day were excluded, resulting in the exclusion of 13 (2.16%) lung cancer cases and 8 (0.77%) controls.

2.4.2 Dietary data in INHANCE consortium study

Intakes of total energy, several nutrients, and food components were derived by combining information from study-specific FFQs, assessing subjects' usual diet during a reference period preceding cancer diagnosis for cases or interview for controls, with information from country-specific food composition databases (69, 70).

The method of estimating GI and GL from the LA study was described in the previous section.

For the Boston, Seattle (1985-1995) and MSKCC studies, GI and GL were estimated from food frequency questionnaires by following steps:

1. Converting the consumption frequency to servings per day

For the Boston and Seattle (1985-1995) studies, the daily serving for each food item had been transformed by DIETSYS Nutrient Analysis System. For the MSCKK study, the raw data from INHANCE consortium only contained the information of frequency per month instead of daily, weekly, monthly and yearly consumption frequency. Hence, daily serving was calculated by: (monthly frequency/30.42) * the serving size. The weights for small, medium and large serving size were 0.5, 1 and 1.25, respectively.

2. Converting daily serving to daily intake in gram

Grams per portion size for each food item were obtained from the U.S. Department of Agriculture (71) . Daily intake (gram) was calculated by multiplying the daily serving of specific food item by its grams per portion size. Available carbohydrate per 100 grams for each food item

was also obtained from the same source. We defined available carbohydrate to be the USDA-based value for grams of carbohydrate per 100 grams minus the USDA value for grams of dietary fiber per 100 grams. Available carbohydrate intake (gram) of each food item was calculated by: daily intake (g) * available carbohydrate (g/100g) / 100; and total available carbohydrates intake was calculated by summing available carbohydrate intake of each food item.

3. Assigned glycemic index value to each food item

We linked glycemic index values (using a scale assuming bread=100) to each food item using the published glycemic index estimates. We firstly searched the similar food item from international table (66, 68) with the values tested among health subjects and conducted in USA or Canada. Average glycemic index value was assigned to that food item if more than one glycemic index values for the same food item were provided in the international table. If the food item cannot be identified, we then searched the glycemic index values compiled by Foster-Powell et al. (67). The process of linkage was by manual review of the glycemic index table to identify the best matches for each food item in the questionnaire.

4. Daily glycemic index and glycemic load calculation

The formula for calculating daily GI and GL were described in section 2.4.1.

2.5 SNP Selection and Genotyping

We identified genes reported by previous literature to be involved in glucose metabolism. The function of genes related with glucose metabolism were shown in Table 2-3. Those target genes have biological function in cancer risk. And then, SNPs of those genes were selected by literature review or using genome variation server 138 (GVS) database (http://gvs.gs.washington.edu/GVS138/). The criteria of SNPs selection were: 1) minor allele frequency value (MAF) ≥ 5% in Caucasian; 2) R^2 threshold=0.80; 3) functional or potentially functional SNPs. Selected gene included EGFR (rs2072454, rs2227983, rs10277413, rs1050171 and rs2293347), ITGB1 (rs2298141), GFPT1 (rs13751, rs7568296 and rs2667), RAP1A (rs6573), PDK1 (rs2290563 and rs6433368), PGM1(rs855314) and ENO1(rs7534552). More detail of candidate SNPs are shown in Table 2-4.

Genotyping was performed by Fluidigm Dynamic 96.96 Array™ Assay platform (Fluidigm, South San Francisco, CA) at the UCLA Genotyping and Sequencing (GenoSeq) Core. For quality control, positive controls (DNA samples purchased from the Coriell Repository) and negative controls (reagent mix with water) for each genotype were included in each reaction plate. The Fluidigm SNP Genotyping software (https://www.fluidigm.com/software) was used to process the genotyping raw data to the analytical dataset.

After genotyping, all SNPs had call rate above 90% and MAF above 5%. One SNP (PDK1 rs2290563) was excluded from the final analyses because of violating Hardy-Weinberg

equilibrium in the chi-square test in controls.

2.6 Statistical Analysis

Frequencies or mean values of cases and controls were calculated for age, sex, race/ethnicity, years of education, tobacco smoking history, alcohol drinking history, and daily dietary factors (total caloric energy intake, grams of sugar, GI and GL). Distributions of categorical variables were compared using Chi-square tests and those of continuous variables were compared using t-tests. Unconditional logistic regression for standard multivariable model and energy-adjusted residual model was performed to estimate adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). The following covariates were included in the models to adjust for potential confounding effects.

Aim 1 model: age, sex, race/ethnicity, body mass index (BMI), number of alcoholic drinks per day, smoking pack-years, energy intake and diabetes history.

Aim 2 model: age, sex, race/ethnicity, education, number of alcoholic drinks per day, pack-years smoking.

The details of aim 3 model were described in the pooled analyses section (2.6.3).

The aORs of dietary sugar, GI and GL on lung and UADT cancers were estimated using per interquartile range (IQR) increase and tertile-level variables. The associations between daily GI/GL intake and histologic subtypes of lung and UADT cancers were also evaluated. Stratified

analyses were performed to estimate the associations between GI/GL from different food sources and the susceptibility of lung and UADT cancers among smokers (at least 100 cigarettes in their lifetime) and never smokers; additionally, the associations between GI/GL from different food sources and UADT cancer among drinkers (at least one alcoholic drink per month for a period of at least 6 months) and never drinkers were estimated since alcohol drinking is an important risk factor for UADT cancer. Interactions of interest in additive and multiplicative scale were assessed using the relative excess risk due to interaction (RERI) and the ratio of odds ratios (ROR). Preventive factors were recoded as risk factors for examining the joint effect in all analyses for interaction (72). In the analyses of interaction between SNPs and dietary GI/GL on lung and UADT cancers, the subset of the data only included the subjects in both aim 1 and aim 2.

2.6.1 Energy intake adjustment (residual method)

In order to adjust for the correlations between nutrients and total energy intake, energy-adjusted residual methods were applied (73). Residuals of nutrients were obtained from a linear regression model where total energy intake was the independent (predictor) variable and nutrient intake was the dependent variable. Applying the residuals of nutrient intake as an independent variable in the final logistic regression model can remove the variation caused by total energy intake. The detailed steps of the residual method were:

1. Run a linear regression: (Y: Nutrient intake) = b_0 + b_1*(X: energy intake)

2. Save the *residual* (nutrient residual) from the linear regression model in the step 1

3. Run the final logistic regression: (Y: lung/UADT cancer) = b'_0 + b'_1*(X: nutrient residual) + possible confounding factors

4. Energy-adjusted aOR from the residual method: aOR = exp (b'_1)

Nutrient residuals were standardized to the mean total energy intake for the purpose of interpretation(73). The standardized nutrient intakes were calculated by using the standardized mean nutrient intake plus residuals. The standardized mean nutrient intake was the nutrient intake at the mean total energy intake. Since the value of standardized nutrient intakes also depended on its residual, the negative value of standardized nutrient intakes could be possible when the negative value of residual was larger than standardized mean nutrient intake. Therefore, the minimum of the negative standardized nutrient intakes were set as zero in order to give results better interpretability. Note that nutrient residuals were used to estimate aOR in the final logistic regression models, and standardized nutrient intakes presented in Table 3-3 and Table 3-12 are for interpretation. The steps of standardized nutrient intakes calculation for the residual method were as follows:

1. Run a linear regression: (Y: nutrient intake) = b_0 + b_1*(X: energy intake)

2. Save the values of b_0 and b_1 from the linear regression model

3. Use b_0 and b_1 to calculate standardized nutrient intake for all subjects by the following formula:

Standardized nutrient intake = $b_0 + b_1$ *(mean energy intake) + residual of each subject

Calculating the nutrient residuals which were uncorrelated with energy intake allowed for the evaluation of independent effects of nutrient intakes on lung and UADT cancers.

2.6.2 Semi-Bayes shrinkage adjustment

Semi-Bayes shrinkage adjustment was applied to mitigate the effects of multiple comparisons and sparse data bias by updating the maximum-likelihood (ML) estimators with prior distributions to obtain posterior probabilities. In the SNPs analyses (Aim 2), null priors were used to generate semi-Bayes odds ratio (sbOR) and 95% posterior interval (PI). The assigned null priors were a coefficient prior with median 0 and a prior variance of 0.50; that is, a prior OR was one and a prior probability of falling within the interval 0.25, 4. Since zero should be a meaningful value for all regressors in the semi-Bayes adjustment, age and education level were re-centered by using mean age and mean education level in the controls. Drinking year and pack-year smoking were re-scaled to obtain the meaningful 1-unit change in the actual data. The null priors were merged with the actual data, and the semi-Bayes adjusted estimates were calculated by this weighted dataset.

2.6.3 Pooled analyses

A wide range of GI and GL from the Switzerland study was observed, therefore, 94 subjects, with GI larger than 200 or GL larger than 1456, were excluded due to unreasonable and extreme values of GI and GL. The Seattle (1985-1995) study didn't include laryngeal cancer (LC) cases, therefore, controls from the Seattle (1985-1995) study combined with the MSKCC study in the LC analyses. Moreover, due to small sample size issue, LC cases and controls from the Milan and Latina centers combined with another study center, Pordenone, in the Italy Multicenter study in the LC analyses.

The cut-off points of quintile categories were decided by the distribution of GI and GL in the controls. For the energy-adjusted GI, the cut-off points were -6.27, -2.19, 1.28 and 5.12; for the energy-adjusted GL, those were: -40.35, -16.25, 5.49 and 34.16, respectively. Heterogeneity of GI and GL intake across studies was assessed using likelihood ratio test. When the p-value of likelihood ratio test was larger than 0.1, fixed-effect logistic regression models were used to estimate pooled aORs of energy-adjusted GI and GL on HNC, OPC and LC; and when p for heterogeneity was less than 0.1, random intercept regression models (PROC GLIMMIX in SAS) were applied to estimate pooled aORs and to adjust the difference between studies. The following covariates were included in the models to control for confounding effects: age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status,

alcohol drinking intensity (number of drinks per day), and the product term for cigarette intensity and alcohol drinking.

CHAPTER 3. RESULTS FOR LUNG AND UADT CANCERS IN LA STUDY

3.1 Distribution of Selected Characteristics

3.1.1 Socio-demographic characteristics

A total of 1026 controls, 589 lung cancer cases and 570 UADT cases were included in the dietary analysis. Table 3-1 shows the distribution of socio-demographic characteristics among cases of lung and UADT cancers and controls. The average age was 52.24 for lung cancer cases, 50.38 for UADT cancer cases, and 49.89 for controls. Lung cancer cases tended to be older than controls. There was a higher proportion of males among UADT cancer cases and controls (75.26% and 60.14% respectively) compared to lung cancer cases (49.92%). The distribution of race/ethnicity were difference between cases and controls with p-values less than 0.0001 for lung cancer and 0.004 for UADT cancer. There were more Caucasians and Hispanics but fewer Blacks and Asians in the controls compared to lung and UADT cancer cases. Education level was higher in the controls with 14.44 average years of education compared to lung cancer cases with 13.29 average years of education and UADT cancer cases with 13.24 average years of education.

3.1.2 Established risk factors and dietary factors

Table 3-2 shows the distribution of tobacco smoking, alcohol drinking and dietary factors among cases of lung and UADT cancers and population healthy controls. The proportion of former tobacco smokers was higher among lung and UADT cancer cases (64.01% and 55.44%

respectively) compared to the controls (36.06%). Moreover, the proportion of current smokers was lower among UADT cancer cases compared to lung cancer cases and controls (13.16% versus 17.66% and 16.76%). The distribution of alcohol drinking status was similar between lung cancer cases and controls. More ever alcohol drinkers were in UADT cancer cases than in controls (80.28% and 75.15% respectively). Lung and UADT cancer cases had higher average energy intake and available carbohydrate than controls (energy intake for lung cancer cases, UADT cancer cases and controls: 1970 Kcal, 2163 Kcal and 1936 Kcal; available carbohydrate for lung cancer cases, UADT cancer cases and controls: 236g, 255g and 234g). GI, GL and sugar intake were significantly higher in UADT cancer cases than in controls (p-value by t-test were less than 0.001, 0.002 and 0.016 respectively). GI intake was significantly higher in lung cancer cases than in controls (p-value by t-test was less than 0.0001).

3.2 Lung Cancer Susceptibility

3.2.1 Cut-off points

Table 3-3 shows the range of nutrient intake in different tertile levels. The 33^{th} and 67^{th} centile cut-off points for total GI intake were 51.83 and 56.62 in the standard multivariable model and 52.2 and 56.06 in the residual model. For total GL, the cut-off points were 90.68 and 142.76 in the standard multivariable model and 118.1 and 138.51 in the residual model. For total dietary sugar, the cut-off points were 63.23 and 105.13 in the standard multivariable model and 83.61

and 112.32 in the residual model. We also present the cut-off points of nutrient intake from different food sources by both percentage of GL/sugar and the exact intake of GL/sugar from different food sources.

3.2.2 Total GI, GL and sugar intake

Table 3-4 shows the aORs and corresponding 95% CIs for associations of GI, GL and dietary sugar intake with lung cancer for both the standard multivariable models as well as the energy-adjusted residual models. Higher dietary GI was positively associated with lung cancer in the standard multivariable model (aOR, 95% CI for the 3rd versus 1st tertile: 1.52, 1.08–2.13) and in the residual model (aOR, 95% CI for the 3rd versus 1st tertile: 1.15, 1.05–2.15) with dose-response relationship (Ptrend= 0.016 and 0.004 in the standard model and the residual model, respectively); however, the aOR for the second versus first tertile widely overlapped the null. GL and sugar intake were not observed to be associated with lung cancer in either model type for continuous or categorical analysis.

3.2.3 Histological subtypes of lung cancer

For histological subtypes of lung cancer (Table 3-5), non-small cell lung cancer (NSCLC) was positively associated with GI for the 3rd tertile compared to the 1st tertile in both models (aOR, 95% CI =1.44, 1.01-2.05 in the standard model; aOR, 95% CI =1.52, 1.10-2.10 in the residual model). Among subtypes of NSCLC, we observed the significant association between GI and

adenocarcinoma in the standard multivariable model (aOR, 95% CI for the 3rd versus 1st tertile: 1.63, 1.08–2.46) and in the residual model (aOR, 95% CI for the 3rd versus 1st tertile: 1.72, 1.18–2.52) with dose-response relationship (Ptrend=0.019 and 0.005 in the standard model and the residual model, respectively). The susceptibility of small cell carcinoma was marginally associated with GI for the 3nd tertile compared to the 1st tertile in both the standard and residual model (aOR, 95% CI =2.74, 1.25-5.99, Ptrend=0.01 in the standard model; aOR, 95% CI =2.48, 1.23-5.03, Ptrend=0.007 in the residual model). We didn't observe any probable association between histological subtypes of lung cancer, GL and sugar intake.

3.2.4 Different sources of dietary GI, GL and sugar

Glycemic Index from different food sources

The associations between GI, GL, sugar and lung cancer appeared to be vary by the food categories. The associations stratified by the source of GI are presented in Table 3-6. A high proportion of GI consumed from starches and salty snacks was associated with lung cancer in both the standard and residual models (aOR, 95% CI for the 3th versus 1st tertile: 1.76, 1.27–2.44, and aOR, 95% CI for the 3th versus 1st tertile: 1.46, 1.06–2.01, respectively). However, we didn't observe the positive association between dietary GI of single food item in starches and salty snacks good group and lung cancer risk. High dietary GI from breakfast food was also positively associated with lung cancer in the both model (aOR, 95% CI for the 3th versus 1st tertile: 1.65,

1.22–2.22, and aOR, 95% CI for the 3th versus 1st tertile: 1.58, 1.17–2.13, respectively). Among all food items in breakfast food, the OR of dietary GI from cold cereals, such as corn flakes or Rice Krispies, on lung cancer was higher than other food items (aOR, 95% CI for the 3th versus 1st tertile: 1.39, 1.00–1.92 in the residual model).

Glycemic Load from different food sources

Table 3-7 displays the association between different sources of dietary GL and lung cancer. Similar as the association between GI and lung cancer, lung cancer was positively associated with GL consumed from breakfast food, starches and salty snacks in the standard and residual models with Ptrend less than 0.05 (breakfast food: aOR, 95% CI for the 3th versus 1st tertile: 1.59, 1.17–2.16, and aOR, 95% CI for the 3th versus 1st tertile: 1.48, 1.09–2.02, respectively; starches and salty snacks: aOR, 95% CI for the 3th versus 1st tertile: 1.39, 1.03–1.89, and aOR, 95% CI for the 3th versus 1st tertile: 1.41, 1.04–1.91, respectively). A high proportion of GL consumed from high carbohydrates/sugar was also associated with lung cancer in the both standard and residual models (aOR, 95% CI for the 3th versus 1st tertile: 1.65, 1.20–2.26, Ptrend: 0.002 and aOR, 95% CI for the 3th versus 1st tertile: 1.69, 1.23–2.31, Ptrend: 0.001, respectively). Increased proportion of GL consumed from vegetables, however, was inversely associated with lung cancer in the standard and residual models (aOR, 95% CI for the 3th versus 1st tertile: 0.63, 0.45–0.87, Ptrend: 0.005 and aOR, 95% CI for the 3th versus 1st tertile: 0.59, 0.43–0.81, Ptrend:

0.002, respectively). For the single food item, the protective effect on lung cancer risk was observed when consuming high proportion of dietary GL from coleslaw (cabbage), carrot and broccoli.

Sugar from different food sources

Table 3-8 shows the association between lung cancer and dietary sugar consumed from different sources. A high proportion of sugar consumed from high carbohydrates/sugar foods was associated with an increased odds of lung cancer in both models with a strong dose-response relationship (aOR, 95% CI for the 3th versus 1st tertile: 1.81, 1.32–2.49, Ptrend: <0.001 and aOR, 95% CI for the 3th versus 1st tertile: 1.78, 1.28–2.49, Ptrend: 0.001 respectively). In contract, a high proportion of sugar consumed from vegetables was inversely associated with lung cancer in the residual model (aOR, 95% CI for the 3th versus 1st tertile: 0.71, 0.52–0.97, Ptrend: 0.035).

3.2.5 Smoking status

Glycemic Index

The associations between lung cancer and GI, GL and sugar stratified by cigarette smoking status are presented in table 3-9, table 3-10 and table 3-11. High GI intake was significantly associated with an elevated lung cancer odds among current/ever smokers with a dose-response relationship in both the standard multivariable and residual models (aOR, 95% CI for the 3th versus 1st tertile: 1.73, 1.15–2.56, Ptrend: 0.009, and aOR, 95% CI for the 3th versus 1st tertile: 1.81, 1.25–2.64,

Ptrend: 0.001, respectively) in table 3-9. Moreover, high GI consumed from breakfast foods was associated with increased lung cancer odds among smokers in both the standard and residual models (aOR, 95% CI for the 3th versus 1st tertile: 1.86, 1.29–2.67, Ptrend: 0.001 in the standard model, and aOR, 95% CI for the 3th versus 1st tertile: 1.69, 1.18–2.42, Ptrend: 0.004 in the residual model, respectively). Among never smokers, high GI consumed from starches and salty snacks was associated with lung cancer in both models (aOR, 95% CI for the 3th versus 1st tertile: 3.14, 1.63–6.04, Ptrend: <0.001 in the standard model, and aOR, 95% CI for the 3th versus 1st tertile: 2.74, 1.42–5.27, Ptrend: 0.001 in the residual model, respectively).

Glycemic Load

There was no evidence of the association between total GL intake and lung cancer among smokers and never smokers (table 3-10). High GL consumed from high carbohydrates/sugar foods was positively associated with lung cancer (aOR, 95% CI for the 3th versus 1st tertile: 1.74, 1.20–2.53, Ptrend: 0.004 in the standard model, and aOR, 95% CI for the 3th versus 1st tertile: 1.74, 1.20–2.53, Ptrend: 0.004 in the residual model, respectively). A high proportion of GL consumed from vegetables, however, showed a protective association with lung cancer among smokers in the standard and residual models (aOR, 95% CI for the 3th versus 1st tertile: 0.53, 0.36–0.79, Ptrend: 0.001, and aOR, 95% CI for the 3th versus 1st tertile: 0.51, 0.34–0.75, Ptrend: 0.001, respectively). Among never smokers, high GL from breakfast food was associated with

increased lung cancer odds with P trend less than 0.05 in both models (aOR, 95% CI for the 3th versus 1st tertile: 2.00, 1.11–3.61, Ptrend: 0.023 in the standard model, and aOR, 95% CI for the 3th versus 1st tertile: 1.97, 1.10–3.54, Ptrend: 0.026 in the residual model, respectively)

Sugar

In table 3-11, the null association between dietary sugar and lung cancer did not vary by smoking status. High dietary sugar consumed from high carbohydrates/sugar foods was positively associated with lung cancer in the standard and residual model with P trend less than 0.001 (aOR, 95% CI for the 3th versus 1st tertile: 2.26, 1.53–3.33 in the standard model, and aOR, 95% CI for the 3th versus 1st tertile: 2.09, 1.39–3.13 in the residual model, respectively). Among smokers, high dietary sugar consumed from meat and mixed dishes was positive associated with lung cancer while high dietary sugar from vegetables was inversely associated with lung cancer in the residual model. (aOR, 95% CI for the 3th versus 1st tertile:1.63, 1.12–2.36, and aOR, 95% CI for the 3th versus 1st tertile: 0.65, 0.44–0.95, respectively).

3.3 UADT Cancer Susceptibility

3.3.1 Cut-off points

Table 3-12 shows the range of nutrient intake in different tertile levels for UADT cancer. The cut-off points in the standard method were decided by the distribution of nutrient intake among controls. Therefore, those were identical to the cut-off points for the analyses on lung cancer. For

residual method, cut-off points were decided by the relationship between nutrient intake and energy intake among UADT cancer cases and controls. Thus, those were different than the cut-off points for the analyses on lung cancer.

The 33th and 67th centile cut-off points for total GI intake were 106.08 and 110.87 in the residual model. For total GL, the cut-off points were 225.38 and 277.46 in the residual model. For total dietary sugar, the cut-off points were 168 and 209.9 in the residual model. We also present the cut-off points of nutrient intake from different food sources by both percentage of GL/sugar and the exact intake of GL/sugar from different food sources.

3.3.2 Total GI, GL and sugar intake

Table 3-13 shows the aORs and corresponding 95% CIs for associations of GI, GL and dietary sugar intake with UADT cancer for both the standard multivariable models as well as the energy-adjusted residual models. High dietary GL was inversely associated with UADT cancer in the standard multivariable model (aOR, 95% CI for the 3rd versus 1st tertile: 0.59, 0.37–0.93, Ptrend: 0.025), but the same association didn't show in the residual model. High sugar intake was also inversely associated with UADT cancer in the standard and residual models (aOR, 95% CI for the 3rd versus 1st tertile: 0.62, 0.43–0.90, Ptrend: 0.009, and aOR, 95% CI for the 3rd versus 1st tertile: 0.70, 0.53–0.93, Ptrend: 0.016, respectively).

3.3.3 Histological subtypes of UADT cancer

For histological subtypes of UADT cancer (Table 3-14), high sugar intake was associated with decreased odds of UADT squamous cell carcinoma (UADT SCC) as well as oropharyngeal squamous cell carcinoma (OSCC) in both models (UADT SCC, aOR, 95% CI for the 3rd versus 1st tertile: 0.64, 0.44–0.93, Ptrend: 0.017 in the standard model; OSCC, aOR, 95% CI for the 3rd versus 1st tertile: 0.54, 0.35–0.84, Ptrend: 0.005 in the standard model).

3.3.4 Different sources of dietary GI, GL and sugar

Glycemic Index from different food sources

The associations between GI, GL, sugar and UADT cancer appeared to be vary by the food categories. We did not observed any protective effect of source-specific GI, GL and sugar on UADT cancer. In table 3-15, a high proportion of GI consumed from starches and salty snacks was positively associated with UADT cancer in the standard and residual models (aOR, 95% CI for the 3rd versus 1st tertile: 1.83, 1.38–2.52, Ptrend: <0.001, and aOR, 95% CI for the 3rd versus 1st tertile: 1.70, 1.27–2.29, Ptrend: <0.001, respectively). When we further checked the association between each food item in starches and salty snacks and UADT cancer, we observed a positive association for rice but inverse association for dark bread, salty snacks and peanuts.

Glycemic Load from different food sources

Table 3-16 presents the association between different sources of dietary GL and UADT cancer. High GL consumed from meat and mixed dishes was associated with elevated UADT cancer

odds in the standard (aOR, 95% CI for the 3rd versus 1st tertile: 1.86, 1.39–2.48, Ptrend: <0.001) and residual models (aOR, 95% CI for the 3rd versus 1st tertile: 1.71, 1.28–2.28, Ptrend: <0.001). In terms of the single food items in meat and mixed dishes, this association was observed when consuming high proportion of GL from pasta, vegetable soup and beef stew. High GL consumed from breakfast foods was also positively associated with UADT cancer risk in both models (aOR, 95% CI for the 3rd versus 1st tertile: 1.52, 1.14–2.01, Ptrend: 0.005 in the standard model, and aOR, 95% CI for the 3rd versus 1st tertile: 1.52, 1.14–2.03, Ptrend: 0.004 in the residual model, respectively). Cooked cereals contributed to this positive association the most compared with other food items in breakfast foods (aOR, 95% CI for the 3rd versus 1st tertile: 1.38, 1.01–1.38).

Sugar from different food sources

Table 3-17 shows the association between UADT cancer and dietary sugar consumed from different sources. Similar to the association between GL consumed from breakfast food and UADT cancer, high sugar consumed from breakfast food was positively associated with UADT cancer in the standard and residual models (aOR, 95% CI for the 3rd versus 1st tertile: 1.68, 1.27–2.23, Ptrend: <0.001, and aOR, 95% CI for the 3rd versus 1st tertile: 1.58, 1.17–2.12, Ptrend: 0.001, respectively). High sugar consumed from meat and mixed dishes also showed the association of increased odds ratio of UADT cancer in both models (aOR, 95% CI for the 3rd

versus 1st tertile: 1.61, 1.22–2.13, Ptrend: <0.001 in the standard model, and aOR, 95% CI for the 3rd versus 1st tertile: 1.59, 1.20–2.10, Ptrend: 0.001 in the residual model, respectively), especially for consuming high proportion of sugar from beef stew compared with other food items in meat and mixed dishes.

3.3.5 Smoking status

Glycemic Index

Table 3-18 reports the associations between daily GI and UADT cancer by smoking status. The estimates of association were generally similar between smokers and never smokers. A similar effect of GI consumed from starches and salty snacks on UADT cancer was still observed across smokers and never smokers.

Glycemic Load

Table 3-19 presents the association between daily GL and UADT cancer stratified by smoking status. No apparent association was observed between daily GL and UADT cancer. High GL consumed from meat and mixed dishes was associated with UADT cancer across smokers and never smokers. Among smokers, high GL consumed from starches and salty snacks was inversely associated with UADT cancer in the standard and residual model (aOR, 95% CI for the 3rd versus 1st tertile: 0.64, 0.44–0.92, Ptrend: 0.015, and aOR, 95% CI for the 3rd versus 1st tertile: 0.64, 0.44–0.92, Ptrend: 0.015, respectively). Among never smokers, high GI consumed from

breakfast was positively associated with UADT cancer in both models (aOR, 95% CI for the 3rd versus 1st tertile: 2.14, 1.32–3.47, Ptrend: 0.002 in the standard model, and aOR, 95% CI for the 3rd versus 1st tertile: 1.94, 1.21–3.12, Ptrend: 0.005 in the residual model, respectively).

Sugar

Table 3-20 presents the association between dietary sugar and UADT cancer by smoking status. The positive associations between UADT cancer and total sugar as well as high sugar consumed from breakfast foods only held among never smokers. Among smokers, there was inverse association between high sugar consumed from starches and salty snacks and UADT cancer in the standard and residual models (aOR, 95% CI for the 3rd versus 1st tertile: 0.57, 0.39–0.83, Ptrend: 0.004, and aOR, 95% CI for the 3rd versus 1st tertile: 0.57, 0.39–0.83, Ptrend: 0.003, respectively). The positive associations between UADT cancer and sugar consumed from meat and mixed dishes were generally similar among smokers and never smokers.

3.3.6 Drinking status

Table 3-21 to Table 3-23 present the associations between GI, GL, sugar and UADT cancer. Among drinkers, high GI consumed from starches and salty snacks was positively associated with UADT cancer risk; however, high sugar consumed from starches and salty snacks was inversely associated with UADT cancer risk (aOR of GI from starches for the 3rd versus 1st tertile: 1.91, 1.36–2.68, Ptrend: <0.001, and aOR of sugar from starches for the 3rd versus 1st

tertile: 0.68, 0.49–0.94, Ptrend: 0.021, in the residual model). In addition, high GL consumed from breakfast food was positively associated with UADT cancer risk among drinkers (aOR for the 3rd versus 1st tertile: 1.57, 1.13–2.17, Ptrend: 0.008 in the standard model, and aOR for the 3rd versus 1st tertile: 1.64, 1.17–2.29, Ptrend: 0.00. in the residual model). The associations between other source-specific nutrient intakes and UADT cancer were generally similar between drinkers and never drinkers.

3.4 Discussion

In this population-based case-control study in Los Angeles, GI was positively associated with lung cancer risk, and this association was confined to smokers. In contract, sugar was inversely associated with UADT cancer risk, and the protective association was confined to never smokers. The results suggest that the associations may be source-dependent. Having a high proportion of GI or GL from breakfast foods and starches was found to be associated with increased odds of lung cancer. Moreover, having a high GL from high carbohydrates and sugary foods was shown to be associated with increased lung cancer risk, whereas having a high GL from vegetables was found to be associated with decreased lung cancer risk. Even though we did not observe an increased risk of UADT cancer with high GI, GL and sugar diet, UADT cancer risk was positively associated with GI from starches food, GL and sugar from breakfast foods and mixed dishes, sugar from high carbohydrates and sugary foods.

It has been suggested that increased sugar intake may contribute to cancer development through hyperglycemia-induced overproduction of oxidative stress, inflammation (74, 75) and glycolysis-linked activation of oncogenic pathways (76). For lung cancer, results based on a hospital-based case-control study in Uruguay reported an increased risk of lung cancer with a high GI diet (41). Recently, Melkonian et al. observed an independent association between dietary GI and lung cancer in non-Hispanic Whites (44). In contrast, Balder et al. reported an inverse relationship between consumption of "sweet foods" and lung cancer in men from the Netherlands Cohort Study (77). A null association between dietary GL and lung cancer from a prospective National Institutes of Health (NIH)–AARP Diet and Health Study and a Canadian nationwide population-based case–control study was reported (42, 43). For UADT cancer, only one published data examined the association between GI/GL and UADT cancer and reported a positive association (45). Furthermore, in stratified analyses, this association remained significant in those with high body mass index. Other studies focused on either HNC or EC. Results based on the NIH–AARP Diet and Health Study indicated a positive association between GI and EC among men and an inverse association between GL and HNC among women (42). A small hospital-based case-control study including 47 esophageal squamous cell carcinoma (ESCC) incident cases and 96 hospital controls suggested an increased risk with higher GI and GL diet (33), while a Australian population-based case-control study revealed an inverse association between higher GL diet and ESCC risk (47). An

Ireland population-based case-control study suggested an increased risk of esophageal adenocarcinoma (EAC) with high GI intake (46). With limited and conflict results, our study added more evidences on the association between GI, GL and the risk of lung and UADT cancers.

In the current study, we accounted for both the quality and quantity of glucose by using GI and GL to evaluate the association between carbohydrate-containing food and cancers of lung and UADT. Total dietary GI appeared to be significantly associated with lung cancer, and the variation by food source suggested that the quality of carbohydrates on impacting the blood glucose levels may influence development of lung and UADT cancers more than the quantity of it. The result suggests that the risk of lung cancer could increase when dietary GI is higher 60 (higher than tertile 3) compared with dietary GI lower than 50 (tertile 1). In addition, the lung and UADT cancer risk could be prevented by avoiding consuming dietary GL higher than 6% from breakfast foods.

High blood glucose concentration stimulates insulin release and elevates the bioavailability of IGF-1, which may play an important role in carcinogenesis (48). IGF-1 is involved in regulating cell proliferation and differentiation and has been detected at higher plasma levels in lung cancer cases than in controls (78). In addition, a cell-based study by Onodera et al. found that sugar uptake may promote oncogenesis by activating the Hypoxia Inducible Factor-1 (HIF-1), AMP activated Protein Kinase (AMPK) and mammalian Target of Rapamycin (mTOR) oncogenic pathways(76). Furthermore, hyperglycemia due to sustained high sugar consumption can upregulate O-

GlcNAcylation which enhances the anchorage-independent growth in lung cancer cells (79-81).

It is not clear why the effect of dietary GI, GL and sugar on lung and UADT cancers varied in terms of strength and direction with respect to the source of GI, GL and sugar. The seemingly protective effect of GL from vegetables could be the net effect of other nutrients. Micronutrients and biologically active compounds from vegetables, including carotenoids, folate, vitamins, minerals, sulforaphane (SFN) and indole-3-carbinol (I3C), may prevent cancer development through modulation of DNA methylation and prevention of DNA damage(82-85). A meta-analysis showed an 8% to 18% decreased risk of lung cancer with higher intakes of fruits and vegetables (13). Another meta-analysis also suggested that intake of vegetables may have a protective effect on lung cancer with a pooled risk ratio (RR) of 0.76 (95 % CI 0.69–0.84) (86). Furthermore, our findings suggest that dietary GI may be associated with non-small cell lung cancer, particularly with adenocarcinoma lung cancer. A few protective associations on UADT cancer observed in our study were conflict with original hypothesis.

Our findings also reveal that the effects of GI, GL and sugar could depend on smoking status. The negative association of GL from vegetables, and the positive associations of overall dietary GI, GI from breakfast foods and GL from high carbohydrates foods on lung cancer development were shown only among smokers. Since tobacco smoking is an important risk factor for lung cancer, an increased risk of lung cancer with GI from starches and salty snacks among never smokers may

reflect an unbiased, independent effect. For UADT cancer, the positive association of GL from breakfast foods, and the negative associations of GL and sugar from starch and salty snacks on UADT cancer risk were confined to smokers and drinkers; and this inverse association of sugar from starches and salty snacks on UADT cancer was also observed among drinkers. In addition, an increased risk of UADT was associated with sugar from breakfast foods and a reduced risk of UADT was associated with total sugar intake among never smokers. The protective association could be linked with quantity of foods due to less foods consuming by UADT cancer cases even before diagnosed.

The current study has several notable strengths. First, it is the first study to report the effect of GI/GL from different food sources on lung and UADT cancers. Second, we obtained a comprehensive assessment of sociodemographic and lifestyle characteristics by questionnaires which allowed us to estimate dietary effects and adjust for potential confounders, including tobacco smoking, alcohol drinking and diabetes history. Third, we applied both standard multivariable models and energy-adjusted residual models to evaluate the associations between dietary factors and cancers of lung and UADT. Forth, differential recall of dietary history by case/control status is unlikely to influence the result because dietary GI, GL and sugar were not an established risk factors for lung and UADT cancers. However, there are several limitations in this study. Since nutritional components for each food item were measured at a single time point, non-

differential exposure misclassification might result if the nutrition components changed over time. In addition, a small number of cases in the analyses of never smokers and histologic subtypes of lung cancer limited our power to detect the strength of association.

An increased risk of lung cancer with a high GI diet and a reduced risk of UADT cancer with high sugar diet were observed in this study. Furthermore, the effect of GI, GL and sugar may be source-dependent and modulated by smoking status. Further research with cohort study design is necessary to verify these associations and to better understand the underlying mechanisms linking GI/GL from different sources and lung and UADT cancers in humans.

CHAPTER 4. RESULTS FOR SNPs AND GxE INTERACTION

4.1 Genetic Susceptibility

Co-dominant, log-additive, dominant and recessive models were applied to estimate the associations between SNPs and cancers of lung and UADT. Table 4-1 shows the adjusted and semi-Bayes adjusted odds ratios (aOR and sbOR) for the associations. For lung cancer, a protective association was observed in GFPT1 rs7568296 (aOR for C:T vs T:T: 0.73, 95% CI: 0.54-0.98). This association was also observed after semi-Bayes adjustment, however, it only presented in the co-dominant model. For UADT cancer, positive associations were observed in EGFR rs2227983 (aOR for A:A vs A:G + G:G: 1.59, 95% CI: 1.02-2.48) and EGFR rs10277413 (aOR for G:G vs A:G + A:A: 1.54, 95% CI: 1.07-2.20), but only the later association remained significant after semi-Bayes adjustment. A protective association was observed between UADT cancer and EFGR rs2293347 in the co-dominant model (aOR for A:G vs G:G: 0.73, 95% CI: 0.54-0.99). We further examined the associations between 4 SNPs above and the histological subtypes of lung and UADT cancers in Table 4-2. Because of the limited sample size for certain cancers' subtypes, we only presented the results for lung squamous cell carcinoma, lung adenocarcinoma and UADT squamous cell carcinoma. EGFR rs2227983 was positively associated with UADT squamous cell carcinoma in the recessive model (aOR for A:A vs A:G +

G:G: 1.62, 95% CI: 1.02-2.58); and EGFR rs10277413 was positively associated with lung adenocarcinoma (aOR for G:G vs A:G + A:A: 1.60, 95% CI: 1.03-2.50) and UADT squamous cell carcinoma (aOR for G:G vs A:G + A:A: 1.66, 95% CI: 1.15-2.30) in the recessive model. The association between EGFR rs2293347 on lung squamous cell carcinoma was significant, but the 95% confident interval was wide due to small sample size and it became no significant after semi-Bayes adjustment.

4.2 GxE interaction

Table 4-3 presents the interaction between four SNPs identified in Table 1 and cancers of lung and UADT. The significant joint effects between SNPs and environmental factors for lung and UADT cancers were observed. The interaction between EGFR rs2293347 and smoking status for lung cancer was apparent in on the additive scale (RERI: 1.48, 95% CI: 0.53-2.44) and multiplicative scale (ROR: 2.02, 95% CI: 1.04-3.93). A sub-multiplicative interaction was observe between GFPT1 rs7568296 and alcohol drinking on UADT cancer (ROR, 95% CI: 0.51, 0.26-0.98.

4.3 Discussion

In this Los Angeles population-based case-control study, two SNPs in EGFR gene (rs10277413 and rs2227983) were positively associated with UADT cancer risk while one SNP in EFGR gene (rs2293347) was inversely associated with UADT cancer risk. A reduced risk of lung cancer with

a SNP in GFPT1 gene (rs7568296) was observed. Thus, both additive and multiplicative interactions were presented between ever smokers and EGFR rs2227983 on lung cancer risk (RERI, 95% CI: 1.48, 0.53- 2.44; ROR, 95%CI: 2.02, 1.04- 3.93). Sub-multiplicative interaction between ever drinkers and GFPT1 rs7568296 in UADT cancer risk was revealed (ROR, 95%CI: 0.51, 0.26- 0.98). However, no interaction between GI, GL and SNPs involved in the glucose metabolism on the risk of lung and UADT cancers was found.

In a cell-based study, Onodera et al. found that sugar uptake may promote oncogenesis by activating the HIF-1, AMPK or mTOR oncogenic pathways (76). Nonetheless, the findings suggested the activation of epidermal growth factor receptor (EGFR) was related to an oncogenic event in the situation of elevated glucose uptake and metabolism in premalignant cells (76). The EGFR gene provides instructions for making a receptor protein called the epidermal growth factor receptor, which involved in cell proliferation, motility, adhesion, invasion, cell survival, and angiogenesis(87). The GFPT1 gene involves in glucose metabolism by encoding the product which is the first and rate-limiting enzyme of the hexosamine pathway; in addition, it controls the flux of glucose into the hexosamine pathway and catalyzes the formation of glucosamine 6-phosphate(88).

In a pooled case-control study with 1424 colon cancer cases and 583 rectum cancer cases and 2555 controls, the risk of colorectal cancer was positively associated with EGFR rs2293347 (OR, 95 CI for CT/TT vas CC: 1.02, 0.88-1.18), EGFR rs10277413 (OR, 95 CI for GG vs. TT: 1.06,

0.88-1.28) and EGFR rs2227983 (OR, 95 CI for AA vs. GG: 1.05, 0.82-1.33) (89). However, all associations found in this study was not statistically significant. Results from a population-based study of 857 bladder cancer cases and 1191 controls from New Hampshire found a slightly increased risk of bladder cancer with EGFR rs2293347 (OR, 95 CI for CT vas CC: 1.1, 0.8-1.4)(90). However, no literature was found to evaluate the association between the risk of lung and UADT cancer and the EGFR SNPs (rs10277413, rs2227983 and rs2293347). Also, at present, there is no current literature in the topic of the relationship between cancer risk and GFPT1 rs7568296.

There are a few of limitations associated with this study that should be acknowledged. Due to small sample size of the study, we did not have sufficient statistical power to further stratify UADT cancer by its sub-sites. Additionally, multiple comparisons may have led to false positives as we investigated a large number of genetic factors. A semi-Bayesian shrinkage approach was applied in order to mitigate the effects of sparse data bias and multiple comparisons.

Despite these limitations, this study comprehensively evaluated the associations of the SNPs involved on the glucose metabolic pathway for the risk of lung and UADT cancer. Thus, we first observed that SNPs in EGFR gene (rs10277413, rs2227983 and rs2293347) and SNPs in GFPT1 gene (rs7568296) may associated with the risk of lung or UADT cancers with potential interaction effect with tobacco smoking or alcohol drinking.

In conclusion, our findings shows that genetic variation in the pathway of glucose metabolism may modulate the risk of lung and UADT cancers, and the interactions with tobacco smoking and alcohol drinking were presented. Although the mechanism remains unknown, the findings of this study suggest that polymorphisms associated with glucose metabolism may play a role in the development of lung and UADT cancers. Further studies are needed to reveal the potential mechanism for those SNPs, and with larger sample size, the effect on the histological subtypes of lung and UADT cancers can be evaluated.

CHAPTER 5. RESULTS FOR HEAD AND NECK CANCER IN INHANCE

The analyses for specific aim 3 included a total of 7345 controls and 4058 head and neck cancer cases (800 for oral cavity, 1150 for oropharynx, 341 for hypopharynx, 436 for oral/pharynx and 1331 for larynx). Distribution of GI and GL among controls for each study center was showed in Figure 5-1 and 5-2. Table 5-1 shows the distribution of selected characteristics among cases of head and neck cancer (HNC), oral and pharyngeal cancer (OPC) and laryngeal cancer (LC) cancers and controls. Among the 10 study centers, the Latina and Seattle study centers did not recruit laryngeal cancer. Cases for all cancer sites had more male, less never smokers and less never drinkers compared with controls.

Table 5-2 presents the distribution of glycemic index and glycemic load in each study center. The Boston study had the highest means of GI and GL, and the North Carolina study had the lowest means of GI and GL. The variation among GL between studies was larger than the variation among GI between studies.

The associations between GI, GL and head and neck cancer were shown in Table 5-3. For GI intake, fixed effect estimates were reported since there were less heterogeneity between studies ($P_{studies} > 0.1$); on the other hand, for GL intake, mixed effect estimates were reported because P for heterogeneity was less than 0.1. High GI intake was positively associated with HNC risk (aOR, 95% CI for the OR 5^{th} vs. 1^{st} quintile: 1.22, 1.04 –1.44) and LC risk (aOR, 95% CI for the

OR 5th vs. 1st quintile: 1.72, 1.33 –2.21). Additionally, a significant linear trend of elevated ORs were observed between GI intake and LC (Ptrend < 0.001). Glycemic load was inversely associated with OP risk (aOR, 95% CI for the OR 5th vs. 1st quintile: 0.80, 0.67 –0.96) with linear trend (Ptrend= 0.02). The strength of associations were consistent in the continuous level of GI and GL. In terms of histological type of head and neck cancer, the similar associations were still held between GI, GL and squamous cell carcinoma (scc) of OP (aOR of GL and OPscc, 95% CI for the OR 5th vs. 1st quintile: 0.69, 0.51 –0.94) and LC (aOR of GI and LCscc, 95% CI for the OR 5th vs. 1st quintile: 1.85, 1.27 –0.94). However, this results was only based on part of the study sites because Italy Multicenter and Milan (2006-2009) studies had the missing information on the histological subtype of head and neck cancer.

Table 5-4 shows the study-specific OR of GI and GL on HNC. A significant association between GI and HNC was observed in the Pordenone, Milan (2006-2009) and Switzerland studies; and a significant protective association of GL on HNC was observed in the MSKCC study.

5.1 Stratified Analysis

Table 5-5 displays the associations between GI and GL on HNC stratified by selected covariates. High GI intake was associated with increased HNC risk among subjects younger than 55 years (aOR, 95% CI for the OR 5th vs. 1st quintile: 1.45, 1.10 –1.90) and former smokers (aOR, 95% CI for the OR 5th vs. 1st quintile: 1.47, 1.16 –1.86). A protective association between GL intake

and HNC was observed among male (aOR, 95% CI for the OR 4th vs. 1st quintile: 0.78, 0.65 – 0.94) and heavy alcohol drinkers (aOR, 95% CI for the OR 2nd vs. 1st quintile: 0.57, 0.39 –0.83; 4th vs. 1st quintile: 0.68, 0.48 –0.98).

5.2 Discussion

In this pooled analysis of 8 case–control studies providing information on dietary GI and GL within the INHANCE consortium, we found an increased risk of HNC and laryngeal cancer with a high GI diet, and a reduced risk of oral and pharyngeal cancer with a high GL diet.

A few plausible mechanisms have been hypothesized for how high GI and GL diet linked with cancer risk, contributing by hyperinsulinemia, oxidative stress and enhanced bioactivity of the IGF axis (75, 91). High blood glucose concentration stimulates insulin release and elevates the bioavailability of IGF-1, which plays an important role in carcinogenesis (48). IGF-1 is involved in regulating cell proliferation and differentiation and has been detected at higher plasma levels in lung cancer cases than in controls (78).

To our knowledge, only two studies had been published on the HNC risk with high GI and GL diet. Result from a pooled hospital case-control study with 1362 UADT cancer cases and 3322 controls reported increased risks of high GI and GL intake on UADT cancer risk (OR for GI, 95% CI: 1.5, 1.1–2.0; OR for GL, 95% CI: 1.8, 1.1–2.9, respectively), but the significant associations did not present in the sub-sites of UADT cancer, including cancers of oral and

pharyngeal, esophagus and larynx (45). In the case-control study, refined grains (high GI foods) were positively associated with the risk of oral cavity and pharyngeal, esophageal and laryngeal cancers (92). Another results from NIH–AARP Diet and Health Study with 1239 HNC cases and a study population of 566,402 participants showed reduced risks of HNC with moderate diet GI among men (OR for 3rd vs. 1st quintile, 95% CI: 0.78, 0.63—0.97) and moderate diet GL among women (OR for 3rd vs. 1st quintile, 95% CI: 0.59, 0.38—0.91) (42). There is no direct evidence for the protective association of GL on the risk of oral and pharyngeal cancer found in our analyses, it could be linked with the quantity of food consumed by cases before diagnosis. It is possible that before patients were diagnosed for oral and pharyngeal cancer, they ate less due to discomfort caused by pre-cancer lesion or symptoms. Different than the previous study (42), we observed a protective association between GL and HNC among men instead of women.

Some limitations warrant consideration when interpreting the finding from this analysis. First of all, systematic and non-differential measurement error from imprecise dietary measurement was hard to avoid. Different food composition tables were used by the country the study was conducted to increase precision. In addition, the assigned GI weights for diet GI and GL calculation were reviewed by two experienced nutritionists. Secondly, GI and GL were estimated from study-specific food frequency questionnaires with different numbers of food item which may influence the estimations. Distribution of GI and GL from Switzerland were relatively wide

and skew; therefore, we excluded participants with extreme value of GI and GL to increase consistency between studies. Third, recall bias may appear in the case-control study design. Since dietary factors were not an important risk factors for head and neck cancer, recall bias should not strongly bias our results.

Our pooled analysis had several strengths. Large sample size provided the statistic power to estimate the association for sub-sites of head and neck cancer, and to control more potential confounders. Since most of the diet GI and GL were calculated from the raw data, we were able to apply uniform criteria to define our exposure of interest.

In conclusion, findings from this large-scale pooled analysis indicated that a high intake of GI may play a positive role on HNC, especially on laryngeal cancers. Future prospective studies are warranted to verify these associations and to better understand the underlying mechanisms linking GI and GL on HNC.

CHAPTER 6. CONCLUSION AND PUBLIC HEALTH IMPLICATIONS

High GI and GL diets were associated with several non-commutable diseases, including metabolic syndrome (93), type 2 diabetes (94) and cancer (30, 35). This is the first estimate of source-specific GI and GL. A high proportion of GI consumed from starches and salty snacks and a high proportion of GL consumed from breakfast foods could be associated with increased risk of lung and UADT cancers. Our results may be informative for policy-making and program planning for lung and UADT cancer prevention.

Furthermore, this is the first large-scale collaborative study on the association between GI and GL on the risk of head and neck cancer. Our results suggest that a high GI diet could be harmfully associated with laryngeal cancer risk even though high GL diet was observed to be inversely associated with the risk of oral and pharyngeal cancer. Therefore, the subsite-specific strategies of cancer prevention are recommended for head and neck cancer. Nonetheless, our results add to the body of evidence that genetic variants in the glucose metabolic pathway were associated with lung and UADT cancers in this large, population-based case-control study. All associations with overall lung and UADT cancer susceptibility have not been reported before, as of January 2018. SNPs with functional evidence and the associations with the risk of lung and UADT cancers should be further studied to evaluate effectiveness for screening and for precision medicine.

A better understanding of dietary factors and how they influence established risk and preventative factors is paramount to understanding lung and UADT cancer etiology to provide effective prevention strategies and to reduce lung and UADT cancer incidence and mortality for public health promotion.

TABLES AND FIGURES

Table 2-1. Characteristics of individual studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium used in the specific aim 3 analysis.

Study, Reference paper	Recruitment period	Source (ca/ co)	Participation rate, %(ca/ co)	Age eligibility (years)	Number of subjects (ca/ co)	Questionnaire, administration, ref. period for the recall	Frequency	Serving size[a]	# Food items (including non-alcoholic beverages)
Italy Multicenter Bosetti et al., 2003[b]	1990-1999	Hospital/Hospital-unhealthy	>95/>95	18-80	1261/2716	FFQ, interviewer-administered, 2 year before disease	Raw data	S/M/L	78 (including 6 non-alcoholic beverages)
Switzerland Levi et al., 1998[b]	1991-1997	Hospital/Hospital-unhealthy	>95/>95	<80	516/883	FFQ, interviewer-administered, 2 year before disease	Raw data	S/M/L	78 (including 6 non-alcoholic beverages)
Los Angeles, CA, USA Cui et al., 2006	1999-2004	Cancer registry/ Neighborhood	49/68	18-65	417/1005	FFQ, interviewer-administered, during the past year	Raw data	M	78 (including 11 non-alcoholic beverages)
Boston, MA, USA Peters et al., 2005	1999-2004	Hospital/ Residential records	88.7/48.7	≥18	584/659	FFQ, self-administered, during the past year	Categories	M	138 (including 12 non-alcoholic bevarges)
New York, MSKCC, USA Schantz et al., 1997	1992-1994	Hospital/Blood donors	NA	NA	134/169	FFQ–diet history, self-administered, during the past year[c]	Raw data	S/M/L	88 (including 5 non-alcoholic beverages)
Milan (2006-2009), Italy Bravi et al., 2013 [b]	2006-2009	Hospital/Hospital-unhealthy	>95/>95	18-80	367/750	FFQ, interviewer-administered, 2 years before disease	Raw data	S/M/L	78 (including 6 non-alcoholic beverages)
North Carolina (2002-2006), USA Divaris et al., 2010[c]	2002-2006	Cancer registry/ DMV files	82/61	20-80	1368/1396	FFQ, interviewer-administered, during the past year	Categories	M	72 (including 5 non-alcoholic beverages) questions
Seattle (1985-1995), WA, USA Rosenblatt et al, 2004 [d]	1985-1995	Cancer registry/ Random digit dialing	54.4/63.3; 63.0/60.9	18-65	407/607	FFQ, interviewer-administered, 5 years ago	Raw data	S/M/L	106 (including 7 non-alcoholic beverages)

ABBREVIATIONS: DMV: Department of Motor Vehicles; FFQ: food-frequency questionnaire; S: small; M: medium; MSKCC: Memorial Sloan Kettering Cancer Center; L: large; NA: not available. ca/co: Cases/Controls; ref.: reference

a. A quantification of the medium serving size was provided in all the studies. b. Italy Multicenter, Milan (2006-2009) and Switzerland studies were based on the same food-frequency questionnaire. c. The food-frequency questionnaire from the North Carolina study provided combined questions concerning consumption of specific food items and corresponding condiment habits or fat content of the food item of interest (i.e. while asking for cooked or raw vegetable consumption, the food frequency questionnaire asked for extra information on fat, sauce, or dressing added after cooking or at the table). d. Two response rates are reported because data were collected in two population-based case-control studies, the first from 1985 to 1989 among men and the second from 1990 to 1995 among men and women.

Table 2-2. Food items from different food sources in the food frequency questionnaire (LA study).

Source	Food item
High Carbohydrates/ Sugar	White potatoes(boiled, baked, potato salad or mashed), Rice, White bread, Corn bread, Cold cereals, Watermelon
Fruits	Apples, Cantaloupe, Watermelon, Oranges, Orange juice, Grapefruit, Peaches, Bananas, Strawberries, Other fruit juices
Vegetables	Beans (baked, pinto, kidney, lima or in chili), Tofu, Raw tomatoes, Tomato, Cooked tomatoes, Salsa, Broccoli, Spinach, Mustard greens, Cole slaw, Carrots, Dark orange, Green salad, Sweet potatoes.
Meat and Mixed Dishes	Hamburgers, Pizza, Burritos, Beef (steaks, roasts, frozen dinners or sandwiches), Beef stew, Liver, Pork, Fried chicken, Chicken or turkey (roasted, stewed or boiled), Fried fish, Spaghetti, Hot dogs, Ham, Vegetable soup.
Starches and Salty Snacks	French fries, white potatoes(boiled, baked, potato salad or mashed), Rice, White bread, Dark bread, Corn bread, Salty snacks, Peanuts, Salad dressing, Margarine, Butter.
Breakfast Foods	High fiber, bran or granola cereals, Highly fortified cereals, Other cold cereals, Cooked cereals, Eggs, Bacon, Sausage.
Sweets	Ice cream, Donuts, Cakes, Cookies, Pies, Chocolate candy.
Dairy Products, Beverages	Cheeses and cheese spreads, Whole milk, 2% milk, Nonfat milk, Regular soft drinks, Beer, Wine, Liquor, Tea, Coffee, Decaffeinated coffee, Milk or cream in coffee or tea, Sugar in coffee or tea.

Table 2-3. The role of genes in glucose metabolism relative mechanism in specific aim 2

Gene	Functions related with glucose metabolism
EGFR	Promote glucose metabolism through the upregulation of glycolysis key enzymes.
ITGB1	Encoding beta 1 integrin which increases with high glucose
GFPT1	Encoding enzyme of the hexosamine pathway, controlling the flux of glucose into the hexosamine pathway, catalyzing the formation of glucosamine 6-phosphate.
RAP1A	Encoding the protein that promotes glucose-stimulated insulin secretion
PGM1	Affects cellular glycogen contents by regulating the balance of glucose-1-phosphate (G-1-P) and G-6-P
ENO1	Regulating glucose metabolism and cell growth in human glioma cells
PDK1	Encoding the enzyme which plays an important role in the differential activation of macrophages in glucose metabolism

Table 2-4. List of selected SNPs (7 genes and 14 SNPs) in specific aim 2

Gene	Location	rs Number	Function Class	Allele	MAF[a]	Freq[b]
EGFR	7p12	rs2072454	synonymous-codon	C/T	0.46	0.21
EGFR	7p12	rs2227983	missense	G/A	0.28	0.08
EGFR	7p12	rs10277413	utr-variant-3-prime	NA/G	0.35	0.17
EGFR	7p12	rs1050171	synonymous-codon	G/A	0.42	0.18
EGFR	7p12	rs2293347	synonymous-codon	C/T	0.10	0.01
ITGB1	10p11.2	rs2298141	synonymous-codon	T/C	0.15	0.03
GFPT1	2p13	rs13751	utr-variant-3-prime	NA/G	0.39	0.17
GFPT1	2p13	rs7568296	utr-variant-3-prime	NA/A	0.38	0.16
GFPT1	2p13	rs2667	utr-variant-3-prime	NA/T	0.41	0.20
RAP1A	1p13.3	rs6573	utr-variant-3-prime	NA/A	0.16	0.04
PDK1	2q31.1	rs2290563	downstream-variant-500B(dbSNP)	T/ A	0.16	0.03
PDK1	2q31.1	rs6433368	intron-variant(dbSNP)	T/C	0.15	0.03
PGM1	1p31	rs855314	missense(dbSNP)	G/A	0.14	0.02
ENO1	1p36.2	rs7534552	intergenic	G/A	0.4	0.20

a. In Caucasian population

b. Genotype Frequency for rare allele homozygotes

Table 3-1. Socio-demographic characteristics of participants in dietary analysis of LA lung and UADT cancer study

Characteristics	Controls(%)	Lung cancer(%)	P-Value[a]	UADT cancer(%)	P-Value[a]
Total	N=1026	N=589		N= 570	
Age	49.89 ±7.31	52.24 ±5.24	<0.001	50.38 ±7.45	0.20
<45	211 (21.54)	59 (10.02)		104 (18.25)	
45-54	489 (47.66)	288 (48.90)		257 (45.09)	
55+	316 (30.80)	242 (41.09)		209 (36.67)	
Sex			<0.001		<0.001
Male	617 (60.14)	294 (49.92)		429 (75.26)	
Female	409 (39.86)	295 (50.08)		141 (24.74)	
Race/Ethnicity			<0.001		0.0042
Caucasian	630 (61.46)	349 (59.35)		333 (58.63)	
Hispanic	200 (19.51)	66 (11.22)		96 (16.90)	
Black	98 (9.56)	91 (15.48)		59 (10.39)	
Asian	61 (5.95)	67 (11.39)		64 (11.27)	
Other	36 (3.51)	15 (2.55)		16 (2.82)	
Education (years of schooling)	14.44 ±3.60	13.29 ±3.36	<0.001	13.24 ±3.62	<0.001
0-12	295 (28.75)	252 (42.78)		254 (44.56)	
13-16	475 (46.30)	267 (45.33)		248 (43.51)	
17+	256 (24.95)	70 (11.88)		68 (11.93)	

a. T-test (continuous variables) or Chi-square (categorical variables) p-value comparing each cancer type to controls

Table 3-2. Distribution of established risk factors and dietary factors in dietary analysis of LA lung and UADT cancer study (N of controls: 1026; lung cancer cases: 589; UADT cancer cases: 570)

	Controls (%)	Lung cancer (%)	P-Value[a]	UADT cancer (%)	P-Value[a]
Tobacco Smoking status			<0.0001		<0.0001
Never	484 (47.17)	108 (18.34)		179 (31.40)	
Former	370 (36.06)	377 (64.01)		316 (55.44)	
Current	172 (16.76)	104 (17.66)		75 (13.16)	
Tobacco Smoking (Pack-year)			<0.0001		<0.0001
0	484 (47.22)	108 (18.34)		179 (31.40)	
>0 ~ <20	351 (34.24)	92 (15.62)		134 (23.51)	
20 ~ <40	129 (12.59)	196 (33.28)		137 (24.04)	
40+	61 (5.95)	193 (32.77)		120 (21.05)	
Alcohol drinking status			0.21		0.0187
Never	255 (24.85)	163 (27.72)		112 (19.72)	
Ever	771 (75.15)	425 (72.28)		456 (80.28)	
Dietary Factors, Mean±SD					
Energy intake(Kcal)	1936.19 ±772.34	1969.91 ±788.93	0.402	2162.91 ±957.92	<0.0001
Available carbohydrate (g)	233.85 ±110.01	236.06 ±114.88	0.7025	255.41 ±131.58	0.0009
Glycemic index	53.76 ±6.09	55.23 ±5.97	<0.0001	55.12 ±5.95	<0.0001
Glycemic load	129.16 ±69.21	133.07 ±71.91	0.282	144.68 ±83.46	0.0002
Total Sugar (g)	101.22 ±69.66	103.46 ±84.33	0.59	111.15 ±83.56	0.0162

a. Chi-square p-value for tobacco smoking and alcohol drinking and t-test p-value for dietary factors, comparing each cancer type to controls

Table 3-3. Range of glycemic index (GI), glycemic load (GL) and dietary sugar intake in controls of lung cancer

	Standard Multivariable method			Residual method[a]		
	Tertile 1	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
Dietary GI						
Total GI	24.5 ~ 51.83	51.83 ~ 56.62	56.62 ~ 68.67	25.5 ~ 52.2	52.2 ~ 56.06	56.06 ~ 70.55
Different food source of GI						
High Carbohydrates/ Sugar	0 ~ 75.15	75.15 ~ 78.06	78.06 ~ 111	0.02 ~ 75.1	75.1 ~ 78.06	78.06 ~ 111.08
Fruits	0 ~ 48.13	48.13 ~ 51.92	51.92 ~ 72	-0.04 ~ 48.14	48.14 ~ 51.91	51.91 ~ 71.99
Vegetables	0 ~ 18.61	18.61 ~ 26.47	26.47 ~ 47.26	-0.18 ~ 18.89	18.89 ~ 26.45	26.45 ~ 48.31
Meat and Mixed Dishes	0 ~ 44	44 ~ 48.46	48.46 ~ 61.56	0.6 ~ 44.1	44.1 ~ 48.49	48.49 ~ 61.56
Starches and Salty Snacks	0 ~ 63.7	63.7 ~ 69.14	69.14 ~ 83.75	1.65 ~ 63.79	63.79 ~ 69.15	69.15 ~ 85.38
Breakfast Foods	0 ~ 48	48 ~ 58.07	58.07 ~ 80	-4.6 ~ 48.3	48.3 ~ 58.36	58.36 ~ 82.14
Sweets	0 ~ 50.8	50.8 ~ 54.86	54.86 ~ 61	-0.9 ~ 50.67	50.67 ~ 55.01	55.01 ~ 62.49
Dairy Products, Beverages	0 ~ 33.34	33.34 ~ 56.29	56.29 ~ 66	-10.77 ~ 35.24	35.24 ~ 53.97	53.97 ~ 72.31
GL						
Total GL (g)	9.1 ~ 90.68	90.68 ~ 142.76	142.76 ~ 456.31	-28.45 ~ 118.1	118.1 ~ 138.51	138.51 ~ 300.85
Different food source of GL (%)						
High Carbohydrates/ Sugar	0 ~ 25.49	25.49 ~ 41.76	41.76 ~ 88.52	0.09 ~ 25.37	25.37 ~ 41.7	41.7 ~ 88.81
Fruits	0 ~ 7.2	7.2 ~ 15.24	15.24 ~ 68.38	-4.23 ~ 8.11	8.11 ~ 15.33	15.33 ~ 65.78
Vegetables	0 ~ 2.6	2.6 ~ 4.76	4.76 ~ 29.03	-0.97 ~ 2.63	2.63 ~ 4.96	4.96 ~ 28.66
Meat and Mixed Dishes	0 ~ 6.22	6.22 ~ 10.53	10.53 ~ 67.51	-1.61 ~ 6.29	6.29 ~ 10.78	10.78 ~ 66.98
Starches and Salty Snacks	0 ~ 37.88	37.88 ~ 51.67	51.67 ~ 93.6	-0.51 ~ 37.87	37.87 ~ 51.73	51.73 ~ 94.11
Breakfast Foods	0 ~ 1.29	1.29 ~ 6.05	6.05 ~ 47.33	-2.21 ~ 1.67	1.67 ~ 6.3	6.3 ~ 45.09
Sweets	0 ~ 3.65	3.65 ~ 8.98	8.98 ~ 45.52	-1.31 ~ 3.62	3.62 ~ 9.02	9.02 ~ 45.04
Dairy Products, Beverages	0 ~ 4.46	4.46 ~ 17.97	17.97 ~ 95.8	-16.55 ~ 6.67	6.67 ~ 17.69	17.69 ~ 103.06

	Standard Multivariable method			Residual method[a]		
	Tertile 1	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
Different food source of GL (g)						
High Carbohydrates/ Sugar	0 ~ 24.97	24.97 ~ 51.81	51.81 ~ 280.13	-67.74 ~ 32.69	32.69 ~ 52.72	52.72 ~ 250
Fruits	0 ~ 8.18	8.18 ~ 17.13	17.13 ~ 101.52	-8.88 ~ 8.64	8.64 ~ 17.28	17.28 ~ 94.66
Vegetables	0 ~ 2.83	2.83 ~ 5.23	5.23 ~ 28.58	-2.66 ~ 3.26	3.26 ~ 5.37	5.37 ~ 25.53
Meat and Mixed Dishes	0 ~ 6.84	6.84 ~ 12.55	12.55 ~ 66.48	-8.29 ~ 8.02	8.02 ~ 12.34	12.34 ~ 58.18
Starches and Salty Snacks	0 ~ 36.28	36.28 ~ 64.34	64.34 ~ 299.41	-65.16 ~ 46.51	46.51 ~ 63.22	63.22 ~ 266.04
Breakfast Foods	0 ~ 1.37	1.37 ~ 7.18	7.18 ~ 62.78	-3.52 ~ 1.75	1.75 ~ 7.35	7.35 ~ 61.78
Sweets	0 ~ 3.66	3.66 ~ 11.14	11.14 ~ 82.14	-15.48 ~ 6.15	6.15 ~ 11.46	11.46 ~ 76.2
Dairy Products, Beverages	0 ~ 4.09	4.09 ~ 21.14	21.14 ~ 309.53	-69.4 ~ 13.18	13.18 ~ 29.78	29.78 ~ 287.45
Dietary Sugar						
Total Sugar (g)	11 ~ 63.23	63.23 ~ 105.13	105.13 ~ 504.55	-142.58 ~ 83.61	83.61 ~ 112.32	112.32 ~ 453.56
Different food source of Sugar (%)						
High Carbohydrates/ Sugar	0 ~ 2.63	2.63 ~ 5.73	5.73 ~ 74.35	-2.32 ~ 2.85	2.85 ~ 6.22	6.22 ~ 73.31
Fruits	0 ~ 16.92	16.92 ~ 33.91	33.91 ~ 84.33	-10.96 ~ 14.13	14.13 ~ 30.1	30.1 ~ 78.5
Vegetables	0 ~ 7.23	7.23 ~ 14.4	14.4 ~ 57.29	-6.4 ~ 5.1	5.1 ~ 11.56	11.56 ~ 53.1
Meat and Mixed Dishes	0 ~ 2.04	2.04 ~ 3.88	3.88 ~ 25.16	-1.3 ~ 1.13	1.13 ~ 3.01	3.01 ~ 23.91
Starches and Salty Snacks	0 ~ 5.95	5.95 ~ 11.42	11.42 ~ 77.72	-1.32 ~ 4.93	4.93 ~ 10.48	10.48 ~ 76.81
Breakfast Foods	0 ~ 0.51	0.51 ~ 2.82	2.82 ~ 57.06	-2.07 ~ 0.05	0.05 ~ 2.34	2.34 ~ 57.2
Sweets	0 ~ 5.71	5.71 ~ 14.95	14.95 ~ 84.27	-2.14 ~ 4.63	4.63 ~ 13.81	13.81 ~ 82.73
Dairy Products, Beverages	0 ~ 12.22	12.22 ~ 37.82	37.82 ~ 98.05	-6.27 ~ 26.3	26.3 ~ 49.57	49.57 ~ 120.06
Different food source of Sugar (g)						
High Carbohydrates/ Sugar	0 ~ 2	2 ~ 4.61	4.61 ~ 123.61	-15.86 ~ 2.89	2.89 ~ 6.25	6.25 ~ 112.99
Fruits	0 ~ 13.37	13.37 ~ 27.34	27.34 ~ 208.4	-11.18 ~ 17.16	17.16 ~ 30.73	30.73 ~ 200.54

	Standard Multivariable method			Residual method[a]		
	Tertile 1	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
Vegetables	0 ~ 6.45	6.45 ~ 10.93	10.93 ~ 46.35	0.19 ~ 9.72	9.72 ~ 13.92	13.92 ~ 45.11
Meat and Mixed Dishes	0 ~ 1.73	1.73 ~ 3.29	3.29 ~ 17.58	-1.97 ~ 3.04	3.04 ~ 4.28	4.28 ~ 15.82
Starches and Salty Snacks	0 ~ 4.57	4.57 ~ 8.82	8.82 ~ 125.24	-8.43 ~ 7.32	7.32 ~ 11.24	11.24 ~ 113.39
Breakfast Foods	0 ~ 0.39	0.39 ~ 2.31	2.31 ~ 75.18	-0.63 ~ 1.17	1.17 ~ 3.02	3.02 ~ 75.45
Sweets	0 ~ 4.28	4.28 ~ 13.59	13.59 ~ 114.89	-15.91 ~ 7.91	7.91 ~ 14.61	14.61 ~ 106.14
Dairy Products, Beverages	0 ~ 8.38	8.38 ~ 35.25	35.25 ~ 491.62	-121.11 ~ 9.59	9.59 ~ 35.27	35.27 ~ 447.24

a. Standardized nutrient intake from the residual method

Table 3-4. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary sugar, glycemic index (GI), glycemic load (GL) for lung cancer

	Standard Multivariable Model			Residual Model		
Dietary intake	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
Glycemic Index						
Per IQR Increase			**1.26 (1.07, 1.49)**			**1.24 (1.06, 1.45)**
T1	142 (24.1)	342 (33.3)	1.00 (ref.)	153 (26.0)	342 (33.3)	1.00 (ref.)
T2	186 (31.6)	342 (33.3)	1.29 (0.93, 1.78)	168 (28.5)	342 (33.3)	1.15 (0.84, 1.59)
T3	261 (44.3)	342 (33.3)	**1.52 (1.08, 2.13)**	268 (45.5)	342 (33.3)	**1.57 (1.15, 2.15)**
P_{trend}			**0.016**			**0.004**
Glycemic Load						
Per IQR Increase			1.16 (0.84, 1.60)			1.06 (0.93, 1.21)
T1	190 (32.3)	341 (33.2)	1.00 (ref.)	198 (33.6)	342 (33.3)	1.00 (ref.)
T2	196 (33.3)	343 (33.4)	1.14 (0.81, 1.59)	176 (29.9)	343 (33.4)	1.00 (0.73, 1.38)
T3	203 (34.5)	342 (33.3)	1.05 (0.64, 1.71)	215 (36.5)	341 (33.2)	1.21 (0.88, 1.65)
P_{trend}			0.77			0.23
Total Sugar						
Per IQR Increase			0.93 (0.79, 1.09)			0.96 (0.86, 1.06)
T1	216 (36.7)	341 (33.2)	1.00 (ref.)	206 (35.0)	341 (33.2)	1.00 (ref.)
T2	175 (29.7)	344 (33.5)	0.95 (0.69, 1.30)	198 (33.6)	344 (33.5)	1.04 (0.76, 1.43)
T3	198 (33.6)	341 (33.2)	0.90 (0.61, 1.34)	185 (31.4)	341 (33.2)	0.88 (0.64, 1.20)
P_{trend}			0.61			0.41

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-5. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary sugar, glycemic index (GI), glycemic load (GL) for lung cancer risk stratified by histological subtypes. (Controls: 1026)

	Standard Multivariable Model			Residual Model		
Histologic subtypes	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
Non-small cell lung cancer						
Glycemic Index						
T1	126 (24.3)	342 (33.3)	1.00 (ref.)	133 (25.7)	342 (33.3)	1.00 (ref.)
T2	166 (32.0)	342 (33.3)	1.25 (0.89, 1.74)	156 (30.1)	342 (33.3)	1.18 (0.85, 1.65)
T3	226 (43.6)	342 (33.3)	**1.44 (1.01, 2.05)**	229 (44.2)	342 (33.3)	**1.52 (1.10, 2.10)**
P_{trend}			**0.042**			**0.011**
Glycemic Load						
T1	169 (32.6)	341 (33.2)	1.00 (ref.)	177 (34.2)	342 (33.3)	1.00 (ref.)
T2	171 (33.0)	343 (33.4)	1.09 (0.77, 1.53)	155 (29.9)	343 (33.4)	1.00 (0.73, 1.39)
T3	178 (34.4)	342 (33.3)	0.98 (0.59, 1.62)	186 (35.9)	341 (33.2)	1.17 (0.85, 1.62)
P_{trend}			0.99			0.33
Total Sugar						
T1	187 (36.1)	341 (33.2)	1.00 (ref.)	185 (35.7)	341 (33.2)	1.00 (ref.)
T2	157 (30.3)	344 (33.5)	0.99 (0.72, 1.37)	167 (32.2)	344 (33.5)	0.99 (0.72, 1.37)
T3	174 (33.6)	341 (33.2)	0.89 (0.60, 1.33)	166 (32.0)	341 (33.2)	0.88 (0.64, 1.21)
P_{trend}			0.59			0.43
Squamous cell carcinoma						
Glycemic Index						
T1	19 (21.1)	342 (33.3)	1.00 (ref.)	22 (24.4)	342 (33.3)	1.00 (ref.)
T2	28 (31.1)	342 (33.3)	0.92 (0.43, 1.94)	32 (35.6)	342 (33.3)	1.09 (0.55, 2.17)
T3	43 (47.8)	342 (33.3)	1.42 (0.68, 2.95)	36 (40.0)	342 (33.3)	1.31 (0.66, 2.60)

	Standard Multivariable Model			Residual Model		
Histologic subtypes	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
P_{trend}			0.28			0.44
Glycemic Load						
T1	32 (35.6)	341 (33.2)	1.00 (ref.)	40 (44.4)	342 (33.3)	1.00 (ref.)
T2	23 (25.6)	343 (33.4)	0.68 (0.32, 1.44)	23 (25.6)	343 (33.4)	0.84 (0.43, 1.64)
T3	35 (38.9)	342 (33.3)	0.65 (0.23, 1.89)	27 (30.0)	341 (33.2)	0.92 (0.48, 1.76)
P_{trend}			0.39			0.79
Total Sugar						
T1	30 (33.3)	341 (33.2)	1.00 (ref.)	34 (37.8)	341 (33.2)	1.00 (ref.)
T2	28 (31.1)	344 (33.5)	1.14 (0.58, 2.26)	28 (31.1)	344 (33.5)	1.29 (0.66, 2.51)
T3	32 (35.6)	341 (33.2)	0.77 (0.33, 1.80)	28 (31.1)	341 (33.2)	0.87 (0.45, 1.66)
P_{trend}			0.58			0.66
Adeno-carcinoma						
Glycemic Index						
T1	74 (25.5)	342 (33.3)	1.00 (ref.)	72 (24.8)	342 (33.3)	1.00 (ref.)
T2	90 (31.0)	342 (33.3)	1.27 (0.86, 1.87)	85 (29.3)	342 (33.3)	1.23 (0.83, 1.81)
T3	126 (43.4)	342 (33.3)	**1.63 (1.08, 2.46)**	133 (45.9)	342 (33.3)	**1.72 (1.18, 2.52)**
P_{trend}			**0.019**			**0.005**
Glycemic Load						
T1	100 (34.5)	341 (33.2)	1.00 (ref.)	91 (31.4)	342 (33.3)	1.00 (ref.)
T2	102 (35.2)	343 (33.4)	1.20 (0.81, 1.79)	89 (30.7)	343 (33.4)	1.01 (0.69, 1.47)
T3	88 (30.3)	342 (33.3)	1.09 (0.59, 2.01)	110 (37.9)	341 (33.2)	1.29 (0.89, 1.87)
P_{trend}			0.67			0.18
Total Sugar						

	Standard Multivariable Model			Residual Model		
Histologic subtypes	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
T1	113 (39.0)	341 (33.2)	1.00 (ref.)	105 (36.2)	341 (33.2)	1.00 (ref.)
T2	85 (29.3)	344 (33.5)	0.95 (0.65, 1.38)	94 (32.4)	344 (33.5)	0.88 (0.61, 1.28)
T3	92 (31.7)	341 (33.2)	0.95 (0.59, 1.52)	91 (31.4)	341 (33.2)	0.80 (0.55, 1.16)
P_{trend}			0.82			0.23
Large cell carcinoma						
Glycemic Index						
T1	25 (22.7)	342 (33.3)	1.00 (ref.)	31 (28.2)	342 (33.3)	1.00 (ref.)
T2	39 (35.5)	342 (33.3)	1.46 (0.78, 2.74)	31 (28.2)	342 (33.3)	0.94 (0.50, 1.76)
T3	46 (41.8)	342 (33.3)	1.57 (0.81, 3.04)	48 (43.6)	342 (33.3)	1.55 (0.86, 2.79)
P_{trend}			0.20			0.12
Glycemic Load						
T1	30 (27.3)	341 (33.2)	1.00 (ref.)	38 (34.5)	342 (33.3)	1.00 (ref.)
T2	38 (34.5)	343 (33.4)	1.51 (0.79, 2.92)	36 (32.7)	343 (33.4)	1.26 (0.70, 2.26)
T3	42 (38.2)	342 (33.3)	1.45 (0.57, 3.72)	36 (32.7)	341 (33.2)	1.09 (0.60, 1.98)
P_{trend}			0.39			0.79
Total Sugar						
T1	37 (33.6)	341 (33.2)	1.00 (ref.)	38 (34.5)	341 (33.2)	1.00 (ref.)
T2	33 (30.0)	344 (33.5)	0.92 (0.51, 1.67)	37 (33.6)	344 (33.5)	1.14 (0.63, 2.05)
T3	40 (36.4)	341 (33.2)	0.82 (0.40, 1.69)	35 (31.8)	341 (33.2)	0.83 (0.46, 1.49)
P_{trend}			0.59			0.52
Small cell carcinoma						
Glycemic Index						
T1	16 (22.5)	342 (33.3)	1.00 (ref.)	20 (28.2)	342 (33.3)	1.00 (ref.)

	Standard Multivariable Model			Residual Model		
Histologic subtypes	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
T2	20 (28.2)	342 (33.3)	1.62 (0.72, 3.61)	12 (16.9)	342 (33.3)	0.67 (0.29, 1.58)
T3	35 (49.3)	342 (33.3)	**2.74 (1.25, 5.99)**	39 (54.9)	342 (33.3)	**2.48 (1.23, 5.03)**
P_{trend}			**0.010**			**0.007**
Glycemic Load						
T1	21 (29.6)	341 (33.2)	1.00 (ref.)	21 (29.6)	342 (33.3)	1.00 (ref.)
T2	25 (35.2)	343 (33.4)	1.93 (0.87, 4.26)	21 (29.6)	343 (33.4)	1.47 (0.68, 3.16)
T3	25 (35.2)	342 (33.3)	2.55 (0.82, 7.95)	29 (40.8)	341 (33.2)	1.99 (0.96, 4.14)
P_{trend}			0.092			0.064
Total Sugar						
T1	29 (40.8)	341 (33.2)	1.00 (ref.)	21 (29.6)	341 (33.2)	1.00 (ref.)
T2	18 (25.4)	344 (33.5)	0.75 (0.36, 1.57)	31 (43.7)	344 (33.5)	2.10 (1.00, 4.39)
T3	24 (33.8)	341 (33.2)	0.97 (0.39, 2.42)	19 (26.8)	341 (33.2)	0.90 (0.41, 2.00)
P_{trend}			0.86			0.69

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-6. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary glycemic index (GI) from different sources for lung cancer. (N of lung cancer: 589; controls: 1026)

	Standard Multivariable Model			Residual Model		
GI source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
High Carbohydrates/Sugar						
T1	213/341	1.00 (ref.)	0.80	211/341	1.00 (ref.)	0.73
T2	151/344	0.78 (0.57, 1.07)		153/343	0.79 (0.57, 1.08)	
T3	225/341	0.96 (0.70, 1.31)		225/342	0.95 (0.69, 1.29)	
Fruits						
T1	197/341	1.00 (ref.)	0.78	197/341	1.00 (ref.)	0.79
T2	161/344	0.94 (0.69, 1.28)		160/343	0.96 (0.70, 1.30)	
T3	231/341	1.04 (0.78, 1.40)		232/342	1.04 (0.77, 1.39)	
Vegetables						
T1	188/341	1.00 (ref.)	0.32	195/341	1.00 (ref.)	0.56
T2	157/344	0.77 (0.56, 1.05)		152/344	**0.69 (0.50, 0.94)**	
T3	244/341	1.19 (0.87, 1.64)		242/341	1.12 (0.82, 1.53)	
Meat and Mixed Dishes						
T1	165/341	1.00 (ref.)	0.39	173/341	1.00 (ref.)	0.39
T2	194/343	1.17 (0.85, 1.59)		183/344	1.06 (0.78, 1.44)	
T3	230/342	1.15 (0.84, 1.56)		233/341	1.14 (0.84, 1.55)	
Starches and Salty Snacks						
T1	156/342	1.00 (ref.)	**0.001**	173/341	1.00 (ref.)	**0.022**
T2	184/343	1.22 (0.88, 1.68)		180/344	1.19 (0.87, 1.63)	
T3	249/341	**1.76 (1.27, 2.44)**		236/341	**1.46 (1.06, 2.01)**	
Breakfast Foods						
T1	212/341	1.00 (ref.)	**0.001**	206/341	1.00 (ref.)	**0.003**
T2	156/344	1.28 (0.93, 1.75)		165/343	1.29 (0.94, 1.76)	
T3	221/341	**1.65 (1.22, 2.22)**		218/342	**1.58 (1.17, 2.13)**	
Sweets						
T1	211/341	1.00 (ref.)	0.71	217/341	1.00 (ref.)	0.92
T2	175/343	0.94 (0.69, 1.27)		176/344	0.86 (0.63, 1.16)	
T3	203/342	1.06 (0.79, 1.42)		196/341	1.02 (0.76, 1.37)	
Dairy Products, Beverages						
T1	177/341	1.00 (ref.)	0.93	184/342	1.00 (ref.)	0.85
T2	200/344	1.30 (0.94, 1.78)		205/343	1.33 (0.96, 1.83)	

	Standard Multivariable Model			Residual Model		
GI source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
T3	212/341	1.02 (0.73, 1.44)		200/341	1.04 (0.75, 1.43)	

ca/co: cases/control.

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-7. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary glycemic load (GL) from different sources for lung cancer. (N of lung cancer: 589; controls: 1026)

	Standard Multivariable Model			Residual Model		
GL source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
High Carbohydrates/Sugar						
T1	180/341	1.00 (ref.)	**0.002**	181/342	1.00 (ref.)	**0.001**
T2	179/344	1.26 (0.92, 1.73)		174/342	1.21 (0.88, 1.66)	
T3	230/341	**1.65 (1.20, 2.26)**		234/342	**1.69 (1.23, 2.31)**	
Fruits						
T1	234/341	1.00 (ref.)	0.39	240/341	1.00 (ref.)	0.75
T2	191/343	1.05 (0.78, 1.42)		183/344	0.92 (0.68, 1.25)	
T3	164/342	1.15 (0.84, 1.59)		166/341	1.06 (0.78, 1.44)	
Vegetables						
T1	272/342	1.00 (ref.)	**0.005**	258/341	1.00 (ref.)	**0.002**
T2	171/343	0.79 (0.58, 1.06)		204/343	0.96 (0.72, 1.28)	
T3	146/341	**0.63 (0.45, 0.87)**		127/342	**0.59 (0.43, 0.81)**	
Meat and Mixed Dishes						
T1	210/341	1.00 (ref.)	0.31	203/341	1.00 (ref.)	0.80
T2	175/344	0.89 (0.66, 1.21)		198/344	1.05 (0.78, 1.42)	
T3	204/341	1.18 (0.86, 1.62)		188/341	1.04 (0.76, 1.43)	
Starches and Salty Snacks						
T1	189/342	1.00 (ref.)	**0.033**	189/341	1.00 (ref.)	**0.027**
T2	188/342	1.16 (0.85, 1.57)		185/343	1.14 (0.83, 1.55)	
T3	212/342	**1.39 (1.03, 1.89)**		215/342	**1.41 (1.04, 1.91)**	
Breakfast Foods						
T1	204/341	1.00 (ref.)	**0.003**	197/341	1.00 (ref.)	**0.013**
T2	179/343	1.27 (0.93, 1.73)		193/344	1.13 (0.82, 1.55)	
T3	206/342	**1.59 (1.17, 2.16)**		199/341	**1.48 (1.09, 2.02)**	
Sweets						
T1	219/341	1.00 (ref.)	0.73	222/341	1.00 (ref.)	0.84
T2	174/344	0.95 (0.70, 1.28)		168/343	0.93 (0.69, 1.26)	
T3	196/341	0.95 (0.70, 1.28)		199/342	0.97 (0.72, 1.31)	
Dairy Products, Beverages						
T1	176/341	1.00 (ref.)	0.45	183/342	1.00 (ref.)	0.11
T2	185/344	1.20 (0.88, 1.63)		181/342	0.95 (0.69, 1.30)	

	Standard Multivariable Model			Residual Model		
GL source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
T3	228/341	0.88 (0.63, 1.22)		225/342	0.78 (0.57, 1.06)	

ca/co: cases/control.

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-8. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary sugar from different sources for lung cancer. (N of lung cancer: 589; controls: 1026)

	Standard Multivariable Model			Residual Model		
Sugar source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
High Carbohydrates/Sugar						
T1	201/342	1.00 (ref.)	**<0.001**	189/341	1.00 (ref.)	**0.001**
T2	172/343	1.04 (0.76, 1.42)		201/344	**1.46 (1.07, 2.00)**	
T3	216/341	**1.81 (1.32, 2.49)**		199/341	**1.78 (1.28, 2.49)**	
Fruits						
T1	236/342	1.00 (ref.)	0.17	242/342	1.00 (ref.)	0.31
T2	180/342	1.10 (0.81, 1.50)		168/342	0.89 (0.66, 1.22)	
T3	173/342	1.25 (0.91, 1.72)		179/342	1.18 (0.87, 1.60)	
Vegetables						
T1	247/342	1.00 (ref.)	0.18	255/342	1.00 (ref.)	**0.035**
T2	202/342	1.10 (0.82, 1.49)		199/343	0.88 (0.66, 1.18)	
T3	140/342	0.78 (0.56, 1.09)		135/341	**0.71 (0.52, 0.97)**	
Meat and Mixed Dishes						
T1	181/342	1.00 (ref.)	0.098	166/342	1.00 (ref.)	**0.012**
T2	184/342	1.08 (0.79, 1.48)		190/343	1.30 (0.95, 1.78)	
T3	224/342	1.30 (0.95, 1.78)		233/341	**1.50 (1.09, 2.05)**	
Starches and Salty Snacks						
T1	252/341	1.00 (ref.)	0.94	251/342	1.00 (ref.)	0.94
T2	154/343	0.80 (0.59, 1.09)		151/343	0.76 (0.55, 1.03)	
T3	183/342	1.00 (0.73, 1.36)		187/341	1.02 (0.75, 1.39)	
Breakfast Foods						
T1	212/342	1.00 (ref.)	0.23	200/341	1.00 (ref.)	0.24
T2	160/342	1.01 (0.74, 1.37)		168/344	0.85 (0.61, 1.19)	
T3	217/342	1.20 (0.89, 1.62)		221/341	1.18 (0.86, 1.60)	
Sweets						
T1	215/341	1.00 (ref.)	0.47	212/342	1.00 (ref.)	0.58
T2	191/343	1.06 (0.79, 1.43)		194/342	1.06 (0.79, 1.42)	
T3	183/342	0.89 (0.65, 1.21)		183/342	0.91 (0.67, 1.24)	
Dairy Products, Beverages						
T1	158/342	1.00 (ref.)	0.19	171/341	1.00 (ref.)	0.87
T2	172/342	1.27 (0.92, 1.74)		173/343	1.07 (0.78, 1.46)	

	Standard Multivariable Model			Residual Model		
Sugar source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
T3	259/342	1.25 (0.91, 1.72)		245/342	0.98 (0.72, 1.33)	

ca/co: cases/control.

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-9. aOR and 95% confidence interval (CI) of dietary glycemic index (GI) from different sources for lung cancer, stratified by smoking status. (Non-smoker cases/controls: 108/484; Current/ever smoker cases/controls: 481/541)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GI source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.12 (0.62, 2.01)	1.40 (0.94, 2.08)	1.22 (0.66, 2.23)	1.10 (0.75, 1.62)
T3	1.07 (0.56, 2.06)	**1.73 (1.15, 2.59)**	1.08 (0.58, 1.99)	**1.81 (1.25, 2.64)**
P_{trend}	0.83	**0.009**	0.87	**0.001**
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.22 (0.68, 2.17)	0.65 (0.44, 0.96)	1.08 (0.61, 1.93)	0.70 (0.47, 1.02)
T3	1.44 (0.77, 2.69)	0.81 (0.56, 1.17)	1.44 (0.77, 2.68)	0.80 (0.55, 1.15)
P_{trend}	0.26	0.29	0.27	0.26
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.78 (0.45, 1.35)	1.03 (0.71, 1.51)	0.80 (0.46, 1.38)	1.04 (0.71, 1.52)
T3	0.80 (0.45, 1.42)	1.17 (0.83, 1.66)	0.81 (0.46, 1.44)	1.16 (0.82, 1.65)
P_{trend}	0.44	0.37	0.47	0.40
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.61 (0.32, 1.17)	0.83 (0.57, 1.20)	0.55 (0.28, 1.06)	0.73 (0.50, 1.05)
T3	1.64 (0.91, 2.96)	1.00 (0.69, 1.46)	1.46 (0.81, 2.63)	0.94 (0.65, 1.37)
P_{trend}	0.088	0.96	0.17	0.70
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.69 (0.40, 1.19)	1.45 (0.99, 2.13)	0.57 (0.32, 1.00)	1.34 (0.92, 1.97)
T3	0.68 (0.38, 1.20)	1.41 (0.97, 2.04)	0.69 (0.40, 1.20)	1.39 (0.96, 2.01)
P_{trend}	0.16	0.086	0.16	0.093
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.13 (0.56, 2.29)	1.28 (0.88, 1.86)	1.35 (0.67, 2.71)	1.21 (0.84, 1.75)
T3	**3.14 (1.63, 6.04)**	1.41 (0.96, 2.07)	**2.74 (1.42, 5.27)**	1.14 (0.78, 1.67)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GI source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
P_{trend}	**<0.001**	0.078	**0.001**	0.48
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.36 (0.76, 2.44)	1.20 (0.82, 1.76)	1.75 (0.97, 3.15)	1.05 (0.72, 1.53)
T3	1.24 (0.69, 2.22)	**1.86 (1.29, 2.67)**	1.35 (0.74, 2.47)	**1.69 (1.18, 2.42)**
P_{trend}	0.50	**0.001**	0.39	**0.004**
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.25 (0.72, 2.19)	0.81 (0.56, 1.17)	1.12 (0.64, 1.99)	0.76 (0.53, 1.10)
T3	1.30 (0.73, 2.32)	0.95 (0.66, 1.34)	1.25 (0.71, 2.21)	0.92 (0.64, 1.31)
P_{trend}	0.37	0.75	0.44	0.61
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.24 (0.70, 2.19)	1.24 (0.84, 1.82)	1.44 (0.80, 2.58)	1.18 (0.80, 1.75)
T3	1.01 (0.53, 1.94)	0.97 (0.64, 1.46)	0.89 (0.48, 1.63)	1.06 (0.72, 1.55)
P_{trend}	0.95	0.83	0.65	0.79

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking , diabetes

Table 3-10. aOR and 95% confidence interval (CI) of dietary glycemic load (GL) from different sources for lung cancer, stratified by smoking status. (Never smoker cases/controls: 108/484; Current/ever smoker cases/controls: 481/541)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GL source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.89 (0.48, 1.65)	1.25 (0.84, 1.87)	0.57 (0.30, 1.09)	1.20 (0.83, 1.73)
T3	0.55 (0.21, 1.48)	1.35 (0.76, 2.42)	0.85 (0.46, 1.57)	1.28 (0.89, 1.86)
P_{trend}	0.29	0.28	0.86	0.18
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.41 (0.73, 2.71)	1.26 (0.87, 1.82)	1.26 (0.65, 2.46)	1.25 (0.86, 1.80)
T3	1.62 (0.85, 3.07)	**1.74 (1.20, 2.53)**	1.73 (0.92, 3.26)	**1.74 (1.20, 2.53)**
P_{trend}	0.15	**0.004**	0.076	**0.004**
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.86 (0.46, 1.61)	1.13 (0.80, 1.61)	0.64 (0.34, 1.19)	1.07 (0.74, 1.53)
T3	1.20 (0.65, 2.21)	1.14 (0.78, 1.68)	1.12 (0.64, 1.97)	1.01 (0.69, 1.47)
P_{trend}	0.46	0.46	0.55	0.93
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.19 (0.67, 2.12)	**0.69 (0.48, 0.99)**	1.36 (0.78, 2.38)	0.86 (0.60, 1.22)
T3	0.96 (0.53, 1.76)	**0.53 (0.36, 0.79)**	0.81 (0.44, 1.49)	**0.51 (0.34, 0.75)**
P_{trend}	0.87	**0.001**	0.53	**0.001**
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.83 (0.46, 1.49)	0.92 (0.64, 1.32)	1.09 (0.63, 1.89)	1.06 (0.73, 1.52)
T3	1.48 (0.82, 2.67)	1.11 (0.76, 1.62)	1.35 (0.73, 2.48)	0.96 (0.66, 1.40)
P_{trend}	0.21	0.60	0.35	0.83
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.28 (0.69, 2.38)	1.18 (0.82, 1.70)	1.24 (0.66, 2.31)	1.16 (0.81, 1.68)
T3	1.60 (0.90, 2.86)	1.40 (0.97, 2.02)	1.66 (0.93, 2.97)	1.39 (0.96, 2.01)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GL source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
P_{trend}	0.11	0.072	0.080	0.077
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.65 (0.88, 3.09)	1.15 (0.80, 1.65)	1.64 (0.87, 3.10)	0.98 (0.68, 1.43)
T3	**2.00 (1.11, 3.61)**	**1.50 (1.03, 2.16)**	**1.97 (1.10, 3.54)**	1.34 (0.92, 1.96)
P_{trend}	**0.023**	**0.033**	**0.026**	0.13
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.93 (0.54, 1.60)	0.95 (0.66, 1.37)	0.86 (0.50, 1.46)	0.96 (0.67, 1.39)
T3	0.77 (0.42, 1.39)	1.03 (0.72, 1.48)	0.72 (0.40, 1.30)	1.11 (0.78, 1.58)
P_{trend}	0.39	0.86	0.27	0.59
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.48 (0.86, 2.55)	1.01 (0.69, 1.48)	0.92 (0.53, 1.60)	0.90 (0.61, 1.33)
T3	1.00 (0.53, 1.87)	0.77 (0.52, 1.15)	0.83 (0.46, 1.51)	0.70 (0.48, 1.02)
P_{trend}	0.89	0.19	0.54	0.059

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes

Table 3-11. aOR and 95% confidence interval (CI) of dietary sugar from different sources for lung cancer, stratified by smoking status. (Never smoker cases/controls: 108/484; Current/ever smoker cases/controls: 481/541)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
Sugar source	Never smokers	Smokers	Never smokers	Smokers
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.05 (0.59, 1.87)	0.89 (0.61, 1.30)	0.89 (0.49, 1.63)	1.08 (0.74, 1.58)
T3	0.64 (0.29, 1.44)	1.02 (0.64, 1.62)	0.73 (0.39, 1.37)	0.86 (0.59, 1.24)
P_{trend}	0.35	0.99	0.32	0.41
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.77 (0.41, 1.42)	1.18 (0.82, 1.70)	1.61 (0.85, 3.03)	**1.44 (1.00, 2.08)**
T3	1.14 (0.64, 2.03)	**2.26 (1.53, 3.33)**	1.35 (0.72, 2.55)	**2.09 (1.39, 3.13)**
P_{trend}	0.63	**<0.001**	0.42	**<0.001**
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.99 (0.52, 1.87)	1.13 (0.79, 1.62)	0.74 (0.40, 1.36)	0.92 (0.64, 1.32)
T3	1.15 (0.62, 2.14)	1.32 (0.90, 1.94)	0.94 (0.53, 1.66)	1.34 (0.92, 1.94)
P_{trend}	0.61	0.16	0.93	0.16
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.66 (0.94, 2.94)	0.95 (0.66, 1.36)	1.16 (0.66, 2.01)	0.78 (0.55, 1.11)
T3	1.11 (0.59, 2.09)	0.68 (0.45, 1.01)	0.87 (0.48, 1.57)	**0.65 (0.44, 0.95)**
P_{trend}	0.78	0.065	0.68	**0.023**
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.20 (0.68, 2.11)	1.11 (0.76, 1.62)	1.51 (0.86, 2.65)	1.35 (0.92, 1.98)
T3	1.13 (0.61, 2.08)	1.41 (0.97, 2.06)	1.30 (0.70, 2.41)	**1.63 (1.12, 2.36)**
P_{trend}	0.68	0.067	0.38	**0.011**
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.94 (0.53, 1.68)	0.76 (0.52, 1.10)	0.88 (0.48, 1.59)	0.72 (0.50, 1.04)
T3	1.07 (0.59, 1.94)	1.01 (0.70, 1.45)	1.12 (0.62, 2.02)	1.01 (0.70, 1.45)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
Sugar source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
P_{trend}	0.84	0.97	0.71	0.96
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.41 (0.77, 2.56)	0.87 (0.60, 1.26)	1.66 (0.89, 3.13)	0.65 (0.43, 0.97)
T3	1.38 (0.77, 2.47)	1.18 (0.82, 1.70)	1.66 (0.92, 2.98)	1.04 (0.72, 1.51)
P_{trend}	0.30	0.40	0.10	0.68
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.07 (0.63, 1.81)	1.04 (0.73, 1.50)	0.93 (0.54, 1.59)	1.09 (0.76, 1.56)
T3	0.76 (0.42, 1.37)	0.96 (0.67, 1.39)	0.77 (0.43, 1.39)	0.99 (0.69, 1.43)
P_{trend}	0.41	0.84	0.40	1.00
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.05 (0.59, 1.86)	1.31 (0.88, 1.94)	1.04 (0.59, 1.83)	1.03 (0.70, 1.51)
T3	1.54 (0.85, 2.80)	1.08 (0.74, 1.60)	1.24 (0.69, 2.20)	0.84 (0.58, 1.21)
P_{trend}	0.15	0.76	0.47	0.32

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-12. Range of glycemic index (GI), glycemic load (GL) and dietary sugar intake in controls of UADT cancer

	Standard Multivariable method			Residual method[a]		
	Tertile 1	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
GI						
Total GI	24.5 ~ 51.83	51.83 ~ 56.62	56.62 ~ 68.67	78.75 ~ 106.08	106.08 ~ 110.87	110.87 ~ 122.92
Different food source of GI						
High Carbohydrates/ Sugar	0 ~ 75.15	75.15 ~ 78.06	78.06 ~ 111	77.74 ~ 152.89	152.89 ~ 155.8	155.8 ~ 188.74
Fruits	0 ~ 48.13	48.13 ~ 51.92	51.92 ~ 72	49.5 ~ 97.63	97.63 ~ 101.42	101.42 ~ 121.5
Vegetables	0 ~ 18.61	18.61 ~ 26.47	26.47 ~ 47.26	23.52 ~ 42.13	42.13 ~ 49.99	49.99 ~ 70.78
Meat and Mixed Dishes	0 ~ 44	44 ~ 48.46	48.46 ~ 61.56	46.18 ~ 90.18	90.18 ~ 94.64	94.64 ~ 107.74
Starches and Salty Snacks	0 ~ 63.7	63.7 ~ 69.14	69.14 ~ 83.75	66.24 ~ 129.94	129.94 ~ 135.38	135.38 ~ 149.99
Breakfast Foods	0 ~ 48	48 ~ 58.07	58.07 ~ 80	46.37 ~ 94.37	94.37 ~ 104.44	104.44 ~ 126.37
Sweets	0 ~ 50.8	50.8 ~ 54.86	54.86 ~ 61	50.86 ~ 101.66	101.66 ~ 105.72	105.72 ~ 111.86
Dairy Products, Beverages	0 ~ 33.34	33.34 ~ 56.29	56.29 ~ 66	43.41 ~ 76.75	76.75 ~ 99.7	99.7 ~ 109.41
GL						
Total GL (g)	9.1 ~ 90.68	90.68 ~ 142.76	142.76 ~ 456.31	143.8 ~ 225.38	225.38 ~ 277.46	277.46 ~ 591.01
Different food source of GL(%)						
High Carbohydrates/ Sugar	0 ~ 25.49	25.49 ~ 41.76	41.76 ~ 88.52	34.72 ~ 60.21	60.21 ~ 76.48	76.48 ~ 123.24
Fruits	0 ~ 7.2	7.2 ~ 15.24	15.24 ~ 68.38	12.32 ~ 19.52	19.52 ~ 27.56	27.56 ~ 80.7
Vegetables	0 ~ 2.6	2.6 ~ 4.76	4.76 ~ 29.03	4.17 ~ 6.77	6.77 ~ 8.93	8.93 ~ 33.2
Meat and Mixed Dishes	0 ~ 6.22	6.22 ~ 10.53	10.53 ~ 67.51	9.74 ~ 15.96	15.96 ~ 20.27	20.27 ~ 77.25
Starches and Salty Snacks	0 ~ 37.88	37.88 ~ 51.67	51.67 ~ 93.6	43.89 ~ 81.77	81.77 ~ 95.56	95.56 ~ 137.49
Breakfast Foods	0 ~ 1.29	1.29 ~ 6.05	6.05 ~ 47.33	5.22 ~ 6.51	6.51 ~ 11.27	11.27 ~ 52.55
Sweets	0 ~ 3.65	3.65 ~ 8.98	8.98 ~ 45.52	7.8 ~ 11.45	11.45 ~ 16.78	16.78 ~ 53.32
Dairy Products, Beverages	0 ~ 4.46	4.46 ~ 17.97	17.97 ~ 95.8	17.21 ~ 21.67	21.67 ~ 35.18	35.18 ~ 113.01

	Standard Multivariable method			Residual method[a]		
	Tertile 1	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
Different food source of GL(g)						
High Carbohydrates/ Sugar	0 ~ 24.97	24.97 ~ 51.81	51.81 ~ 280.13	48.89 ~ 73.86	73.86 ~ 100.7	100.7 ~ 329.02
Fruits	0 ~ 8.18	8.18 ~ 17.13	17.13 ~ 101.52	14.18 ~ 22.36	22.36 ~ 31.31	31.31 ~ 115.7
Vegetables	0 ~ 2.83	2.83 ~ 5.23	5.23 ~ 28.58	4.73 ~ 7.56	7.56 ~ 9.96	9.96 ~ 33.31
Meat and Mixed Dishes	0 ~ 6.84	6.84 ~ 12.55	12.55 ~ 66.48	11.59 ~ 18.43	18.43 ~ 24.14	24.14 ~ 78.07
Starches and Salty Snacks	0 ~ 36.28	36.28 ~ 64.34	64.34 ~ 299.41	59.4 ~ 95.68	95.68 ~ 123.74	123.74 ~ 358.81
Breakfast Foods	0 ~ 1.37	1.37 ~ 7.18	7.18 ~ 62.78	6.05 ~ 7.42	7.42 ~ 13.23	13.23 ~ 68.83
Sweets	0 ~ 3.66	3.66 ~ 11.14	11.14 ~ 82.14	10.24 ~ 13.9	13.9 ~ 21.38	21.38 ~ 92.38
Dairy Products, Beverages	0 ~ 4.09	4.09 ~ 21.14	21.14 ~ 309.53	28.99 ~ 33.08	33.08 ~ 50.13	50.13 ~ 338.52
Dietary Sugar						
Total Sugar (g)	11 ~ 63.23	63.23 ~ 105.13	105.13 ~ 504.55	115.77 ~ 168	168 ~ 209.9	209.9 ~ 609.32
Different food source of Sugar(%)						
High Carbohydrates/ Sugar	0 ~ 2.63	2.63 ~ 5.73	5.73 ~ 74.35	6.79 ~ 9.42	9.42 ~ 12.52	12.52 ~ 81.14
Fruits	0 ~ 16.92	16.92 ~ 33.91	33.91 ~ 84.33	25.67 ~ 42.59	42.59 ~ 59.58	59.58 ~ 110
Vegetables	0 ~ 7.23	7.23 ~ 14.4	14.4 ~ 57.29	12.01 ~ 19.24	19.24 ~ 26.41	26.41 ~ 69.3
Meat and Mixed Dishes	0 ~ 2.04	2.04 ~ 3.88	3.88 ~ 25.16	4.09 ~ 6.13	6.13 ~ 7.97	7.97 ~ 29.25
Starches and Salty Snacks	0 ~ 5.95	5.95 ~ 11.42	11.42 ~ 77.72	10.47 ~ 16.42	16.42 ~ 21.89	21.89 ~ 88.19
Breakfast Foods	0 ~ 0.51	0.51 ~ 2.82	2.82 ~ 57.06	3.49 ~ 4	4 ~ 6.31	6.31 ~ 60.55
Sweets	0 ~ 5.71	5.71 ~ 14.95	14.95 ~ 84.27	12.59 ~ 18.3	18.3 ~ 27.54	27.54 ~ 96.86
Dairy Products, Beverages	0 ~ 12.22	12.22 ~ 37.82	37.82 ~ 98.05	31.68 ~ 43.9	43.9 ~ 69.5	69.5 ~ 129.73
Different food source of Sugar(g)						
High Carbohydrates/ Sugar	0 ~ 2	2 ~ 4.61	4.61 ~ 123.61	7.72 ~ 9.72	9.72 ~ 12.33	12.33 ~ 131.33
Fruits	0 ~ 13.37	13.37 ~ 27.34	27.34 ~ 208.4	22.81 ~ 36.18	36.18 ~ 50.15	50.15 ~ 231.21

	Standard Multivariable method			Residual method[a]		
	Tertile 1	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
Vegetables	0 ~ 6.45	6.45 ~ 10.93	10.93 ~ 46.35	9.25 ~ 15.7	15.7 ~ 20.18	20.18 ~ 55.6
Meat and Mixed Dishes	0 ~ 1.73	1.73 ~ 3.29	3.29 ~ 17.58	3.26 ~ 4.99	4.99 ~ 6.55	6.55 ~ 20.84
Starches and Salty Snacks	0 ~ 4.57	4.57 ~ 8.82	8.82 ~ 125.24	10.19 ~ 14.76	14.76 ~ 19.01	19.01 ~ 135.43
Breakfast Foods	0 ~ 0.39	0.39 ~ 2.31	2.31 ~ 75.18	2.91 ~ 3.3	3.3 ~ 5.22	5.22 ~ 78.09
Sweets	0 ~ 4.28	4.28 ~ 13.59	13.59 ~ 114.89	11.89 ~ 16.17	16.17 ~ 25.48	25.48 ~ 126.78
Dairy Products, Beverages	0 ~ 8.38	8.38 ~ 35.25	35.25 ~ 491.62	44.46 ~ 52.84	52.84 ~ 79.71	79.71 ~ 536.08

a. Standardized nutrient intake from the residual method

Table 3-13. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary sugar, glycemic index (GI), glycemic load (GL) for UADT cancer.

	Standard Multivariable Model			Residual Model		
Dietary intake	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
Glycemic Index						
Per IQR Increase			0.98 (0.84, 1.14)			0.98 (0.85, 1.13)
T1	152 (26.7)	342 (33.3)	1.00 (ref.)	183 (32.1)	342 (33.3)	1.00 (ref.)
T2	174 (30.5)	342 (33.3)	0.91 (0.68, 1.22)	171 (30.0)	343 (33.4)	0.82 (0.61, 1.08)
T3	244 (42.8)	342 (33.3)	0.89 (0.65, 1.22)	216 (37.9)	341 (33.2)	0.89 (0.66, 1.18)
P_{trend}			0.49			0.41
Glycemic Load						
Per IQR Increase			0.79 (0.59, 1.05)			0.91 (0.81, 1.02)
T1	162 (28.4)	341 (33.2)	1.00 (ref.)	226 (39.6)	341 (33.2)	1.00 (ref.)
T2	180 (31.6)	343 (33.4)	0.82 (0.60, 1.12)	155 (27.2)	344 (33.5)	0.78 (0.58, 1.03)
T3	228 (40.0)	342 (33.3)	**0.59 (0.37, 0.93)**	189 (33.2)	341 (33.2)	0.78 (0.58, 1.03)
P_{trend}			**0.025**			0.077
Total Sugar						
Per IQR Increase			**0.84 (0.73, 0.98)**			**0.90 (0.82, 0.99)**
T1	198 (34.7)	341 (33.2)	1.00 (ref.)	229 (40.2)	342 (33.3)	1.00 (ref.)
T2	153 (26.8)	344 (33.5)	**0.72 (0.54, 0.97)**	178 (31.2)	342 (33.3)	1.03 (0.78, 1.37)
T3	219 (38.4)	341 (33.2)	**0.62 (0.43, 0.90)**	163 (28.6)	342 (33.3)	**0.70 (0.53, 0.93)**
P_{trend}			**0.009**			**0.016**

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-14. Adjusted Odds ratio (aOR) and 95% confidence interval (CI) of dietary sugar, glycemic index (GI), glycemic load (GL) for lung cancer risk stratified by histologic subtypes. (Controls: 1026)

	Standard Multivariable Model			Residual Model		
Histologic subtypes	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
UADT squamous cell carcinoma						
Glycemic Index						
T1	131 (26.4)	342 (33.3)	1.00 (ref.)	160 (32.2)	342 (33.3)	1.00 (ref.)
T2	148 (29.8)	342 (33.3)	0.89 (0.65, 1.21)	148 (29.8)	343 (33.4)	0.80 (0.60, 1.08)
T3	218 (43.9)	342 (33.3)	0.90 (0.65, 1.25)	189 (38.0)	341 (33.2)	0.88 (0.65, 1.19)
P_{trend}			0.55			0.41
Glycemic Load						
T1	141 (28.4)	341 (33.2)	1.00 (ref.)	194 (39.0)	341 (33.2)	1.00 (ref.)
T2	155 (31.2)	343 (33.4)	0.79 (0.57, 1.10)	135 (27.2)	344 (33.5)	0.78 (0.58, 1.06)
T3	201 (40.4)	342 (33.3)	**0.56 (0.35, 0.91)**	168 (33.8)	341 (33.2)	0.81 (0.60, 1.09)
P_{trend}			**0.020**			0.16
Total Sugar						
T1	170 (34.2)	341 (33.2)	1.00 (ref.)	201 (40.4)	342 (33.3)	1.00 (ref.)
T2	133 (26.8)	344 (33.5)	**0.73 (0.53, 0.99)**	150 (30.2)	342 (33.3)	0.98 (0.73, 1.32)
T3	194 (39.0)	341 (33.2)	**0.64 (0.44, 0.93)**	146 (29.4)	342 (33.3)	**0.72 (0.54, 0.97)**
P_{trend}			**0.017**			**0.03**
Oropharyngeal squamous cell carcinoma						
Glycemic Index						
T1	98 (30.6)	342 (33.3)	1.00 (ref.)	114 (35.6)	342 (33.3)	1.00 (ref.)
T2	95 (29.7)	342 (33.3)	0.82 (0.58, 1.16)	98 (30.6)	343 (33.4)	0.76 (0.54, 1.06)
T3	127 (39.7)	342 (33.3)	0.81 (0.56, 1.17)	108 (33.8)	341 (33.2)	0.81 (0.57, 1.14)

	Standard Multivariable Model			Residual Model		
Histologic subtypes	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
P_{trend}			0.28			0.22
Glycemic Load						
T1	99 (30.9)	341 (33.2)	1.00 (ref.)	134 (41.9)	341 (33.2)	1.00 (ref.)
T2	98 (30.6)	343 (33.4)	0.73 (0.50, 1.06)	91 (28.4)	344 (33.5)	0.78 (0.56, 1.10)
T3	123 (38.4)	342 (33.3)	**0.51 (0.29, 0.88)**	95 (29.7)	341 (33.2)	0.73 (0.52, 1.03)
P_{trend}			**0.015**			0.067
Total Sugar						
T1	118 (36.9)	341 (33.2)	1.00 (ref.)	136 (42.5)	342 (33.3)	1.00 (ref.)
T2	85 (26.6)	344 (33.5)	**0.64 (0.45, 0.91)**	98 (30.6)	342 (33.3)	0.92 (0.66, 1.29)
T3	117 (36.6)	341 (33.2)	**0.54 (0.35, 0.84)**	86 (26.9)	342 (33.3)	**0.64 (0.46, 0.90)**
P_{trend}			**0.005**			**0.011**
Esophageal adenocarcinoma						
Glycemic Index						
T1	21 (28.8)	342 (33.3)	1.00 (ref.)	23 (31.5)	342 (33.3)	1.00 (ref.)
T2	26 (35.6)	342 (33.3)	1.05 (0.55, 2.00)	23 (31.5)	343 (33.4)	0.90 (0.48, 1.69)
T3	26 (35.6)	342 (33.3)	0.78 (0.38, 1.60)	27 (37.0)	341 (33.2)	1.00 (0.53, 1.90)
P_{trend}			0.48			1.00
Glycemic Load						
T1	21 (28.8)	341 (33.2)	1.00 (ref.)	32 (43.8)	341 (33.2)	1.00 (ref.)
T2	25 (34.2)	343 (33.4)	1.00 (0.49, 2.01)	20 (27.4)	344 (33.5)	0.68 (0.36, 1.29)
T3	27 (37.0)	342 (33.3)	0.82 (0.30, 2.23)	21 (28.8)	341 (33.2)	0.60 (0.31, 1.15)
P_{trend}			0.72			0.11
Total Sugar						

	Standard Multivariable Model			Residual Model		
Histologic subtypes	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**	**Cases (%)**	**Controls (%)**	**aOR[a] (95% CI)**
T1	28 (38.4)	341 (33.2)	1.00 (ref.)	28 (38.4)	342 (33.3)	1.00 (ref.)
T2	20 (27.4)	344 (33.5)	0.69 (0.36, 1.34)	28 (38.4)	342 (33.3)	1.30 (0.71, 2.38)
T3	25 (34.2)	341 (33.2)	0.53 (0.24, 1.21)	17 (23.3)	342 (33.3)	0.58 (0.30, 1.14)
P_{trend}			0.13			0.15

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-15. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary glycemic index (GI) from different sources for UADT cancer. (N of lung cancer: 570; controls: 1026)

	Standard Multivariable Model			Residual Model		
GI source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
High Carbohydrates/Sugar						
T1	180/341	1.00 (ref.)	0.19	179/341	1.00 (ref.)	0.14
T2	182/344	1.06 (0.79, 1.41)		177/344	1.00 (0.75, 1.34)	
T3	208/341	1.21 (0.91, 1.62)		214/341	1.24 (0.93, 1.66)	
Fruits						
T1	193/341	1.00 (ref.)	0.60	208/341	1.00 (ref.)	0.66
T2	178/344	0.99 (0.75, 1.31)		160/344	0.88 (0.67, 1.16)	
T3	199/341	1.07 (0.82, 1.41)		202/341	1.06 (0.81, 1.39)	
Vegetables						
T1	152/341	1.00 (ref.)	0.36	174/341	1.00 (ref.)	0.68
T2	187/344	1.21 (0.91, 1.61)		172/344	1.01 (0.76, 1.34)	
T3	231/341	1.15 (0.85, 1.55)		224/341	1.06 (0.79, 1.43)	
Meat and Mixed Dishes						
T1	184/341	1.00 (ref.)	0.32	190/342	1.00 (ref.)	0.23
T2	191/343	1.06 (0.81, 1.40)		198/342	1.10 (0.84, 1.45)	
T3	195/342	0.87 (0.65, 1.15)		182/342	0.84 (0.63, 1.12)	
Starches and Salty Snacks						
T1	125/342	1.00 (ref.)	**<0.001**	143/341	1.00 (ref.)	**<0.001**
T2	168/343	1.24 (0.91, 1.67)		175/344	1.16 (0.87, 1.56)	
T3	275/341	**1.86 (1.38, 2.52)**		250/341	**1.70 (1.27, 2.29)**	
Breakfast Foods						
T1	231/341	1.00 (ref.)	0.95	227/341	1.00 (ref.)	0.73
T2	142/344	0.89 (0.67, 1.18)		151/343	1.07 (0.80, 1.42)	
T3	197/341	0.99 (0.76, 1.30)		192/342	1.05 (0.80, 1.38)	
Sweets						
T1	190/341	1.00 (ref.)	0.84	202/342	1.00 (ref.)	0.88
T2	179/343	0.89 (0.68, 1.18)		183/342	0.90 (0.68, 1.19)	
T3	201/342	1.03 (0.78, 1.35)		185/342	0.98 (0.74, 1.29)	
Dairy Products, Beverages						
T1	152/341	1.00 (ref.)	0.48	172/341	1.00 (ref.)	0.20

	Standard Multivariable Model			Residual Model		
GI source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
T2	185/344	0.97 (0.72, 1.31)		214/343	0.93 (0.69, 1.25)	
T3	233/341	0.89 (0.65, 1.22)		184/342	0.82 (0.61, 1.11)	

ca/co: cases/control.

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-16. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary glycemic load (GL) from different sources for UADT cancer. (N of lung cancer: 570; controls: 1026)

	Standard Multivariable Model			Residual Model		
GL source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
High Carbohydrates/Sugar						
T1	190/341	1.00 (ref.)	0.97	198/341	1.00 (ref.)	0.96
T2	194/344	1.10 (0.84, 1.45)		187/343	1.07 (0.81, 1.41)	
T3	186/341	1.00 (0.75, 1.35)		185/342	0.99 (0.74, 1.33)	
Fruits						
T1	258/341	1.00 (ref.)	0.79	231/342	1.00 (ref.)	0.95
T2	163/343	0.89 (0.67, 1.17)		175/343	0.85 (0.64, 1.12)	
T3	149/342	0.97 (0.73, 1.30)		164/341	1.02 (0.77, 1.35)	
Vegetables						
T1	245/342	1.00 (ref.)	0.86	214/342	1.00 (ref.)	0.94
T2	163/343	0.87 (0.66, 1.15)		187/343	0.90 (0.68, 1.19)	
T3	162/341	1.04 (0.78, 1.39)		169/341	0.99 (0.74, 1.32)	
Meat and Mixed Dishes						
T1	162/341	1.00 (ref.)	**<0.001**	155/341	1.00 (ref.)	**<0.001**
T2	168/344	1.15 (0.86, 1.55)		175/344	1.22 (0.91, 1.64)	
T3	240/341	**1.86 (1.39, 2.48)**		240/341	**1.71 (1.28, 2.28)**	
Starches and Salty Snacks						
T1	234/342	1.00 (ref.)	0.079	234/341	1.00 (ref.)	0.076
T2	163/342	0.83 (0.63, 1.09)		163/343	0.82 (0.63, 1.08)	
T3	173/342	0.78 (0.59, 1.04)		173/342	0.78 (0.59, 1.03)	
Breakfast Foods						
T1	213/341	1.00 (ref.)	**0.005**	183/341	1.00 (ref.)	**0.004**
T2	170/343	1.07 (0.81, 1.42)		193/344	1.03 (0.77, 1.38)	
T3	187/342	**1.52 (1.14, 2.01)**		194/341	**1.52 (1.14, 2.03)**	
Sweets						
T1	196/341	1.00 (ref.)	0.93	198/342	1.00 (ref.)	0.95
T2	182/344	0.96 (0.73, 1.27)		187/342	1.02 (0.78, 1.35)	
T3	192/341	1.01 (0.77, 1.34)		185/342	0.99 (0.75, 1.31)	
Dairy Products, Beverages						
T1	159/341	1.00 (ref.)	0.35	167/342	1.00 (ref.)	0.65

	Standard Multivariable Model			Residual Model		
GL source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
T2	167/344	0.94 (0.70, 1.25)		165/343	0.93 (0.69, 1.24)	
T3	244/341	0.87 (0.64, 1.17)		238/341	0.93 (0.70, 1.24)	

ca/co: cases/control.

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-17. Adjusted odds ratio (aOR) and 95% confidence interval (CI) of dietary sugar from different sources for UADT cancer. (N of lung cancer: 570; controls: 1026)

	Standard Multivariable Model			Residual Model		
Sugar source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
High Carbohydrates/Sugar						
T1	207/342	1.00 (ref.)	**0.040**	212/342	1.00 (ref.)	**0.014**
T2	155/343	0.91 (0.68, 1.20)		162/342	1.13 (0.85, 1.52)	
T3	208/341	**1.37 (1.03, 1.83)**		196/342	**1.46 (1.08, 1.97)**	
Fruits						
T1	260/342	1.00 (ref.)	0.74	230/342	1.00 (ref.)	0.65
T2	163/342	0.84 (0.64, 1.11)		174/342	0.91 (0.69, 1.21)	
T3	147/342	0.97 (0.72, 1.30)		166/342	1.07 (0.81, 1.42)	
Vegetables						
T1	233/342	1.00 (ref.)	0.62	207/341	1.00 (ref.)	0.80
T2	187/342	1.18 (0.90, 1.55)		201/344	1.06 (0.80, 1.40)	
T3	150/342	1.07 (0.79, 1.44)		162/341	1.04 (0.78, 1.38)	
Meat and Mixed Dishes						
T1	160/342	1.00 (ref.)	**<0.001**	154/342	1.00 (ref.)	**0.001**
T2	150/342	0.99 (0.74, 1.34)		152/342	0.98 (0.73, 1.32)	
T3	260/342	**1.61 (1.22, 2.13)**		264/342	**1.59 (1.20, 2.10)**	
Starches and Salty Snacks						
T1	251/341	1.00 (ref.)	0.069	251/342	1.00 (ref.)	0.14
T2	167/343	0.89 (0.68, 1.17)		169/342	0.95 (0.72, 1.25)	
T3	152/342	0.76 (0.57, 1.02)		150/342	0.80 (0.60, 1.07)	
Breakfast Foods						
T1	204/342	1.00 (ref.)	**<0.001**	175/341	1.00 (ref.)	**0.001**
T2	155/342	0.98 (0.74, 1.30)		175/343	0.86 (0.63, 1.18)	
T3	211/342	**1.68 (1.27, 2.23)**		220/342	**1.58 (1.17, 2.12)**	
Sweets						
T1	202/341	1.00 (ref.)	0.27	203/342	1.00 (ref.)	0.34
T2	198/343	1.00 (0.76, 1.31)		196/342	0.99 (0.75, 1.29)	
T3	170/342	0.85 (0.64, 1.13)		171/342	0.87 (0.66, 1.15)	
Dairy Products, Beverages						
T1	153/342	1.00 (ref.)	0.99	172/341	1.00 (ref.)	0.42
T2	161/342	0.94 (0.70, 1.26)		162/343	0.85 (0.64, 1.13)	

	Standard Multivariable Model			Residual Model		
Sugar source	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**	**ca/co**	**aOR[a] (95% CI)**	**P_{trend}**
T3	256/342	1.00 (0.74, 1.34)		236/342	0.89 (0.67, 1.18)	

ca/co: cases/control.

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-18. aOR and 95% confidence interval (CI) of dietary glycemic index (GI) from different sources for UADT cancer, stratified by smoking status. (Never smoker cases/controls: 179/484; Current/ever smoker cases/controls: 391/541)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GI source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.85 (0.55, 1.34)	0.92 (0.62, 1.36)	0.86 (0.55, 1.34)	0.74 (0.51, 1.06)
T3	0.78 (0.47, 1.29)	0.90 (0.60, 1.35)	0.64 (0.40, 1.03)	1.00 (0.69, 1.45)
P_{trend}	0.32	0.64	0.067	0.99
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.28 (0.80, 2.05)	0.96 (0.66, 1.40)	1.25 (0.78, 2.00)	0.89 (0.61, 1.30)
T3	1.51 (0.93, 2.43)	1.08 (0.74, 1.56)	**1.61 (1.00, 2.60)**	1.07 (0.73, 1.55)
P_{trend}	0.095	0.69	**0.049**	0.71
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.83 (0.54, 1.29)	1.11 (0.77, 1.60)	0.79 (0.51, 1.22)	0.93 (0.65, 1.34)
T3	1.12 (0.72, 1.74)	1.07 (0.75, 1.53)	1.13 (0.73, 1.74)	1.05 (0.74, 1.49)
P_{trend}	0.64	0.71	0.63	0.78
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.36 (0.87, 2.13)	1.11 (0.76, 1.61)	1.33 (0.85, 2.07)	0.83 (0.57, 1.20)
T3	1.31 (0.81, 2.14)	1.08 (0.73, 1.58)	1.29 (0.80, 2.08)	0.96 (0.66, 1.40)
P_{trend}	0.26	0.72	0.29	0.84
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.00 (0.65, 1.54)	1.14 (0.79, 1.64)	1.02 (0.66, 1.57)	1.18 (0.82, 1.69)
T3	0.68 (0.43, 1.07)	0.99 (0.68, 1.43)	0.63 (0.39, 1.00)	0.98 (0.68, 1.42)
P_{trend}	0.11	0.93	0.053	0.92
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.30 (0.81, 2.10)	1.16 (0.78, 1.72)	1.04 (0.64, 1.67)	1.24 (0.85, 1.80)
T3	**1.90 (1.15, 3.13)**	**1.85 (1.26, 2.72)**	**1.73 (1.07, 2.79)**	**1.68 (1.14, 2.47)**

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GI source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
P_{trend}	**0.011**	**0.001**	**0.021**	**0.008**
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.01 (0.63, 1.62)	0.82 (0.56, 1.18)	1.45 (0.90, 2.34)	0.90 (0.63, 1.30)
T3	1.00 (0.64, 1.59)	0.91 (0.64, 1.29)	1.20 (0.75, 1.92)	0.91 (0.64, 1.29)
P_{trend}	0.99	0.54	0.54	0.58
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.79 (0.50, 1.23)	1.04 (0.72, 1.49)	0.85 (0.54, 1.33)	0.99 (0.69, 1.42)
T3	1.07 (0.69, 1.65)	1.03 (0.72, 1.47)	0.98 (0.63, 1.52)	1.01 (0.70, 1.46)
P_{trend}	0.76	0.86	0.93	0.95
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.78 (0.50, 1.21)	1.08 (0.73, 1.62)	0.75 (0.47, 1.19)	0.97 (0.65, 1.45)
T3	0.68 (0.42, 1.13)	1.05 (0.69, 1.58)	0.62 (0.39, 1.00)	0.95 (0.65, 1.38)
P_{trend}	0.13	0.87	0.052	0.78

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes

Table 3-19. aOR and 95% confidence interval (CI) of dietary glycemic load (GL) from different sources for UADT cancer, stratified by smoking status. (Never smoker cases/controls: 179/484; Current/ever smoker cases/controls: 391/541)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GL source	Never smokers	Smokers	Never smokers	Smokers
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.86 (0.53, 1.41)	0.79 (0.52, 1.20)	0.90 (0.57, 1.43)	0.67 (0.46, 0.97)
T3	0.54 (0.25, 1.15)	0.62 (0.35, 1.12)	0.69 (0.43, 1.12)	0.80 (0.55, 1.15)
P_{trend}	0.14	0.11	0.13	0.18
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.03 (0.65, 1.62)	1.17 (0.82, 1.67)	1.06 (0.67, 1.67)	1.11 (0.78, 1.58)
T3	0.96 (0.59, 1.56)	0.98 (0.67, 1.43)	0.98 (0.61, 1.59)	0.95 (0.65, 1.38)
P_{trend}	0.87	0.97	0.94	0.84
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.95 (0.61, 1.50)	0.83 (0.58, 1.17)	0.87 (0.55, 1.36)	0.84 (0.59, 1.20)
T3	0.89 (0.55, 1.44)	1.07 (0.73, 1.56)	0.97 (0.62, 1.51)	1.09 (0.76, 1.57)
P_{trend}	0.63	0.91	0.89	0.72
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.81 (0.51, 1.28)	0.94 (0.66, 1.33)	1.00 (0.64, 1.58)	0.87 (0.61, 1.24)
T3	1.15 (0.73, 1.83)	0.99 (0.68, 1.45)	1.29 (0.82, 2.03)	0.87 (0.59, 1.26)
P_{trend}	0.54	0.95	0.28	0.45
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.29 (0.79, 2.11)	1.08 (0.74, 1.58)	1.02 (0.63, 1.65)	1.35 (0.92, 1.97)
T3	**2.28 (1.41, 3.69)**	**1.70 (1.17, 2.48)**	**2.10 (1.32, 3.34)**	**1.54 (1.06, 2.24)**
P_{trend}	**0.001**	**0.004**	**0.001**	**0.024**
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.99 (0.63, 1.54)	0.76 (0.53, 1.08)	0.98 (0.63, 1.52)	0.76 (0.53, 1.08)
T3	1.01 (0.64, 1.58)	**0.64 (0.44, 0.92)**	1.00 (0.64, 1.57)	**0.64 (0.44, 0.92)**

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GL source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
P_{trend}	0.98	**0.015**	1.00	**0.015**
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.51 (0.92, 2.48)	0.89 (0.63, 1.27)	1.33 (0.80, 2.23)	0.86 (0.60, 1.25)
T3	**2.14 (1.32, 3.47)**	1.25 (0.86, 1.80)	**1.94 (1.21, 3.12)**	1.29 (0.88, 1.88)
P_{trend}	**0.002**	0.31	**0.005**	0.21
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.79 (0.51, 1.24)	1.09 (0.76, 1.57)	0.90 (0.58, 1.40)	1.12 (0.78, 1.60)
T3	1.03 (0.66, 1.61)	1.02 (0.72, 1.46)	0.96 (0.61, 1.51)	1.04 (0.73, 1.48)
P_{trend}	0.89	0.90	0.85	0.84
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.78 (0.50, 1.20)	1.08 (0.73, 1.62)	0.73 (0.47, 1.13)	1.06 (0.71, 1.58)
T3	0.62 (0.38, 1.02)	1.05 (0.71, 1.56)	0.74 (0.46, 1.17)	1.05 (0.73, 1.52)
P_{trend}	0.058	0.82	0.19	0.80

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes

Table 3-20. aOR and 95% confidence interval (CI) of dietary sugar from different sources for UADT cancer, stratified by smoking status. (Never smoker cases/controls: 179/484; Current/ever smoker cases/controls: 391/541)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
Sugar source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	**0.58 (0.36, 0.92)**	0.85 (0.57, 1.25)	0.96 (0.62, 1.51)	1.00 (0.69, 1.44)
T3	**0.40 (0.21, 0.75)**	0.80 (0.50, 1.26)	**0.52 (0.32, 0.85)**	0.81 (0.56, 1.15)
P_{trend}	**0.003**	0.33	**0.008**	0.25
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.07 (0.67, 1.71)	0.82 (0.57, 1.17)	1.36 (0.83, 2.21)	1.04 (0.71, 1.51)
T3	1.56 (0.98, 2.49)	1.26 (0.87, 1.83)	1.55 (0.95, 2.54)	1.42 (0.96, 2.09)
P_{trend}	0.059	0.30	0.085	0.088
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.67 (0.42, 1.07)	0.99 (0.70, 1.41)	1.00 (0.63, 1.59)	0.91 (0.64, 1.29)
T3	0.99 (0.62, 1.57)	0.93 (0.63, 1.37)	1.09 (0.69, 1.71)	1.09 (0.75, 1.57)
P_{trend}	0.99	0.72	0.70	0.72
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.10 (0.71, 1.72)	1.28 (0.90, 1.84)	1.11 (0.71, 1.73)	1.05 (0.74, 1.51)
T3	1.12 (0.69, 1.81)	1.10 (0.74, 1.62)	1.06 (0.67, 1.67)	1.08 (0.74, 1.57)
P_{trend}	0.64	0.57	0.79	0.67
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.17 (0.73, 1.87)	0.89 (0.60, 1.31)	0.99 (0.61, 1.59)	0.99 (0.67, 1.47)
T3	**1.83 (1.14, 2.91)**	**1.53 (1.07, 2.19)**	**1.75 (1.11, 2.77)**	**1.54 (1.08, 2.21)**
P_{trend}	**0.009**	**0.012**	**0.011**	**0.011**
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.15 (0.74, 1.79)	0.78 (0.55, 1.12)	1.50 (0.96, 2.35)	0.74 (0.52, 1.06)
T3	1.25 (0.79, 2.00)	**0.57 (0.39, 0.83)**	1.45 (0.89, 2.35)	**0.57 (0.39, 0.83)**

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
Sugar source	**Never smokers**	**Smokers**	**Never smokers**	**Smokers**
P_{trend}	0.34	**0.004**	0.13	**0.003**
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.07 (0.65, 1.76)	0.91 (0.64, 1.31)	1.33 (0.78, 2.26)	0.64 (0.43, 0.96)
T3	**2.48 (1.55, 3.98)**	1.31 (0.91, 1.88)	**2.99 (1.83, 4.86)**	1.04 (0.70, 1.53)
P_{trend}	**<0.001**	0.17	**<0.001**	0.68
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.97 (0.63, 1.50)	1.03 (0.72, 1.46)	0.97 (0.63, 1.49)	1.00 (0.71, 1.42)
T3	0.84 (0.53, 1.32)	0.85 (0.59, 1.23)	0.81 (0.52, 1.27)	0.91 (0.63, 1.31)
P_{trend}	0.45	0.40	0.37	0.61
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.78 (0.50, 1.21)	1.08 (0.72, 1.62)	0.67 (0.43, 1.03)	0.99 (0.67, 1.45)
T3	0.69 (0.42, 1.12)	1.21 (0.83, 1.77)	0.68 (0.43, 1.07)	1.01 (0.70, 1.46)
P_{trend}	0.13	0.31	0.088	0.95

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 3-21. aOR and 95% confidence interval (CI) of dietary glycemic index (GI) from different sources for UADT cancer, stratified by drinking status. (Never drinker cases/controls: 112/255; Drinker cases/controls: 456/771)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GI source	Never drinkers	Drinks	Never drinkers	Drinks
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.66 (0.34, 1.29)	0.95 (0.69, 1.33)	1.24 (0.64, 2.42)	0.72 (0.52, 0.99)
T3	0.63 (0.32, 1.25)	0.93 (0.65, 1.33)	0.95 (0.49, 1.83)	0.87 (0.62, 1.20)
P_{trend}	0.22	0.71	0.75	0.35
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.56 (0.83, 2.94)	0.96 (0.69, 1.33)	1.56 (0.83, 2.95)	0.90 (0.64, 1.25)
T3	1.77 (0.90, 3.49)	1.12 (0.81, 1.56)	1.85 (0.94, 3.64)	1.14 (0.82, 1.58)
P_{trend}	0.092	0.47	0.070	0.40
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.05 (0.57, 1.96)	0.97 (0.71, 1.32)	0.97 (0.52, 1.82)	0.85 (0.62, 1.16)
T3	1.58 (0.87, 2.88)	0.97 (0.71, 1.32)	1.56 (0.86, 2.83)	0.96 (0.70, 1.31)
P_{trend}	0.13	0.84	0.13	0.78
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.07 (0.55, 2.10)	1.24 (0.90, 1.70)	1.00 (0.51, 1.97)	1.02 (0.75, 1.40)
T3	1.24 (0.64, 2.41)	1.10 (0.78, 1.55)	1.12 (0.58, 2.15)	1.04 (0.74, 1.45)
P_{trend}	0.51	0.55	0.71	0.84
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.88 (0.47, 1.62)	1.14 (0.83, 1.56)	1.14 (0.62, 2.11)	1.12 (0.82, 1.53)
T3	0.74 (0.41, 1.33)	0.91 (0.66, 1.27)	0.76 (0.42, 1.38)	0.88 (0.63, 1.22)
P_{trend}	0.31	0.58	0.37	0.43
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.94 (0.46, 1.91)	1.31 (0.94, 1.83)	0.70 (0.34, 1.42)	1.32 (0.95, 1.82)
T3	1.29 (0.66, 2.54)	**2.05 (1.46, 2.88)**	1.08 (0.57, 2.06)	**1.91 (1.36, 2.68)**

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GI source	**Never drinkers**	**Drinks**	**Never drinkers**	**Drinks**
P_{trend}	0.37	**<0.001**	0.61	**<0.001**
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.99 (0.53, 1.85)	0.86 (0.63, 1.19)	1.72 (0.92, 3.22)	0.95 (0.69, 1.32)
T3	0.93 (0.52, 1.65)	1.02 (0.74, 1.39)	0.99 (0.55, 1.80)	1.07 (0.79, 1.47)
P_{trend}	0.79	0.93	0.94	0.66
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.61 (0.32, 1.15)	1.00 (0.73, 1.37)	0.60 (0.32, 1.13)	1.01 (0.74, 1.39)
T3	0.93 (0.52, 1.65)	1.05 (0.77, 1.43)	0.91 (0.51, 1.64)	0.99 (0.72, 1.37)
P_{trend}	0.83	0.76	0.75	0.96
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.56 (0.30, 1.06)	1.11 (0.79, 1.56)	0.49 (0.26, 0.94)	1.08 (0.77, 1.52)
T3	0.53 (0.27, 1.05)	1.02 (0.71, 1.45)	0.46 (0.24, 0.87)	0.95 (0.68, 1.33)
P_{trend}	0.079	0.98	0.019	0.76

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes

Table 3-22. aOR and 95% confidence interval (CI) of dietary glycemic load (GL) from different sources for UADT cancer, stratified by drinking status. (Never drinker cases/controls: 112/255; Drinker cases/controls: 456/771)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GL source	**Never drinkers**	**Drinks**	**Never drinkers**	**Drinks**
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.60 (0.30, 1.18)	0.88 (0.61, 1.25)	0.76 (0.38, 1.54)	0.79 (0.57, 1.08)
T3	0.44 (0.16, 1.19)	0.62 (0.37, 1.05)	0.79 (0.42, 1.50)	0.75 (0.54, 1.04)
P_{trend}	0.092	0.086	0.53	0.074
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.00 (0.52, 1.93)	1.15 (0.84, 1.56)	1.22 (0.64, 2.32)	1.06 (0.78, 1.44)
T3	0.94 (0.48, 1.84)	1.01 (0.73, 1.41)	0.90 (0.46, 1.75)	1.02 (0.74, 1.42)
P_{trend}	0.84	0.88	0.68	0.87
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.20 (0.66, 2.17)	0.82 (0.60, 1.11)	0.59 (0.32, 1.11)	0.92 (0.67, 1.26)
T3	1.22 (0.65, 2.30)	0.92 (0.66, 1.28)	1.09 (0.60, 1.99)	1.00 (0.73, 1.37)
P_{trend}	0.53	0.53	0.78	0.97
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.64 (0.34, 1.19)	0.94 (0.69, 1.28)	0.89 (0.47, 1.67)	0.90 (0.66, 1.23)
T3	1.19 (0.65, 2.21)	1.02 (0.73, 1.42)	1.37 (0.74, 2.54)	0.92 (0.66, 1.28)
P_{trend}	0.65	0.93	0.33	0.61
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.85 (0.44, 1.64)	1.26 (0.90, 1.77)	1.21 (0.64, 2.26)	1.23 (0.88, 1.72)
T3	**2.54 (1.36, 4.73)**	**1.76 (1.26, 2.46)**	**2.67 (1.43, 4.98)**	**1.54 (1.11, 2.14)**
P_{trend}	**0.003**	**0.001**	**0.002**	**0.010**
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.15 (0.63, 2.12)	0.77 (0.57, 1.05)	1.15 (0.63, 2.12)	0.77 (0.56, 1.04)
T3	0.84 (0.46, 1.56)	0.76 (0.55, 1.04)	0.84 (0.46, 1.56)	0.75 (0.55, 1.04)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
GL source	**Never drinkers**	**Drinks**	**Never drinkers**	**Drinks**
P_{trend}	0.60	0.074	0.60	0.071
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.38 (0.74, 2.57)	1.00 (0.73, 1.38)	1.20 (0.63, 2.31)	1.00 (0.71, 1.40)
T3	1.46 (0.80, 2.65)	**1.57 (1.13, 2.17)**	1.26 (0.70, 2.29)	**1.64 (1.17, 2.29)**
P_{trend}	0.22	**0.008**	0.45	**0.003**
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.80 (0.44, 1.44)	1.02 (0.74, 1.39)	0.71 (0.40, 1.28)	1.14 (0.83, 1.56)
T3	1.12 (0.61, 2.05)	1.01 (0.74, 1.38)	0.98 (0.53, 1.80)	1.02 (0.74, 1.40)
P_{trend}	0.76	0.96	0.87	0.91
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.57 (0.31, 1.05)	1.13 (0.81, 1.58)	0.42 (0.22, 0.80)	1.16 (0.83, 1.62)
T3	**0.49 (0.26, 0.93)**	1.04 (0.74, 1.47)	0.57 (0.31, 1.04)	1.09 (0.78, 1.50)
P_{trend}	**0.025**	0.86	0.066	0.66

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes

Table 3-23. aOR and 95% confidence interval (CI) of dietary sugar from different sources for UADT cancer, stratified by drinking status. (Never drinker cases/controls: 112/255; Drinker cases/controls: 456/771)

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
Sugar source	**Never drinkers**	**Drinks**	**Never drinkers**	**Drinks**
Total				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.43 (0.22, 0.86)	0.80 (0.58, 1.12)	0.67 (0.34, 1.29)	1.13 (0.82, 1.55)
T3	0.49 (0.22, 1.08)	0.66 (0.44, 1.00)	0.57 (0.31, 1.08)	0.72 (0.52, 0.99)
P_{trend}	0.067	0.050	0.094	0.060
High Carbohydrates/ Sugar				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.98 (0.52, 1.85)	0.90 (0.66, 1.24)	1.22 (0.62, 2.40)	1.14 (0.82, 1.58)
T3	1.41 (0.76, 2.62)	1.38 (0.99, 1.92)	1.72 (0.89, 3.33)	1.41 (1.00, 1.99)
P_{trend}	0.27	0.075	0.10	0.051
Fruits				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.90 (0.49, 1.63)	0.82 (0.60, 1.12)	1.29 (0.69, 2.39)	0.84 (0.62, 1.15)
T3	0.96 (0.51, 1.81)	0.96 (0.69, 1.34)	1.33 (0.72, 2.48)	1.01 (0.74, 1.40)
P_{trend}	0.89	0.73	0.37	1.00
Vegetables				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.84 (1.02, 3.30)	1.03 (0.75, 1.41)	1.87 (1.03, 3.40)	0.91 (0.66, 1.25)
T3	1.29 (0.67, 2.51)	1.02 (0.73, 1.44)	1.05 (0.56, 1.98)	1.02 (0.74, 1.42)
P_{trend}	0.35	0.89	0.73	0.89
Meat and Mixed Dishes				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.71 (0.37, 1.36)	1.09 (0.77, 1.53)	0.70 (0.37, 1.34)	1.08 (0.76, 1.52)
T3	**2.01 (1.10, 3.66)**	**1.54 (1.12, 2.13)**	**1.95 (1.08, 3.52)**	**1.53 (1.11, 2.11)**
P_{trend}	**0.020**	**0.006**	**0.026**	**0.006**
Starches and Salty Snacks				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.05 (0.57, 1.94)	0.86 (0.63, 1.16)	1.46 (0.79, 2.69)	0.85 (0.63, 1.17)
T3	1.18 (0.63, 2.20)	**0.67 (0.48, 0.93)**	1.45 (0.76, 2.76)	**0.68 (0.49, 0.94)**

	aOR[a] (95% CI)			
	Standard Multivariable Model		Residual Model	
Sugar source	**Never drinkers**	**Drinks**	**Never drinkers**	**Drinks**
P_{trend}	0.61	**0.017**	0.24	**0.021**
Breakfast Foods				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	1.18 (0.61, 2.27)	0.91 (0.66, 1.26)	0.91 (0.45, 1.85)	0.85 (0.60, 1.20)
T3	**1.93 (1.06, 3.50)**	**1.62 (1.17, 2.23)**	1.72 (0.92, 3.20)	**1.55 (1.10, 2.17)**
P_{trend}	**0.029**	**0.004**	0.062	**0.005**
Sweets				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.81 (0.45, 1.45)	1.08 (0.79, 1.47)	0.90 (0.50, 1.60)	1.03 (0.75, 1.40)
T3	0.94 (0.51, 1.74)	0.84 (0.61, 1.15)	0.95 (0.51, 1.79)	0.86 (0.63, 1.18)
P_{trend}	0.80	0.28	0.86	0.36
Dairy Products, Beverages				
T1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
T2	0.66 (0.35, 1.25)	1.06 (0.76, 1.49)	0.53 (0.29, 0.99)	0.98 (0.71, 1.36)
T3	0.54 (0.29, 1.03)	1.18 (0.85, 1.65)	0.43 (0.23, 0.79)	1.10 (0.80, 1.52)
P_{trend}	0.067	0.32	0.007	0.53

a. Adjusted for age, sex, race/ethnicity, education, energy intake, BMI, number of alcoholic drinks per day, pack-years smoking, diabetes.

Table 4-1. Associations between SNP's and susceptibility of lung and UADT cancers compared to controls in LA study

Gene	SNP	Genotype/ Model	Lung Cancer			UADT Cancer		
			ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]
Total			550/949			489/949		
EGFR	rs2072454	T:T	134/245	1.00 (ref.)	1.00 (ref.)	130/245	1.00 (ref.)	1.00 (ref.)
		C:T	261/465	1.07 (0.78, 1.47)	1.03 (0.77, 1.39)	237/465	0.99 (0.75, 1.33)	0.92 (0.70, 1.20)
		C:C	138/218	1.13 (0.79, 1.63)	1.09 (0.77, 1.54)	100/218	0.83 (0.59, 1.18)	0.78 (0.56, 1.08)
		Log-Additive		1.06 (0.89, 1.28)	1.06 (0.89, 1.27)		0.92 (0.77, 1.09)	0.92 (0.77, 1.09)
		Dominant		1.09 (0.81, 1.47)	1.09 (0.81, 1.45)		0.94 (0.72, 1.24)	0.94 (0.72, 1.22)
		Recessive		1.08 (0.80, 1.46)	1.08 (0.81, 1.45)		0.84 (0.63, 1.12)	0.84 (0.63, 1.12)
	rs2227983	G:G	290/479	1.00 (ref.)	1.00 (ref.)	239/479	1.00 (ref.)	1.00 (ref.)
		A:G	198/386	0.83 (0.62, 1.10)	0.83 (0.63, 1.09)	182/386	0.96 (0.74, 1.25)	0.90 (0.70, 1.16)
		A:A	47/66	1.32 (0.80, 2.16)	1.27 (0.80, 2.02)	41/66	1.56 (0.98, 2.47)	1.39 (0.90, 2.15)
		Log-Additive		1.00 (0.81, 1.24)	1.00 (0.81, 1.23)		1.12 (0.92, 1.36)	1.11 (0.91, 1.34)
		Dominant		0.89 (0.68, 1.17)	0.89 (0.69, 1.17)		1.04 (0.81, 1.33)	1.03 (0.80, 1.31)
		Recessive		1.45 (0.90, 2.33)	1.38 (0.88, 2.17)		**1.59 (1.02, 2.48)**	1.50 (0.98, 2.29)
	rs10277413	T:T	212/352	1.00 (ref.)	1.00 (ref.)	179/352	1.00 (ref.)	1.00 (ref.)
		G:T	256/473	0.91 (0.69, 1.21)	0.92 (0.70, 1.20)	221/473	1.06 (0.81, 1.38)	0.99 (0.77, 1.28)
		G:G	67/100	1.20 (0.78, 1.84)	1.19 (0.79, 1.78)	67/100	**1.59 (1.07, 2.35)**	**1.46 (1.01, 2.12)**
		Log-Additive		1.04 (0.85, 1.27)	1.03 (0.85, 1.26)		1.20 (1.00, 1.45)	1.19 (0.99, 1.43)
		Dominant		0.96 (0.73, 1.25)	0.96 (0.74, 1.25)		1.15 (0.89, 1.48)	1.13 (0.88, 1.45)
		Recessive		1.26 (0.85, 1.88)	1.24 (0.85, 1.82)		**1.54 (1.07, 2.20)**	**1.49 (1.05, 2.11)**
	rs1050171	A:A	164/280	1.00 (ref.)	1.00 (ref.)	150/280	1.00 (ref.)	1.00 (ref.)
		A:G	233/469	0.78 (0.57, 1.05)	0.78 (0.58, 1.04)	212/469	0.79 (0.60, 1.05)	0.75 (0.58, 0.98)

Gene	SNP	Genotype/ Model	Lung Cancer			UADT Cancer		
			ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]
		G:G	139/179	1.14 (0.78, 1.65)	1.14 (0.80, 1.61)	104/179	0.89 (0.62, 1.27)	0.86 (0.61, 1.20)
		Log-Additive		1.04 (0.86, 1.26)	1.04 (0.86, 1.25)		0.92 (0.77, 1.10)	0.92 (0.77, 1.10)
		Dominant		0.87 (0.65, 1.16)	0.87 (0.66, 1.15)		0.82 (0.63, 1.07)	0.82 (0.63, 1.06)
		Recessive		1.34 (0.97, 1.84)	1.32 (0.97, 1.80)		1.03 (0.75, 1.40)	1.03 (0.76, 1.39)
	rs2293347	G:G	432/711	1.00 (ref.)	1.00 (ref.)	369/711	1.00 (ref.)	1.00 (ref.)
		A:G	97/202	0.78 (0.56, 1.08)	0.81 (0.59, 1.11)	91/202	**0.73 (0.54, 0.99)**	0.75 (0.56, 1.01)
		A:A	12/15	1.48 (0.59, 3.73)	1.35 (0.62, 2.91)	10/15	1.04 (0.43, 2.51)	1.03 (0.49, 2.16)
		Log-Additive		0.89 (0.67, 1.18)	0.90 (0.68, 1.18)		0.81 (0.62, 1.05)	0.82 (0.63, 1.06)
		Dominant		0.82 (0.60, 1.13)	0.83 (0.61, 1.13)		0.75 (0.56, 1.01)	0.77 (0.58, 1.03)
		Recessive		1.60 (0.64, 3.99)	1.38 (0.64, 2.99)		1.14 (0.48, 2.72)	1.10 (0.52, 2.30)
GFPT1	rs13751	C:C	224/337	1.00 (ref.)	1.00 (ref.)	154/337	1.00 (ref.)	1.00 (ref.)
		C:T	211/430	0.73 (0.55, 0.98)	0.74 (0.56, 0.98)	238/430	1.20 (0.91, 1.57)	1.13 (0.87, 1.46)
		T:T	100/162	1.01 (0.70, 1.48)	1.02 (0.71, 1.45)	77/162	0.99 (0.69, 1.44)	0.95 (0.67, 1.35)
		Log-Additive		0.96 (0.80, 1.15)	0.96 (0.80, 1.15)		1.03 (0.86, 1.23)	1.03 (0.87, 1.23)
		Dominant		0.80 (0.61, 1.06)	0.81 (0.62, 1.06)		1.14 (0.88, 1.48)	1.14 (0.88, 1.47)
		Recessive		1.21 (0.87, 1.69)	1.19 (0.86, 1.65)		0.89 (0.64, 1.24)	0.90 (0.66, 1.24)
	rs7568296	T:T	234/346	1.00 (ref.)	1.00 (ref.)	157/346	1.00 (ref.)	1.00 (ref.)
		C:T	203/422	**0.73 (0.54, 0.98)**	**0.73 (0.55, 0.97)**	233/422	1.20 (0.92, 1.58)	1.11 (0.86, 1.44)
		C:C	97/163	0.98 (0.67, 1.43)	0.97 (0.68, 1.39)	76/163	0.99 (0.68, 1.43)	0.93 (0.65, 1.31)
		Log-Additive		0.94 (0.78, 1.14)	0.94 (0.78, 1.13)		1.03 (0.86, 1.23)	1.03 (0.87, 1.23)
		Dominant		0.80 (0.60, 1.05)	0.80 (0.61, 1.05)		1.15 (0.88, 1.49)	1.14 (0.89, 1.48)
		Recessive		1.17 (0.83, 1.64)	1.15 (0.83, 1.60)		0.88 (0.63, 1.23)	0.90 (0.65, 1.23)
	rs2667	T:T	217/328	1.00 (ref.)	1.00 (ref.)	153/328	1.00 (ref.)	1.00 (ref.)

Gene	SNP	Genotype/ Model	Lung Cancer			UADT Cancer		
			ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]
		G:T	229/444	0.78 (0.59, 1.05)	0.81 (0.62, 1.08)	244/444	1.15 (0.88, 1.51)	1.07 (0.83, 1.38)
		G:G	95/160	0.95 (0.65, 1.39)	0.99 (0.69, 1.42)	71/160	0.89 (0.61, 1.30)	0.85 (0.59, 1.21)
		Log-Additive		0.94 (0.78, 1.13)	0.94 (0.78, 1.13)		0.98 (0.82, 1.17)	0.99 (0.83, 1.18)
		Dominant		0.83 (0.63, 1.08)	0.83 (0.64, 1.09)		1.09 (0.84, 1.41)	1.09 (0.84, 1.40)
		Recessive		1.10 (0.78, 1.54)	1.09 (0.78, 1.51)		0.82 (0.58, 1.15)	0.84 (0.60, 1.16)
PDK1	rs2290563	A:A	257/464	1.00 (ref.)	1.00 (ref.)	219/464	1.00 (ref.)	1.00 (ref.)
		A:T	188/349	0.85 (0.63, 1.15)	0.84 (0.63, 1.12)	184/349	0.99 (0.76, 1.30)	0.93 (0.72, 1.20)
		T:T	86/113	0.81 (0.53, 1.25)	0.81 (0.54, 1.21)	61/113	0.77 (0.50, 1.18)	0.73 (0.49, 1.09)
		Log-Additive		0.89 (0.73, 1.09)	0.89 (0.73, 1.09)		0.91 (0.75, 1.11)	0.91 (0.75, 1.10)
		Dominant		0.84 (0.64, 1.12)	0.85 (0.65, 1.12)		0.95 (0.73, 1.23)	0.94 (0.73, 1.22)
		Recessive		0.89 (0.60, 1.32)	0.89 (0.61, 1.31)		0.78 (0.52, 1.15)	0.79 (0.54, 1.16)
	rs6433368	C:C	260/468	1.00 (ref.)	1.00 (ref.)	226/468	1.00 (ref.)	1.00 (ref.)
		C:T	209/370	0.88 (0.66, 1.18)	0.91 (0.69, 1.20)	187/370	0.93 (0.71, 1.21)	0.90 (0.70, 1.16)
		T:T	70/92	0.77 (0.49, 1.21)	0.82 (0.54, 1.25)	55/92	0.82 (0.53, 1.28)	0.81 (0.54, 1.23)
		Log-Additive		0.88 (0.71, 1.08)	0.88 (0.72, 1.08)		0.91 (0.75, 1.11)	0.91 (0.75, 1.11)
		Dominant		0.86 (0.65, 1.13)	0.86 (0.66, 1.14)		0.91 (0.70, 1.18)	0.91 (0.70, 1.17)
		Recessive		0.83 (0.54, 1.26)	0.84 (0.56, 1.25)		0.86 (0.57, 1.30)	0.87 (0.58, 1.29)
PGM1	rs855314	T:T	396/710	1.00 (ref.)	1.00 (ref.)	368/710	1.00 (ref.)	1.00 (ref.)
		C:T	136/210	1.15 (0.84, 1.56)	1.14 (0.85, 1.54)	96/210	0.99 (0.73, 1.33)	0.96 (0.72, 1.28)
		C:C	11/16	1.21 (0.44, 3.33)	1.13 (0.50, 2.57)	7/16	1.20 (0.47, 3.04)	1.11 (0.51, 2.40)
		Log-Additive		1.13 (0.86, 1.49)	1.13 (0.86, 1.47)		1.02 (0.78, 1.32)	1.01 (0.78, 1.31)
		Dominant		1.15 (0.85, 1.55)	1.14 (0.85, 1.53)		1.00 (0.75, 1.34)	1.00 (0.75, 1.33)
		Recessive		1.16 (0.42, 3.20)	1.10 (0.48, 2.50)		1.20 (0.48, 3.04)	1.13 (0.52, 2.46)

Gene	SNP	Genotype/ Model	Lung Cancer			UADT Cancer		
			ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]
ENO1	rs7534552	A:A	207/331	1.00 (ref.)	1.00 (ref.)	176/331	1.00 (ref.)	1.00 (ref.)
		A:G	230/417	1.02 (0.76, 1.37)	1.05 (0.79, 1.39)	200/417	0.95 (0.72, 1.25)	0.89 (0.69, 1.16)
		G:G	99/176	0.84 (0.57, 1.23)	0.87 (0.61, 1.26)	85/176	0.82 (0.57, 1.18)	0.79 (0.56, 1.10)
		Log-Additive		0.93 (0.77, 1.12)	0.93 (0.77, 1.12)		0.91 (0.77, 1.09)	0.91 (0.77, 1.08)
		Dominant		0.97 (0.73, 1.28)	0.97 (0.74, 1.27)		0.91 (0.71, 1.18)	0.91 (0.71, 1.17)
		Recessive		0.83 (0.58, 1.17)	0.83 (0.60, 1.16)		0.85 (0.61, 1.17)	0.85 (0.62, 1.16)
RAP1A	rs6573	C:C	403/695	1.00 (ref.)	1.00 (ref.)	353/695	1.00 (ref.)	1.00 (ref.)
		A:C	122/214	1.01 (0.74, 1.39)	1.02 (0.75, 1.38)	106/214	1.00 (0.75, 1.34)	0.97 (0.73, 1.29)
		A:A	13/24	1.18 (0.52, 2.67)	1.14 (0.56, 2.29)	10/24	0.82 (0.35, 1.91)	0.85 (0.42, 1.73)
		Log-Additive		1.04 (0.80, 1.35)	1.04 (0.80, 1.35)		0.97 (0.76, 1.24)	0.97 (0.76, 1.23)
		Dominant		1.03 (0.76, 1.40)	1.03 (0.77, 1.39)		0.98 (0.74, 1.31)	0.98 (0.74, 1.29)
		Recessive		1.18 (0.52, 2.65)	1.13 (0.56, 2.28)		0.82 (0.36, 1.90)	0.86 (0.42, 1.76)
ITGB1	rs2298141	A:A	373/626	1.00 (ref.)	1.00 (ref.)	320/626	1.00 (ref.)	1.00 (ref.)
		A:G	142/278	1.01 (0.76, 1.35)	1.01 (0.76, 1.33)	133/278	0.89 (0.68, 1.17)	0.86 (0.66, 1.13)
		G:G	23/29	1.57 (0.81, 3.05)	1.45 (0.80, 2.64)	14/29	0.80 (0.39, 1.64)	0.82 (0.44, 1.54)
		Log-Additive		1.11 (0.88, 1.40)	1.10 (0.88, 1.39)		0.89 (0.71, 1.12)	0.89 (0.71, 1.11)
		Dominant		1.07 (0.81, 1.41)	1.07 (0.81, 1.40)		0.88 (0.68, 1.14)	0.88 (0.68, 1.14)
		Recessive		1.57 (0.81, 3.02)	1.44 (0.80, 2.62)		0.83 (0.41, 1.69)	0.86 (0.46, 1.62)

ca/co, cases/controls; aOR, adjusted odds ratio; sbOR, semi-Bayes adjusted odds ratio; CI, confident interval; PI, posterior interval

a. Adjusted for age, sex, race/ethnicity, education, number of alcoholic drinks per day, pack-years smoking

Table 4-2. Associations between selected SNPs and histological subtypes of lung and UADT cancers

Gene/SNP	Genotype/ Model	Lung squamous cell carcinoma			Lung adenocarcinoma			UADT squamous cell carcinoma		
		ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]
EGFR	G:G	48/479	1.00 (ref.)	1.00 (ref.)	135/479	1.00 (ref.)	1.00 (ref.)	208/479	1.00 (ref.)	1.00 (ref.)
rs2227983	A:G	31/386	1.05 (0.56, 1.94)	0.97 (0.57, 1.66)	101/386	0.91 (0.64, 1.27)	0.92 (0.67, 1.28)	152/386	0.92 (0.70, 1.22)	0.87 (0.67, 1.13)
	A:A	5/66	2.19 (0.71, 6.78)	1.53 (0.63, 3.72)	26/66	1.52 (0.86, 2.69)	1.45 (0.86, 2.46)	36/66	1.56 (0.96, 2.52)	1.39 (0.89, 2.18)
	Log-Additive		1.26 (0.77, 2.06)	1.22 (0.77, 1.95)		1.09 (0.85, 1.41)	1.09 (0.85, 1.39)		1.10 (0.89, 1.35)	1.09 (0.89, 1.34)
	Dominant		1.14 (0.63, 2.07)	1.12 (0.64, 1.93)		0.98 (0.71, 1.36)	0.98 (0.72, 1.35)		1.00 (0.77, 1.31)	1.00 (0.77, 1.29)
	Recessive		2.14 (0.73, 6.29)	1.58 (0.65, 3.84)		1.60 (0.93, 2.75)	1.49 (0.90, 2.48)		**1.62 (1.02, 2.58)**	1.52 (0.98, 2.36)
EGFR	T:T	40/352	1.00 (ref.)	1.00 (ref.)	96/352	1.00 (ref.)	1.00 (ref.)	156/352	1.00 (ref.)	1.00 (ref.)
rs10277413	G:T	36/473	0.79 (0.44, 1.43)	0.81 (0.48, 1.37)	126/473	0.97 (0.69, 1.36)	0.99 (0.72, 1.37)	184/473	1.01 (0.76, 1.33)	0.95 (0.73, 1.24)
	G:G	9/100	1.34 (0.52, 3.44)	1.24 (0.57, 2.68)	40/100	1.57 (0.96, 2.56)	1.55 (0.98, 2.46)	61/100	**1.67 (1.11, 2.51)**	**1.53 (1.04, 2.24)**
	Log-Additive		1.01 (0.65, 1.58)	1.01 (0.66, 1.54)		1.17 (0.93, 1.49)	1.17 (0.93, 1.48)		**1.21 (1.00, 1.47)**	1.20 (0.99, 1.46)
	Dominant		0.86 (0.49, 1.52)	0.88 (0.52, 1.49)		1.06 (0.77, 1.47)	1.06 (0.77, 1.45)		1.12 (0.86, 1.46)	1.10 (0.85, 1.43)
	Recessive		1.54 (0.64, 3.71)	1.35 (0.64, 2.89)		**1.60 (1.03, 2.50)**	**1.53 (1.00, 2.35)**		**1.66 (1.15, 2.41)**	**1.60 (1.12, 2.30)**
EGFR	G:G	68/711	1.00 (ref.)	1.00 (ref.)	205/711	1.00 (ref.)	1.00 (ref.)	320/711	1.00 (ref.)	1.00 (ref.)
rs2293347	A:G	14/202	0.86 (0.42, 1.74)	0.86 (0.46, 1.59)	52/202	0.88 (0.60, 1.29)	0.92 (0.63, 1.32)	73/202	0.69 (0.49, 0.96)	0.71 (0.52, 0.97)
	A:A	3/15	**8.05 (1.82, 35.58)**	2.30 (0.74, 7.14)	7/15	1.73 (0.61, 4.91)	1.45 (0.62, 3.39)	10/15	1.26 (0.52, 3.02)	1.18 (0.56, 2.47)
	Log-Additive		1.31 (0.72, 2.37)	1.25 (0.72, 2.17)		1.00 (0.71, 1.39)	1.00 (0.72, 1.38)		0.81 (0.61, 1.07)	0.82 (0.62, 1.08)
	Dominant		1.05 (0.54, 2.04)	1.04 (0.57, 1.89)		0.93 (0.64, 1.35)	0.93 (0.65, 1.34)		0.73 (0.53, 1.00)	0.75 (0.55, 1.02)
	Recessive		8.42 (1.93, 36.71)	2.37 (0.76, 7.41)		1.80 (0.64, 5.08)	1.45 (0.62, 3.39)		1.39 (0.58, 3.32)	1.27 (0.60, 2.66)
GFPT1	T:T	39/346	1.00 (ref.)	1.00 (ref.)	114/346	1.00 (ref.)	1.00 (ref.)	137/346	1.00 (ref.)	1.00 (ref.)
rs7568296	C:T	32/422	0.89 (0.47, 1.68)	0.82 (0.48, 1.41)	101/422	0.74 (0.52, 1.06)	0.78 (0.56, 1.08)	194/422	1.16 (0.87, 1.55)	1.06 (0.81, 1.39)
	C:C	12/163	1.11 (0.48, 2.60)	0.99 (0.49, 1.98)	47/163	0.96 (0.62, 1.50)	1.00 (0.66, 1.52)	68/163	1.04 (0.71, 1.53)	0.96 (0.67, 1.38)
	Log-Additive		1.02 (0.67, 1.55)	1.02 (0.68, 1.52)		0.94 (0.75, 1.17)	0.94 (0.75, 1.17)		1.04 (0.87, 1.25)	1.05 (0.87, 1.26)

Gene/SNP	Genotype/ Model	Lung squamous cell carcinoma			Lung adenocarcinoma			UADT squamous cell carcinoma		
		ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]	ca/co	aOR (95% CI)[a]	sbOR (95% PI)[a]
	Dominant		0.94 (0.52, 1.71)	0.95 (0.55, 1.64)		0.80 (0.58, 1.11)	0.81 (0.59, 1.11)		1.13 (0.86, 1.49)	1.13 (0.86, 1.48)
	Recessive		1.19 (0.55, 2.57)	1.14 (0.58, 2.24)		1.14 (0.76, 1.70)	1.12 (0.76, 1.65)		0.95 (0.67, 1.34)	0.96 (0.69, 1.34)

ca/co, cases/controls; aOR, adjusted odds ratio; sbOR, semi-Bayes adjusted odds ratio; CI, confident interval; PI, posterior interval

a. Adjusted for age, sex, race/ethnicity, education, number of alcoholic drinks per day, pack-years smoking

Table 4-3. Joint associations between selected SNPs, glycemic index, glycemic load, smoking status and drinking status on lung and UADT cancers.

	Lung cancer			UADT cancer		
	aOR[a]	**RERI**[a]	**ROR**[a]	**aOR**[a]	**RERI**[a]	**ROR**[a]
Glycemic Intake						
GI high and rs10277413 GT+ TT	1.31 (0.98, 1.76)	-0.26 (-1.45, 0.94)	0.79 (0.35, 1.81)	0.95 (0.72, 1.26)	-0.19 (-1.3, 0.92)	0.9 (0.44, 1.86)
GI low and rs10277413 GG	1.44 (0.75, 2.75)			**1.69 (1.00, 2.87)**		
GI high and rs10277413 GG	1.50 (0.88, 2.56)			1.46 (0.88, 2.42)		
GI high and rs2227983 AG+GG	**1.33 (1.00, 1.77)**	-0.61 (-2.35, 1.14)	0.64 (0.24, 1.71)	1.00 (0.76, 1.31)	-1.49 (-3.32, 0.34)	0.43 (0.18, 1.06)
GI low and rs2227983 AA	1.92 (0.89, 4.11)			**2.62 (1.37, 5.02)**		
GI high and rs2227983 AA	1.64 (0.87, 3.10)			1.13 (0.60, 2.13)		
GI high and rs2293347 AG	1.20 (0.66, 2.18)	0.17 (-0.55, 0.89)	1.09 (0.56, 2.12)	0.78 (0.45, 1.37)	0.2 (-0.35, 0.75)	1.26 (0.68, 2.34)
GI low and rs2293347 GG	1.19 (0.72, 1.98)			1.19 (0.75, 1.87)		
GI high and rs2293347 GG	1.56 (0.94, 2.57)			1.17 (0.74, 1.85)		
GI high and rs7568296 CT	1.48 (0.96, 2.27)	0.05 (-0.82, 0.92)	0.92 (0.51, 1.68)	1.02 (0.70, 1.47)	-0.14 (-0.66, 0.38)	0.84 (0.49, 1.47)
GI low and rs7568296 CC	1.44 (0.91, 2.27)			0.88 (0.59, 1.30)		
GI high and rs7568296 CC	**1.96 (1.27, 3.02)**			0.75 (0.50, 1.14)		
Glycemic Load						
GL high and rs10277413 GT+ TT	1.02 (0.76, 1.37)	0.77 (-0.3, 1.84)	1.81 (0.8, 4.08)	0.90 (0.68, 1.19)	-0.16 (-1.21, 0.9)	0.94 (0.45, 1.94)
GL low and rs10277413 GG	0.94 (0.52, 1.70)			**1.64 (1.01, 2.68)**		
GL high and rs10277413 GG	1.73 (0.98, 3.06)			1.39 (0.81, 2.39)		
GL high and rs2227983 AG+GG	1.08 (0.81, 1.44)	0.61 (-0.82, 2.04)	1.47 (0.55, 3.92)	0.91 (0.69, 1.19)	-0.54 (-1.99, 0.91)	0.74 (0.3, 1.81)
GL low and rs2227983 AA	1.18 (0.55, 2.52)			**1.94 (1.03, 3.66)**		
GL high and rs2227983 AA	1.87 (0.98, 3.56)			1.31 (0.69, 2.48)		
GL high and rs2293347 AG	0.97 (0.54, 1.75)	0.12 (-0.53, 0.77)	1.11 (0.58, 2.12)	1.10 (0.63, 1.93)	-0.28 (-1.05, 0.49)	0.8 (0.43, 1.48)

	Lung cancer			UADT cancer		
	aOR[a]	**RERI**[a]	**ROR**[a]	**aOR**[a]	**RERI**[a]	**ROR**[a]
GL low and rs2293347 GG	1.18 (0.75, 1.87)			1.51 (0.96, 2.36)		
GL high and rs2293347 GG	1.27 (0.81, 2.02)			1.33 (0.84, 2.09)		
GL high and rs7568296 CT	1.23 (0.80, 1.88)	0.05 (-0.74, 0.84)	0.98 (0.54, 1.75)	0.94 (0.65, 1.35)	-0.1 (-0.59, 0.4)	0.87 (0.5, 1.52)
GL low and rs7568296 CC	1.40 (0.91, 2.15)			0.86 (0.59, 1.26)		
GL high and rs7568296 CC	**1.68 (1.09, 2.59)**			0.70 (0.46, 1.06)		
Smoking Status						
Ever smokers and rs10277413 GT+ TT	**3.74 (2.74, 5.10)**	1.16 (-0.96, 3.28)	1.42 (0.61, 3.31)	**1.39 (1.05, 1.85)**	0.4 (-0.8, 1.6)	1.13 (0.55, 2.32)
Never smokers and rs10277413 GG	0.90 (0.44, 1.86)			1.39 (0.80, 2.43)		
Ever smokers and rs10277413 GG	**4.80 (2.96, 7.81)**			**2.19 (1.36, 3.54)**		
Ever smokers and rs2227983 AG+GG	3.80 (2.79, 5.16)	1.9 (-1.38, 5.18)	1.38 (0.55, 3.48)	**1.35 (1.02, 1.77)**	0.55 (-1.02, 2.12)	1.23 (0.51, 2.94)
Never smokers and rs2227983 AA	1.11 (0.53, 2.34)			1.37 (0.73, 2.59)		
Ever smokers and rs2227983 AA	**5.81 (3.19, 10.58)**			**2.27 (1.22, 4.21)**		
Ever smokers and rs2293347 AG	**2.22 (1.23, 4.00)**	**1.48 (0.53, 2.44)**	**2.02 (1.04, 3.93)**	1.18 (0.67, 2.07)	0.28 (-0.35, 0.91)	1.18 (0.63, 2.21)
Never smokers and rs2293347 GG	0.77 (0.44, 1.37)			1.16 (0.70, 1.93)		
Ever smokers and rs2293347 GG	**3.47 (2.04, 5.93)**			1.61 (0.97, 2.67)		
Ever smokers and rs7568296 CT	**4.21 (2.64, 6.73)**	1.31 (-0.36, 2.99)	1.02 (0.54, 1.9)	1.32 (0.91, 1.92)	-0.01 (-0.56, 0.55)	1.06 (0.61, 1.84)
Never smokers and rs7568296 CC	1.38 (0.80, 2.40)			0.78 (0.51, 1.21)		
Ever smokers and rs7568296 CC	**5.90 (3.66, 9.52)**			1.10 (0.73, 1.65)		
Drinking Status						
Ever drinkers and rs10277413 GT+ TT	**1.49 (1.06, 2.08)**	-0.56 (-1.81, 0.69)	0.64 (0.26, 1.56)	0.90 (0.64, 1.27)	0.28 (-0.92, 1.48)	1.25 (0.55, 2.86)
Never drinkers and rs10277413 GG	1.44 (0.90, 2.29)			1.40 (0.93, 2.11)		
Ever drinkers and rs10277413 GG	1.36 (0.64, 2.89)			1.58 (0.80, 3.13)		
Ever drinkers and rs2227983 AG+GG	1.38 (0.99, 1.92)	-0.08 (-1.76, 1.59)	0.87 (0.32, 2.33)	0.92 (0.66, 1.28)	-0.08 (-1.46, 1.31)	0.98 (0.37, 2.62)

	Lung cancer			UADT cancer		
	aOR[a]	**RERI**[a]	**ROR**[a]	**aOR**[a]	**RERI**[a]	**ROR**[a]
Never drinkers and rs2227983 AA	1.53 (0.86, 2.72)			1.56 (0.93, 2.61)		
Ever drinkers and rs2227983 AA	1.82 (0.81, 4.08)			1.40 (0.62, 3.18)		
Ever drinkers and rs2293347 AG	1.66 (0.88, 3.13)	-0.14 (-1.24, 0.96)	0.84 (0.42, 1.68)	1.10 (0.57, 2.12)	-0.21 (-1.07, 0.65)	0.84 (0.41, 1.74)
Never drinkers and rs2293347 GG	1.34 (0.91, 1.97)			**1.46 (1.03, 2.06)**		
Ever drinkers and rs2293347 GG	**1.86 (1.18, 2.95)**			1.35 (0.87, 2.10)		
Ever drinkers and rs7568296 CT[b]	1.00 (0.61, 1.63)	0.95 (-0.02, 1.91)	1.81 (0.94, 3.48)	1.34 (0.81, 2.21)	-0.78 (-1.62, 0.07)	**0.51 (0.26, 0.98)**
Never drinkers and rs7568296 CC[b]	1.16 (0.83, 1.64)			**1.36 (1.00, 1.85)**		
Ever drinkers and rs7568296 CC[b]	**2.11 (1.31, 3.39)**			0.92 (0.57, 1.49)		

aOR, adjusted odds ratio; RERI, relative excess risk due to interaction; ROR, ratio of odds ratios

a. Adjusted for age, sex, race/ethnicity, education, number of alcoholic drinks per day(when not included in interaction term), pack-years smoking (when not included in interaction term); for GI and GL, additional adjusted for BMI, energy intake and diabetes.

b. SNP coding was reverse for UADT cancer. (Ever drinkers and rs7568296 CC, Never drinkers and rs7568296 CT, Ever drinkers and rs7568296 CT)

Table 5-1. Distribution of cases of oral and pharyngeal cancer combined, laryngeal cancer and controls according to selected variables. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	HNC cases (%)	OPC cases (%)	LC cases (%)	Controls (%)
Total	4058 (100.0)	2727 (100.0)	1331 (100.0)	7345 (100.0)
Age				
<40	151 (3.7)	129 (4.7)	22 (1.7)	459 (6.2)
>=40to<=44	196 (4.8)	150 (5.5)	46 (3.5)	429 (5.8)
>=45to<=49	471 (11.6)	362 (13.3)	109 (8.2)	715 (9.7)
>=50to<=54	665 (16.4)	497 (18.2)	168 (12.6)	1195 (16.3)
>=55to<=59	815 (20.1)	560 (20.5)	255 (19.2)	1322 (18.0)
>=60to<=64	638 (15.7)	396 (14.5)	242 (18.2)	1077 (14.7)
>=65to<=69	564 (13.9)	334 (12.2)	230 (17.3)	1014 (13.8)
>=70to<=74	388 (9.6)	203 (7.4)	185 (13.9)	839 (11.4)
>=75	170 (4.2)	96 (3.5)	74 (5.6)	293 (4.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Sex				
Female	867 (21.4)	672 (24.6)	195 (14.7)	2358 (32.1)
Male	3186 (78.5)	2051 (75.2)	1135 (85.3)	4982 (67.8)
Missing	5 (0.1)	4 (0.1)	1 (0.1)	5 (0.1)
Race				
Black	335 (8.3)	217 (8.0)	118 (8.9)	340 (4.6)
Others (with Asians)	76 (1.9)	61 (2.2)	15 (1.1)	107 (1.5)
White (with Hispanics)	3630 (89.5)	2437 (89.4)	1193 (89.6)	6855 (93.3)
Missing	17 (0.4)	12 (0.4)	5 (0.4)	43 (0.6)
Study center				
Boston	359 (8.8)	295 (10.8)	64 (4.8)	611 (8.3)
Italy Multicenter				
Milan	193 (4.8)	169 (6.2)	24 (1.8)	621 (8.5)
Pordenone	880 (21.7)	444 (16.3)	436 (32.8)	1528 (20.8)
Latina	95 (2.3)	95 (3.5)	0 (0.0)	425 (5.8)
Los Angeles	400 (9.9)	317 (11.6)	83 (6.2)	1018 (13.9)
MSKCC	106 (2.6)	74 (2.7)	32 (2.4)	123 (1.7)

Milan (2006-2009)	331 (8.2)	128 (4.7)	203 (15.3)	691 (9.4)
North Carolina (2002-2006)	1061 (26.1)	687 (25.2)	374 (28.1)	1120 (15.2)
Seattle (1985-1995)	176 (4.3)	176 (6.5)	0 (0.0)	394 (5.4)
Switzerland	457 (11.3)	342 (12.5)	115 (8.6)	814 (11.1)
Education				
No education	14 (0.3)	9 (0.3)	5 (0.4)	20 (0.3)
<= Junior high school	1387 (34.2)	794 (29.1)	593 (44.6)	2601 (35.4)
Some high school	664 (16.4)	451 (16.5)	213 (16.0)	781 (10.6)
High school graduate	654 (16.1)	461 (16.9)	193 (14.5)	902 (12.3)
Technical school, some college	744 (18.3)	542 (19.9)	202 (15.2)	1494 (20.3)
>= college graduate	588 (14.5)	465 (17.1)	123 (9.2)	1543 (21.0)
Missing	7 (0.2)	5 (0.2)	2 (0.2)	4 (0.1)
Cigarette smoking status				
Never	575 (14.2)	495 (18.2)	81 (6.1)	3079 (41.9)
Former	1735 (42.8)	1053 (38.6)	682 (51.2)	3052 (41.6)
Current	1732 (42.7)	1172 (43.0)	560 (42.1)	1188 (16.2)
Missing	16 (0.4)	7 (0.3)	8 (0.6)	26 (0.4)
Cigarette smoking intensity (number of cigarettes/day)				
Never smoker	576 (14.2)	495 (18.2)	81 (6.1)	3079 (41.9)
>0to<=10	459 (11.3)	321 (11.8)	138 (10.4)	1362 (18.5)
>10to<=20	1482 (36.5)	924 (33.9)	558 (41.9)	1775 (24.2)
>20	1497 (36.9)	957 (35.1)	540 (40.6)	1061 (14.4)
Missing	44 (1.1)	30 (1.1)	14 (1.1)	68 (0.9)
Cigarette smoking duration (years)				
Never smoker	576 (14.2)	495 (18.2)	81 (6.1)	3079 (41.9)
>0to<=20	404 (10.0)	318 (11.7)	86 (6.5)	1411 (19.2)
>20	3066 (75.6)	1906 (69.9)	1160 (87.2)	2837 (38.6)
Missing	12 (0.3)	8 (0.3)	4 (0.3)	18 (0.2)
Cigar smoking status				
Never cigar user	3706 (91.3)	2495 (91.5)	1211 (91.0)	6918 (94.2)
Ever smoked ≥100 cigars in a lifetime	330 (8.1)	217 (8.0)	113 (8.5)	402 (5.5)
Missing	22 (0.5)	15 (0.6)	7 (0.5)	25 (0.3)
Pipe smoking status				
Never pipe user	3724 (91.8)	2497 (91.6)	1227 (92.2)	6812 (92.7)
Ever smoked≥100 pipes in a lifetime	311 (7.7)	220 (8.1)	91 (6.8)	504 (6.9)
Missing	23 (0.6)	10 (0.4)	13 (1.0)	29 (0.4)

Alcohol drinking intensity (number of drinks/day)				
Never drinker	392 (9.7)	277 (10.2)	115 (8.6)	1703 (23.2)
<1	736 (18.1)	537 (19.7)	199 (15.0)	2319 (31.6)
>=1 to 3	817 (20.1)	534 (19.6)	283 (21.3)	1880 (25.6)
>=3 to 5	596 (14.7)	385 (14.1)	211 (15.9)	791 (10.8)
>=5	1517 (37.4)	994 (36.5)	523 (39.3)	652 (8.9)

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center, HNC: Head and Neck cancer; OPC: Oral and pharyngeal cancer; LC: Laryngeal cancer.

Table 5-2. Descriptive statistic on raw value of glycemic index and glycemic load across studies and in all the studies combined. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

Study Center	20%	Median	Mean	80%
Glycemic Index				
Total	70.34	76.19	76.68	82.05
Boston	78.76	83.03	82.63	86.48
Italy Multicenter				
Milan	69.39	74.52	74.04	78.87
Pordenone	69.85	74.90	74.48	79.71
Latina	71.28	76.08	75.68	80.34
Los Angeles	71.12	77.97	77.47	84.40
MSKCC	75.99	80.73	80.61	85.48
Milan (2006-2009)	74.04	78.69	78.11	82.44
North Carolina (2002-2006)	68.57	73.05	73.02	77.61
Seattle (1985-1995)	76.42	80.62	80.86	85.79
Switzerland	64.87	73.73	80.07	82.11
Glycemic Load				
Total	129.22	190.87	204.48	267.79
Boston	154.41	224.26	238.44	310.08
Italy Multicenter				
Milan	136.89	192.22	199.25	254.97
Pordenone	163.19	219.55	232.81	294.71
Latina	151.97	211.12	223.11	272.19
Los Angeles	106.41	168.04	196.76	275.47
MSKCC	92.49	143.58	151.84	195.66
Milan (2006-2009)	158.59	204.29	215.35	266.72
North Carolina (2002-2006)	115.23	168.01	178.82	238.79
Seattle (1985-1995)	112.99	171.56	186.27	244.32
Switzerland	95.43	160.50	182.12	242.56

ABBREVIATIONS: MSKCC: Memorial Sloan Kettering Cancer Center

Table 5-3. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of glycemic index and glycemic load on head and neck cancer, oral and pharyngeal cancer, and laryngeal cancer. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	Head and Neck Cancer			Oral and pharyngeal cancer			Laryngeal cancer		
	ca/co	**OR (95% CI)[c]**	**$P_{studies}$[d]**	**ca/co**	**OR (95% CI)[c]**	**$P_{studies}$[d]**	**ca/co**	**OR (95% CI)[c]**	**$P_{studies}$[d]**
Glycemic Index									
10 units increased		1.02 (0.97, 1.07)	0.60		0.97 (0.92, 1.03)	0.60		**1.10 (1.02, 1.18)**	0.213
I Quintile[b]	859/1469	1 (Reference)	0.38	629/1469	1 (Reference)	0.62	230/1469	1 (Reference)	0.166
II Quintile[b]	839/1469	1.07 (0.92, 1.25)		540/1469	0.97 (0.82, 1.14)		299/1469	**1.31 (1.04, 1.65)**	
III Quintile[b]	715/1469	0.97 (0.82, 1.13)		462/1469	**0.83 (0.70, 0.99)**		253/1469	1.18 (0.93, 1.50)	
IV Quintile[b]	719/1469	1.04 (0.89, 1.22)		454/1469	0.87 (0.73, 1.04)		265/1469	**1.33 (1.04, 1.69)**	
V Quintile[b]	926/1469	**1.22 (1.04, 1.44)**		642/1469	1.01 (0.84, 1.21)		284/1469	**1.72 (1.33, 2.21)**	
$P_{for\ linear\ trend}$		0.058			0.63			**<0.001**	
Glycemic Load									
100 units increased		0.96 (0.88, 1.05)	**0.06**		**0.89 (0.81, 0.99)**	0.89		1.07 (0.95, 1.22)	0.537
I Quintile[b]	948/1469	1 (Reference)	**0.013**	647/1469	1 (Reference)	**0.013**	301/1469	1 (Reference)	**0.019**
II Quintile[b]	707/1469	0.89 (0.76, 1.04)		480/1469	0.83 (0.70, 0.99)		227/1469	0.96 (0.76, 1.22)	
III Quintile[b]	687/1469	0.92 (0.79, 1.08)		472/1469	0.90 (0.75, 1.07)		215/1469	0.90 (0.70, 1.14)	
IV Quintile[b]	681/1469	0.86 (0.73, 1.01)		444/1469	**0.81 (0.67, 0.97)**		237/1469	0.93 (0.73, 1.19)	
V Quintile[b]	1035/1469	0.91 (0.77, 1.06)		684/1469	**0.80 (0.67, 0.96)**		351/1469	1.07 (0.85, 1.35)	
$P_{for\ linear\ trend}$		0.22			**0.020**			0.65	

	Head and Neck Cancer			Oral and pharyngeal cancer			Laryngeal cancer		
	ca/co	OR (95% CI)[c]	$P_{studies}$[d]	ca/co	OR (95% CI)[c]	$P_{studies}$[d]	ca/co	OR (95% CI)[c]	$P_{studies}$[d]

a. Estimated from multiple logistic regression models adjusted for age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity (number of drinks per day), and the product (interaction) term for cigarette intensity and alcohol drinking. b. The cut-offs for the quintile categories of glycemic index were: -6.27, -2.19, 1.28 and 5.12, respectively, and that of glycemic load were: -40.35, -16.25, 5.49 and 34.16, respectively. c. Based on likelihood ratio test, we reported the fixed-effects estimates for the GI intakes ($P_{studies} > 0.1$); and we reported the mixed-effects estimates for the GL intakes ($P_{studies} < 0.1$). d. P for heterogeneity between studies.

Table 5-4. Adjusted odds ratios (ORs)[a, b] and 95% confidence intervals (CIs) of glycemic index and glycemic load on head and neck cancer, in strata of each study center. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	OR (95% CI)				
	II Quintile	**III Quintile**	**IV Quintile**	**V Quintile**	**P_{trend}**
Glycemic Index					
Boston	0.76 (0.20, 2.89)	0.55 (0.16, 1.82)	0.44 (0.14, 1.38)	0.53 (0.17, 1.61)	0.39
Italy Multicenter					
Milan	1.25 (0.64, 2.44)	1.10 (0.57, 2.15)	1.36 (0.64, 2.90)	1.47 (0.46, 4.72)	0.46
Pordenone	**1.41 (1.03, 1.93)**	1.22 (0.88, 1.68)	1.09 (0.78, 1.52)	**1.70 (1.13, 2.54)**	0.17
Latina	1.22 (0.51, 2.92)	0.63 (0.26, 1.56)	0.91 (0.37, 2.26)	0.61 (0.20, 1.88)	0.25
Los Angeles	0.96 (0.57, 1.61)	0.66 (0.39, 1.13)	0.97 (0.59, 1.60)	0.87 (0.54, 1.40)	0.70
MSKCC	0.08 (0.00, 1.81)	0.27 (0.01, 5.29)	0.26 (0.01, 4.99)	0.24 (0.01, 4.18)	0.65
Milan (2006-2009)	**0.46 (0.23, 0.93)**	0.88 (0.47, 1.64)	1.12 (0.62, 2.03)	1.27 (0.69, 2.32)	**0.007**
North Carolina (2002-2006)	1.02 (0.78, 1.33)	0.95 (0.70, 1.29)	1.07 (0.75, 1.55)	1.32 (0.83, 2.10)	0.43
Seattle (1985-1995)	1.57 (0.26, 9.29)	1.89 (0.35, 10.21)	2.87 (0.56, 14.85)	3.32 (0.66, 16.71)	**0.011**
Switzerland	**2.24 (1.23, 4.06)**	1.30 (0.65, 2.63)	1.28 (0.62, 2.65)	**2.14 (1.16, 3.96)**	0.071
Glycemic Load					
Boston	0.91 (0.27, 3.07)	1.29 (0.42, 4.04)	0.99 (0.33, 3.02)	0.86 (0.29, 2.55)	0.30
Italy Multicenter					
Milan	1.46 (0.62, 3.44)	0.81 (0.35, 1.87)	1.04 (0.45, 2.43)	1.26 (0.52, 3.06)	0.99
Pordenone	0.87 (0.61, 1.23)	0.93 (0.66, 1.32)	0.88 (0.62, 1.25)	1.18 (0.84, 1.64)	0.32
Latina	0.85 (0.33, 2.15)	0.46 (0.17, 1.21)	0.59 (0.24, 1.44)	0.62 (0.25, 1.56)	0.22
Los Angeles	1.13 (0.68, 1.90)	1.18 (0.70, 2.01)	1.20 (0.70, 2.08)	0.87 (0.50, 1.51)	0.63
MSKCC	**0.03 (0.00, 0.32)**	**0.07 (0.01, 0.52)**	**0.07 (0.01, 0.51)**	0.22 (0.03, 1.50)	0.68
Milan (2006-2009)	0.96 (0.39, 2.39)	0.98 (0.42, 2.32)	0.90 (0.39, 2.07)	1.05 (0.46, 2.42)	0.87

North Carolina (2002-2006)	0.82 (0.62, 1.08)	1.04 (0.76, 1.44)	0.92 (0.63, 1.36)	0.62 (0.40, 0.97)	0.17
Seattle (1985-1995)	0.72 (0.36, 1.45)	0.87 (0.45, 1.67)	0.45 (0.22, 0.92)	0.96 (0.46, 1.99)	0.40
Switzerland	1.13 (0.65, 1.95)	1.37 (0.71, 2.66)	1.57 (0.68, 3.60)	1.21 (0.66, 2.24)	0.33

a. Estimated from multiple logistic regression models adjusted for age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity (number of drinks per day), and the product (interaction) term for cigarette intensity and alcohol drinking.
b. The cut-offs for the quintile categories of glycemic index were: -6.27, -2.19, 1.28 and 5.12, respectively, and that of glycemic load were: -40.35, -16.25, 5.49 and 34.16, respectively.

Table 5-5. Adjusted odds ratios (ORs)[a, b] and 95% confidence intervals (CIs) of glycemic index and glycemic load on head and neck cancer, in strata of selected covariates. International Head and Neck Cancer Epidemiology (INHANCE) consortium.

	OR (95% CI)				
	II Quintile	**III Quintile**	**IV Quintile**	**V Quintile**	**$P_{studies}$[c]**
Glycemic Index					
Age					
<55	1.13 (0.87, 1.47)	1.12 (0.86, 1.47)	1.06 (0.81, 1.39)	**1.45 (1.10, 1.90)**	0.69
≥55	1.06 (0.87, 1.28)	0.91 (0.74, 1.11)	1.08 (0.88, 1.32)	1.13 (0.91, 1.39)	0.29
Sex					
Female	0.96 (0.69, 1.34)	0.95 (0.67, 1.35)	1.11 (0.77, 1.59)	1.34 (0.93, 1.95)	**0.089**
Male	1.07 (0.90, 1.27)	0.93 (0.78, 1.12)	1.00 (0.83, 1.20)	1.15 (0.95, 1.38)	0.12
Tobacco smoking status					
Never	0.72 (0.50, 1.04)	0.89 (0.62, 1.28)	1.17 (0.81, 1.69)	0.75 (0.51, 1.13)	0.62
Former	1.19 (0.97, 1.48)	0.97 (0.78, 1.21)	1.02 (0.82, 1.28)	**1.47 (1.16, 1.86)**	0.27
Current	1.05 (0.79, 1.39)	1.03 (0.76, 1.39)	0.97 (0.72, 1.31)	1.27 (0.94, 1.71)	0.40
Alcohol drinking intensity					
Never/light	1.09 (0.87, 1.37)	1.06 (0.84, 1.34)	0.91 (0.71, 1.17)	1.17 (0.91, 1.49)	0.83
Moderate	1.18 (0.93, 1.49)	0.97 (0.76, 1.25)	1.16 (0.90, 1.48)	**1.35 (1.05, 1.75)**	0.45
Heavy	1.04 (0.76, 1.43)	1.04 (0.75, 1.44)	1.00 (0.71, 1.40)	1.34 (0.94, 1.93)	0.43
Glycemic Load					
Age					
<55	0.90 (0.70, 1.17)	0.94 (0.72, 1.23)	0.82 (0.63, 1.08)	0.95 (0.73, 1.24)	0.89
≥55	0.89 (0.73, 1.09)	0.92 (0.76, 1.13)	0.90 (0.73, 1.11)	0.90 (0.74, 1.10)	**0.027**
Sex					
Female	0.99 (0.70, 1.40)	1.10 (0.78, 1.56)	1.02 (0.70, 1.48)	0.85 (0.56, 1.30)	0.45
Male	0.85 (0.71, 1.01)	0.85 (0.71, 1.02)	**0.78 (0.65, 0.94)**	0.86 (0.73, 1.03)	**0.059**
Tobacco smoking status					
Never	0.87 (0.60, 1.26)	0.97 (0.67, 1.41)	0.88 (0.59, 1.31)	0.81 (0.53, 1.23)	0.93
Former	0.90 (0.72, 1.13)	0.91 (0.73, 1.14)	0.77 (0.61, 0.97)	0.97 (0.78, 1.20)	0.35
Current	0.84 (0.64, 1.11)	0.92 (0.69, 1.23)	1.05 (0.77, 1.41)	0.90 (0.68, 1.20)	**0.008**
Alcohol drinking intensity					
Never/light	1.00 (0.81, 1.24)	0.99 (0.78, 1.24)	0.86 (0.67, 1.10)	0.96 (0.74, 1.24)	0.29
Moderate	1.03 (0.80, 1.31)	0.93 (0.73, 1.19)	0.85 (0.66, 1.10)	1.02 (0.79, 1.32)	0.18
Heavy	**0.57 (0.39, 0.83)**	0.91 (0.62, 1.34)	**0.68 (0.48, 0.98)**	0.72 (0.53, 1.00)	0.20

a. Adjusted for age, sex, race, study center, education, cigarette smoking status, cigarette smoking intensity (number of cigarettes per day), cigarette smoking duration, cigar smoking status, pipe smoking status, alcohol drinking intensity (number of drinks per day), and the product (interaction) term for cigarette intensity and alcohol drinking, when appropriate. b. The I Quintile category was considered as the reference one. c. P for heterogeneity between studies. When the p-value was less than 0.1 within strata, we reported mixed-effects estimates derived from the corresponding generalized linear mixed model.

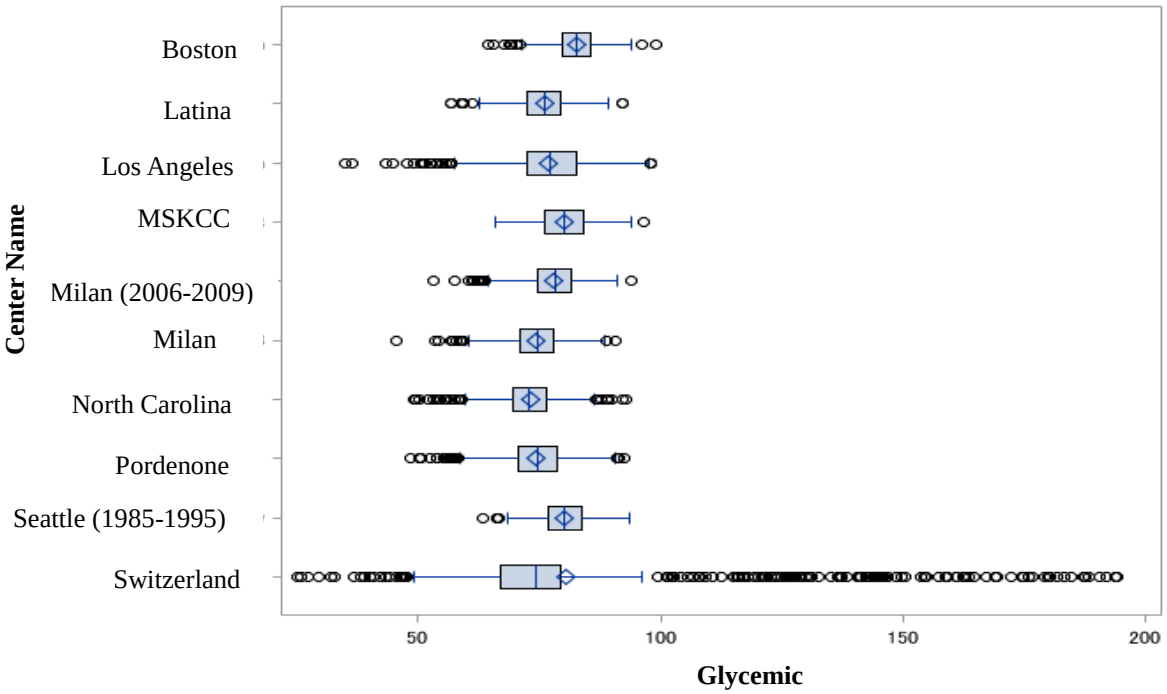

Figure 5-1. Distribution of glycemic index among controls in each study from the International Head and Neck Cancer Epidemiology (INHANCE) consortium.

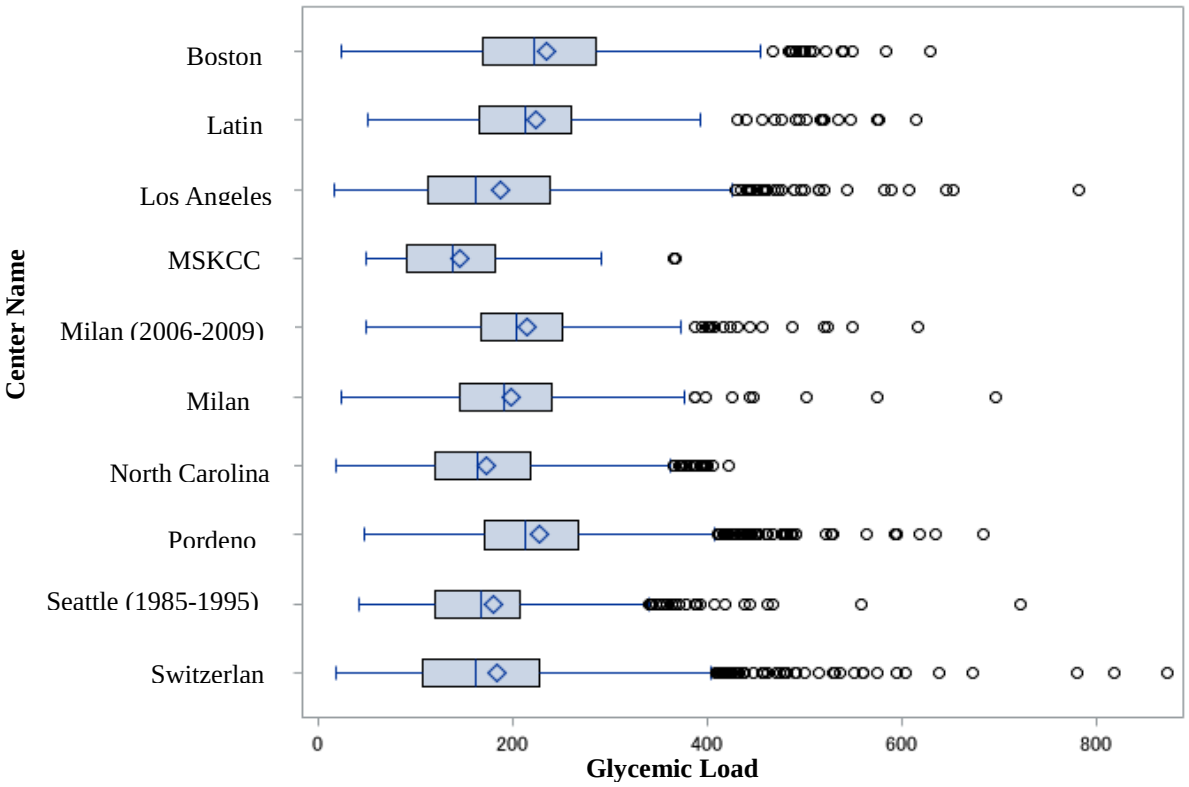

Figure 5-2. Distribution of glycemic load among controls in each study from the International Head and Neck Cancer Epidemiology (INHANCE) consortium.

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