BMC Cancer

RESEARCH

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Combined effect of areca nut, cigarettes, alcohol and SNPs in glycosyltransferase family genes on lung cancer development in Hainan, China

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Abstract

Background Abnormal glycosylation modification is closely related to the development and metastasis of cancers. As a carcinogen by the International Agency for Research on Cancer (IARC) of the WHO, areca nut lacked of combined effect' study with genetic factors related to lung cancer. The aim of this study was to investigate the combined effect of polymorphisms of glycosyltransferase family genes and behavioral factors on the susceptibility of lung cancer.

Methods A case–control study was conducted in Hainan, which included 428 patients with lung cancer and 428 cancer-free controls. Six single-nucleotide polymorphisms (SNPs) (FUT2 rs1047781, rs601338, FUT3 rs28362459, rs3745635, ST6Gal-I rs2239611 and MGAT5 rs34944508) were detected by the MassARRAY System. The association between these SNPs and the risk of lung cancer, clinicopathological characteristics, and combined effect of behavioral factors (areca nuts, cigarettes, alcohol) and genotypes on lung cancer were estimated using by logistic regression analysis.

Results In this study, individuals with AA genotype in ST6Gal-I rs2239611 significantly increased lung cancer risk ($OR_{adj}=2.077$; 95%CI:1.191–3.624; $P_{adj}=0.010$), particularly in smokers ($P_{adj}=0.038$) and alcohol consumers ($P_{adj}=0.049$). FUT2 rs1047781 was associated with clinical stage ($P_{adj}=0.047$) and lymph node metastasis ($P_{adj}=0.014$). Significant gene-environment interactions were observed between behavioral factors (cigarette smoking, alcohol drinking, and betel quid chewing) and both FUT2 rs1047781 ($P_{adj}=0.013$) and ST6Gal-I rs2239611 ($P_{adj}=0.047$), collectively elevating lung cancer risk.

Conclusion ST6Gal-I rs2239611 was a potential genetic biomarker for lung cancer. Areca nut chewing, cigarette smoking, alcohol drinking interacts with glycosyltransferase gene polymorphisms (FUT2 rs1047781 and ST6Gal-I rs2239611), increasing lung cancer risk—a novel finding given the lack of prior studies on this combination.

Keywords Lung cancer, Single-nucleotide polymorphisms, Areca nut, Cigarettes, Alcohol, ST6Gal-I, FUTs, MGAT5

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Introduction

Lung cancer is the leading cause of cancer death in the world. According to global data in 2022, lung cancer accounted for 12.4% and 18.7% of the total cancer incidence and death [1]. The National Cancer Center (NCC) of China regularly reported the latest data that the estimated number of cases and deaths of lung cancer was about 1,060,600 and 733,300 in 2022 [2]. Lung cancer has often been diagnosed at advanced stages, leading to diminished patient survival due to poor response to therapies, high treatment costs, drug resistance, and the lack of specific biological biomarkers for early detection [3]. Thus, identifying specific lung cancer biomarkers is crucial for personalized prevention and mechanistic biology.

Glycosylation modification of protein plays an important biological role in cell recognition and adhesion, receptor activation, signal transmission and other processes [4]. Glycosyltransferases, classified into subfamilies like salivary acyltransferases, fucosyltransferases, and N-acetylglucosamine transferases, form unique glycosidic bonds by acting on specific substrates [5]. Abnormal glycosylation modification is a common feature of the occurrence, development and metastasis of malignant tumors [6]. β-galactoside: α2-6-sialyltransferase (ST6Gal-I), fucosyltransferases (FUTs), β1, 6-N-acetylglucosaminyltransferase V (MGAT5) are the members of salivary acyltransferase family, fucosyltransferase family, N-acetylglucosamine transferase family, respectively [7–9]. ST6Gal-I played a critical role in angiogenesis [10], and highly expressed in colon cancer [11] and ovarian cancer tissues [12], which could mediate the migration and invasion of tumor cells. FUT2 and FUT3 were essential for ABO blood group determination and disease susceptibility [13]. The expression changes of FUT2 and FUT3 were related to the low survival rate of patients with non-small cell lung cancer (NSCLC) [14]. The amount of MGAT5 polysaccharide products in malignant tumors usually increased and was associated with disease progression [15, 16]. MGAT5 had been shown to reshape the tumor microenvironment and accelerate tumor cell growth by promoting the breakdown of extracellular matrix and enhancing the release of glycosyltransferase bound cytokines [17]. Several studies have proposed that single-nucleotide polymorphisms (SNPs) of glycosyltransferase family genes are associated with lung cancer, the ST6Gal-I rs2239611 [18], MGAT5 rs34944508 [19] have been identified as potential genetic markers indicative of susceptibility to lung cancer. However, there was a critical gap in previous research that systematically investigated the combined effects of glycosyltransferase gene variants and behavioral risk factors on lung cancer susceptibility.

Areca nut, derived from the seeds of the tropical palm tree. Areca catechu was extensively chewed and consumed by approximately 600 million individuals globally, particularly in South Asia, Southeast Asia, and the Asia Pacific region [20]. Areca nuts were cultivated primarily in the eastern, central, and southern regions of Hainan, and areca nut chewing was commonly observed among the native population in Hainan [21]. Arecoline released by long-term chewing betel nut had strong cytotoxicity [22], which can induce oral submucosal fibrosis, cardiovascular diseases, hypertension, kidney damage and even cause cancer [23, 24]. Areca nuts were also listed as Class I human carcinogens by the International Agency for Research on Cancer (IARC) in 2003 [25]. Prior studies had shown that long-term exposure to areca nut could increase the risk of cancer in the oral cavity, esophagus, and other locations [26, 27]. A global systematic review based on 62 studies concluded that consumption of areca nut affects almost all organs of the human body, including lungs [28]. After treating human alveolar basal epithelial cells (A549 cells) with areca nuts extract aqueous solution for 48 h, the toxic nature of areca nut induced the cell vitality decreased, the production of reactive oxygen species and G1/S phase cell cycle arrest [29]. Relevant research regarding the the relationship between chewing areca nut and lung cancer is limited. Smoking tobacco and drinking alcohol had been generally regarded as the important factors causing lung cancer [30].

In this case–control study, we investigated the potential interaction between areca nut, cigarettes, alcohol and SNPs in glycosyltransferase family genes on lung cancer development, and provided a previously unexplored dimension in cancer genetic susceptibility.

Materials and methods

Study subjects

In our study, a 1:1 matched case–control study method was adopted. The selected subjects were 428 newly diagnosed lung cancer patients in the Hainan General Hospital and the First Affiliated Hospital of Hainan Medical College from November 2021 to June 2023, as well as 428 people who were physically examined in the hospital during the same period but were cancer-free as control. The control group and the case group were matched 1:1 according to the same sex and age of 3 years. The case group should meet the gold standard of lung cancer diagnosis, all of them are new cases and have no history of other cancers before suffering from lung cancer, which belongs to the primary disease. The control inclusion criteria were no history of lung cancer, and they were physical examination personnel in the same hospital in the

same year. They had no history of cancer, radiotherapy and chemotherapy before this investigation.

Smoking was defined as smoking at least one cigarette every day at any time in a person's life for at least six consecutive months. Alcohol consumption was defined as drinking liquor > 30 g or beer > 150 mL per day for more than one year during a person's life. Areca nuts chewing was defined as having chewed at least one petal daily for at least six consecutive months at any time during a person's life.

Ethics statement

The plan and consent form were approved by the Ethics Committee of Hainan Medical University (HYLL-2021–187). All subjects involved in human activities fully abide by government policies and the Helsinki Declaration. After explaining the nature and possible consequences of the study in detail, informed consent was obtained from each participant. Each participant donated 2 ml of venous blood and their demographic data (gender, age, ethnic background, smoking status, alcohol consumption, medical history and clinical characteristics, such as tumor type, lymph node metastasis and clinical stage) were collected. The questionnaire was presented in supplementary file 2.

Genotyping assays

Venous blood was drawn from each subject and incubated with sodium citrate anticoagulation, DNA was isolated by phenol–chloroform extraction. The concentration and purity of DNA were determined by ultraviolet spectrophotometry. It was required that the extracted DNA concentration was not less than 30 ng/μL and the purity (260/280 ratio) was greater than 1.8. Finally, the DNA was frozen at -20℃.

At first, a total of 200 bp gDNA sequences including SNP sites to be detected were summarized by using the dbSNP database, and then the genomic homology of gene sequences of SNP sites was verified by the UCSC database, to assess the potential risks of typing detection, and then the primer design of multiple SNP sites was evaluated by using Assa Designer4.0 software of Agena company. At the same time, the design parameters were adjusted according to different site information, and three primers corresponding to each SNP site were synthesized by the PAGE primer purification method, namely two PCR primers and one UEP primer. The detailed primers were shown in the supplementary Table 1. Next, the primer was configured and the DNA quality was checked. The gene fragment containing SNP site was amplified from gDNA genome by PCR amplification, and the product length was between 100 and 200 bp. Then, the product was subjected to an alkaline phosphoric acid reaction, and after a single base extension reaction and resin purification, the MassARRAY Nanodispenser RS1000 spotter was started for chip spotting. MALDI-TOF mass spectrometer was used for analysis, and TYPER4.0 software was used to obtain the original data and genotyping map. The integrity and correctness of the data file were checked, and the results were stored in the corresponding storage media and analyzed.

Quality control

The quality control of the questionnaire included verifying the accuracy of the survey questions and survey content and combining the answers to the closed questions with the answers to the open questions. Doctors were trained uniformly, thus improving the reliability and validity of the questionnaire results. A face-to-face paper questionnaire survey was used to collect data on demographic characteristics, living environment, dietary behavior and lifestyle. After the questionnaires were received, timely checks and codes were performed, invalid questionnaires were eliminated, and valid questionnaires were subsequently input into the data analysis results.

Statistical analysis

The questionnaire results were entered into Epidata software (version 3.1) by two people, and a database was established after storage.The questionnaire counting data were expressed by rate or composition ratio, and analyzed by χ^2 test when comparing. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were used to assess the association between genotype frequencies with lung cancer risk, clinical factors and multiplicative interaction effects by multiple logistic regression analysis. Adjusted P values(P_{adj}), OR_{adj}, with adjustment for potential confounding factors, including sex, age and behavioral factors (areca nuts, cigarettes, alcohol), were obtained by logistic regression models. The data were analysed with IBM SPSS 25.0 software. In this study, all the analysis results were statistically significant when $P < 0.05$, and both sides were tested.

Results

Demographics of the cases and controls

The distribution of demographic characteristics of the study subjects was summarized in Table 1. A total of 428 patients with lung cancer and 428 controls matched by age and sex were included in the study. The average age of the subjects in the controls and patients was 58.79 ± 10.35 and 58.55 ± 10.15 years, respectively. There was a significant difference in smoking between lung cancer patients and the control group ($P < 0.001$). In terms of histological

Table 1 Characteristics of selected demographic and exposure variables in lung cancer cases and controls

Variables		Cases, *n*(%)	Controls, *n*(%)	*P*[a]
Age($\overline{X}$±S)		**58.79 ± 10.35**	**58.55 ± 10.15**	**0.729**
Age	≤ 60	221(51.6)	221(51.6)	
	> 60	207(48.4)	207(48.4)	
Gender	Male	282(65.9)	282(65.9)	1.000
	Female	146(34.1)	146(34.1)	
Smoking	Yes	251(58.6)	149(34.8)	< 0.001
	No	177(41.4)	279(65.2)	
Alcohol consumption	Yes	115(26.9)	111(25.9)	0.757
	No	313(73.1)	317(74.1)	
Chewing areca nut	Yes	31(7.2)	22(5.1)	0.202
	No	397(92.8)	406(94.9)	
Histological type	Adenocarcinoma	320(74.8)		
	Squamous carcinoma	64(15.0)		
	Small cell carcinoma	44(10.2)		
Pathological staging	I + II	143(33.4)		
	III + IV	285(66.6)		
Lymphatic metastasis	Yes	219(51.2)		
	No	209(48.8)		

[a] Pearson χ^2 test for difference in distributions between the case and control groups

type, 74.8% were adenocarcinoma, 15.0% were squamous carcinoma, and 10.2% were small cell carcinoma. 33.4% and 66.6% of the cases were classified as stages I + II and III + IV, respectively. Additionally, the frequencies of the lymphatic metastasis in cases were 51.2%.

Genetic polymorphisms of FUT2, FUT3, ST6Gal-I and MGAT5

The genotypic and allelic frequencies of FUT2, FUT3, ST6Gal-I and MGAT5 SNPs in lung cancer casess and controls were shown in Table 2. Taking genotype GG as the reference group in the polymorphism of ST6Gal-I rs2239611, the results showed that the risk of lung cancer increased in subjects that carrying the genotype AA (AA vs. GG: OR = 1.908, 95%CI = 1.125–3.237, $P = 0.017$). At the same time, the difference was still statistically significant after adjustment for gender, age, smoking, drinking status and chewing betel nut (AA vs. GG: $OR_{adj} = 2.077$, 95%CI = 1.191–3.624, $P_{adj} = 0.010$). Nonetheless, other polymorphisms (i.e., FUT2 rs1047781, rs601338, FUT3 rs28362459, rs3745635 and MGAT5 rs34944508) had no significant association with the risk of lung cancer among casess and controls ($P > 0.05$).

The effect of genetic polymorphisms on the risk of lung cancer was modified by the subjects' lifestyles

Subjects carrying the ST6Gal-I rs2239611 AA genotype had a higher risk of lung cancer in smokers (OR = 2.587; 95% CI: 1.019–6.565; $P = 0.046$; Table 3) and in alcohol drinkers (OR = 3.033; 95% CI: 1.016–9.054; $P = 0.047$; Table 4). Moreover, the relationship was still existed after adjustment ($P_{adj} < 0.05$; Tables 3 and 4). There was no association between the risk of lung cancer and FUT2, FUT3, MGAT5 polymorphisms in our present study after modified by smoking status and alcohol consumption ($P > 0.05$; Tables 3 and 4).

Associations between FUT2 rs1047781 and the clinicopathologic status of lung cancer

We further clarified the role of FUT2 rs1047781 polymorphism in the clinicopathological state of lung cancer, such as tumor histological type, clinical stage and lymph node metastasis (Table 5). Among 428 patients with lung cancer, a significant association was found between the FUT2 rs1047781 polymorphism and clinical stage (OR = 0.492; 95% CI: 0.297–0.831; $P = 0.006$). Moreover, the results showed that carrying FUT2 rs1047781 AT (OR = 0.468; 95% CI: 0.301–0.730; $P < 0.001$) or TT (OR = 0.394; 95% CI: 0.220–0.706; $P = 0.002$) genotype was a protective factor for lymph node metastasis of lung cancer.The relationship was still existed after adjustment ($P_{adj} < 0.05$; Table 5). However, no significant differences were observed in histological type ($P > 0.05$).

Combined effect of genetic polymorphisms and behavioral factors on lung cancer development

Compared with the wild-type non-smokers of FUT2 rs1047781, FUT3 rs28362459, rs3745635, ST6Gal-I

Table 2 Association between single nucleotide polymorphisms of FUT2, FUT3, ST6Gal-I, MGAT5 and the risk of lung cancer

SNPs	Cases(428)		Controls(428)		*OR*(95%*CI*)	*P*	OR_{adj}(95%*CI*)	P_{adj}
	n	%	*n*	%				
FUT2 rs1047781								
AA	133	29.2	139	32.5	1.000		1.000	
AT	221	51.6	219	51.2	1.055(0.779,1.427)	0.730	1.002(0.729,1.376)	0.992
TT	74	17.3	70	16.4	1.105(0.738,1.655)	0.629	1.014(0.662,1.553)	0.949
TT + AT	295	68.9	289	67.5	1.069(0.747,1.530)	0.715	1.013(0.694,1.477)	0.948
A	487	56.9	497	58.1	1.000		1.000	
T	369	43.1	359	41.9	1.049(0.866,1.271)	0.625	1.006(0.822,1.230)	0.955
FUT2 rs601338								
GG	421	98.4	426	99.5	1.000		1.000	
GA	7	1.6	2	0.5	3.542(0.731,17.147)	0.116	3.802(0.726,19.901)	0.114
G	849	99.2	854	99.8	1.000		1.000	
A	7	0.8	2	0.2	3.521(0.729,16.996)	0.117	3.773(0.724,19.652)	0.115
FUT3 rs28362459								
AA	196	45.8	187	43.7	1.000		1.000	
AC	179	41.8	183	42.8	0.933(0.700,1.244)	0.637	0.920(0.681,1.244)	0.589
CC	53	12.4	58	13.6	0.872(0.571,1.331)	0.525	0.748(0.479,1.170)	0.204
CC + AC	232	54.2	241	56.3	0.902(0.605,1.344)	0.611	0.779(0.511,1.188)	0.247
A	571	66.7	557	65.1	1.000		1.000	
C	285	33.3	299	34.9	0.930(0.761,1.136)	0.475	0.875(0.709,1.079)	0.213
FUT3 rs3745635								
CC	322	75.2	301	70.3	1.000		1.000	
CT + TT	106	24.8	127	29.7	0.780(0.577,1.055)	0.107	0.757(0.552,1.039)	0.085
C	749	87.5	729	85.2	1.000		1.000	
T	107	12.5	127	14.8	0.820(0.622,1.081)	0.160	0.805(0.603,1.075)	0.142
ST6Gal-I rs2239611								
GG	225	52.6	229	53.5	1.000		1.000	
GA	158	36.9	175	40.9	0.919(0.692,1.220)	0.558	0.886(0.658,1.193)	0.425
AA	45	10.5	24	5.6	1.908(1.125,3.237)	**0.017**	2.077(1.191,3.624)	**0.010**
AA + GA					1.038(0.794,1.358)	0.784	1.021(0.770,1.354)	0.884
G	608	71.0	633	73.9	1.000		1.000	
A	248	29.0	223	26.1	1.158(0.936,1.432)	0.176	1.166(0.933,1.457)	0.176
MGAT5 rs34944508								
CC	311	72.7	313	73.1	1.000		1.000	
CT	109	25.5	103	24.1	1.065(0.780,1.455)	0.692	1.026(0.739,1.424)	0.879
TT	8	1.9	12	2.8	0.671(0.271,1.664)	0.386	0.944(0.363,2.453)	0.906
TT + CT	117	27.3	115	26.8	1.024(0.757,1.384)	0.878	1.020(0.743,1.401)	0.901
C	731	85.4	729	85.2	1.000		1.000	
T	125	14.6	127	14.8	0.982(0.751,1.282)	0.891	1.010(0.762,1.339)	0.944

OR_{adj} and P_{adj} were estimated by multiple logistic regression models after adjusted for age, gender, smoking, alcohol drinking and betel quid chewing

rs2239611 and MGAT5 rs34944508. The risk of lung cancer with mutant or heterozygote genotype smokers was up to 3.757, 2.899, 2.628, 3.402 and 4.264 times ($P_{adj} < 0.05$). The combined effect of FUT2 rs1047781, FUT3 rs28362459, FUT3 rs3745635, ST6Gal-I rs2239611, MGAT5 rs34944508 polymorphisms, cigarette smoking and alcohol drinking made the risk of lung cancer increased to 2.561 ($P_{adj} = 0.013$), 3.454 ($P_{adj} < 0.001$), 3.171($P_{adj} = 0.002$), 5.328 ($P_{adj} < 0.001$), 2.970 ($P_{adj} = 0.007$), respectively. Moreover, the interaction between smoking, drinking and chewing betel nut and FUT2 rs1047781, ST6Gal-I rs2239611 increased the risk of lung cancer to 5.877 ($P_{adj} = 0.013$), 9.861 ($P_{adj} = 0.047$) times (Table 6).

Table 3 The relationship between the single nucleotide polymorphisms and the risk of lung cancer, stratified by smoking status

SNPs	Smoking		*OR*(95%*CI*)	OR_{adj}(95%*CI*)	No smoking		*OR*(95%*CI*)	OR_{adj}(95%*CI*)
	Cases(%)	Controls(%)			Cases(%)	Controls(%)		
FUT2 rs1047781								
AA	80(31.9)	39(26.2)	1.000	1.000	53(29.9)	100(35.8)	1.000	1.000
AT	127(50.6)	82(55.0)	0.755(0.471,1.212)	0.728(0.451,1.177)	94(53.1)	137(49.1)	1.295(0.847,1.978)	1.286(0.833,1.985)
TT	44(17.5)	28(18.8)	0.766(0.417,1.409)	0.690(0.370,1.286)	30(16.9)	42(15.1)	1.348(0.759,2.395)	1.350(0.744,2.449)
FUT2 rs601338								
GG	248(98.8)	148(99.3)	1.000	1.000	173(97.7)	278(99.6)	1.000	1.000
GA	3(1.2)	1(0.7)	1.790(0.185,17.369)	1.431(0.141,14.478)	4(2.3)	1(0.4)	6.428(0.713,57.982)	7.134(0.753,67.577)
FUT3 rs28362459								
AA	115(45.8)	68(45.6)	1.000	1.000	81(45.8)	119(42.7)	1.000	1.000
AC	97(38.6)	58(38.9)	0.989(0.635,1.539)	0.992(0.634,1.552)	82(46.3)	125(44.8)	0.964(0.648,1.433)	0.871(0.578,1.314)
CC	39(15.5)	23(15.4)	1.003(0.552,1.820)	0.994(0.541,1.828)	14(7.9)	35(12.5)	0.588(0.297,1.161)	0.522(0.259,1.051)
FUT3 rs3745635								
CC	189(75.3)	108(72.5)	1.000	1.000	133(75.1)	193(69.2)	1.000	1.000
CT+TT	62(24.7)	41(27.5)	0.864(0.546,1.369)	0.870(0.546,1.387)	44(24.9)	86(30.8)	0.742(0.485,1.136)	0.679(0.438,1.052)
ST6Gal-I rs2239611								
GG	129(51.4)	77(51.7)	1.000	1.000	96(54.2)	152(54.5)	1.000	1.000
GA	96(38.2)	66(44.3)	0.868(0.569,1.324)	0.875(0.571,1.342)	62(35.0)	109(39.1)	0.901(0.602,1.348)	0.894(0.589,1.356)
AA	26(10.4)	6(4.0)	**2.587(1.019,6.565)**[a]	**2.700(1.056,6.903)**[b]	19(10.7)	18(6.5)	1.671(0.835,3.344)	1.798(0.878,3.682)
MGAT5 rs34944508								
CC	178(70.9)	118(79.2)	1.000	1.000	133(75.1)	195(69.9)	1.000	1.000
CT	70(27.9)	30(20.1)	1.547(0.951,2.517)	1.425(0.868,2.341)	39(22.0)	73(26.2)	0.783(0.501,1.225)	0.744(0.469,1.181)
TT	3(1.2)	1(0.7)	1.989(0.204,19.348)	2.099(0.215,20.525)	5(2.8)	11(3.9)	0.666(0.226,1.962)	0.706(0.233,2.138)

OR_{adj} were estimated by multiple logistic regression models after controlling for age, gender, alcohol drinking and betel quid chewing

[a] $P=0.046$

[b] $P=0.038$

Discussion

Our study revealed several important findings regarding genetic and environmental risk factors for lung cancer in the Chinese population. First, we demonstrated that individuals carrying the AA genotype of ST6Gal-I rs2239611 had a significantly increased risk of lung cancer. This genetic susceptibility was particularly pronounced among smokers and alcohol drinkers, suggesting a synergistic effect between these behavioral factors and the ST6Gal-I variant. Second, we identified that the FUT2 rs1047781 polymorphism was significantly associated with aggressive clinical characteristics, including clinical stage and lymph node metastasis. Most notably, we observed significant gene-environment interactions between ST6Gal-I rs2239611, FUT2 rs1047781and behavioral risk factors(cigarette smoking, alcohol consumption, and betel quid chewing)—a combination not previously explored in lung cancer. Given the high prevalence of betel quid use in certain South Asia, our findings showed a distinct risk profile. These findings highlighted the importance of personalized prevention strategies targeting high-risk populations with specific genetic and lifestyle profiles.

Glycosylation patterns of plasma proteins were related to many human inflammatory diseases and tumors, which made them potential candidates for finding reliable and easily available biomarkers [31, 32]. FUT2 and FUT3 polymorphisms were mainly related to Crohn disease (CD) [33, 34], ulcerative colitis (UC) [35], and pancreatic cancer [36]. But our data showed that FUT2 and FUT3 polymorphisms were not associated with the risk of lung cancer. Similarly, previous studies had also suggested that the FUT2 rs601338 polymorphism could not affect the risk of lung cancer [19]. Rs2239611 in the ST6Gal-I gene were associated with decreased lung cancer risk among ≥ 50 years in the Chinese population [18]. However, our study found that ST6GAL-I rs2239611 AA genotype carriers had higher risk of lung cancer than GG genotype carriers. This might be caused by the age and their different regions of China among the participants. A previous study used high throughput multiplex SNP-analysis in chronic obstructive pulmonary disease and

Table 4 The relationship between the single nucleotide polymorphisms and the risk of lung cancer, stratified by alcohol consumption

SNPs	Alcohol consumption		*OR*(95%*CI*)	OR_{adj}(95%*CI*)	No alcohol consumption		*OR*(95%*CI*)	OR_{adj}(95%*CI*)
	Cases(%)	Controls(%)			Cases(%)	Controls(%)		
FUT2 rs1047781								
AA	49(42.6)	35(31.5)	1.000	1.000	84(26.8)	104(32.8)	1.000	1.000
AT	52(45.2)	56(50.5)	0.663(0.373,1.179)	0.611(0.336,1.112)	169(54.0)	163(51.4)	1.284(0.896,1.838)	1.221(0.837,1.780)
TT	14(12.2)	20(18.0)	0.500(0.223,1.123)	0.454(0.196,1.052)	60(19.1)	50(15.8)	1.486(0.926,2.384)	1.347(0.815,2.226)
FUT2 rs601338								
GG	115(100.0)	110(99.1)	1.000	1.000	306(97.8)	316(99.7)	1.000	1.000
GA	0	1(0.9)	-	-	7(2.2)	1(0.3)	7.229(0.884,59.101)	8.770(0.992,77.529)
FUT3 rs28362459								
AA	51(44.3)	50(2145.0)	1.000	1.000	145(46.3)	137(43.2)	1.000	1.000
AC	43(37.4)	41(36.9)	1.028(0.576,1.835)	0.925(0.504,1.696)	136(43.5)	142(44.8)	0.905(0.650,1.260)	0.928(0.655,1.316)
CC	21(18.3)	20(18.0)	1.029(0.498,2.128)	0.897(0.421,1.909)	32(10.2)	38(12.0)	0.796(0.471,1.345)	0.673(0.385,1.176)
FUT3 rs3745635								
CC	87(75.7)	77(69.4)	1.000	1.000	235(75.1)	224(70.7)	1.000	1.000
CT+TT	28(24.3)	34(30.6)	0.729(0.405,1.311)	0.726(0.396,1.331)	78(24.9)	93(29.3)	0.799(0.562,1.137)	0.775(0.534,1.124)
ST6Gal-I rs2239611								
GG	54(47.0)	63(56.8)	1.000	1.000	171(54.6)	166(52.4)	1.000	1.000
GA	48(41.7)	43(38.7)	1.302(0.752,2.255)	1.217(0.677,2.188)	110(35.1)	132(41.6)	0.809(0.581,1.126)	0.768(0.541,1.090)
AA	13(11.3)	5(4.5)	**3.033(1.016,9.054)**[a]	**3.108(1.008,9.675)**[b]	32(10.2)	19(6.0)	1.635(0.891,2.999)	1.806(0.950,3.434)
MGAT5 rs34944508								
CC	87(75.7)	84(75.7)	1.000	1.000	224(71.6)	229(72.2)	1.000	1.000
CT	25(21.7)	25(22.5)	0.966(0.514,1.813)	0.927(0.467,1.840)	84(26.8)	78(24.6)	1.101(0.769,1.577)	1.010(0.691,1.477)
TT	3(2.6)	2(1.8)	1.448(0.236,8.886)	2.908(0.409,20.644)	5(1.6)	10(3.1)	0.511(0.172,1.519)	0.651(0.210,2.017)

OR_{adj} were estimated by multiple logistic regression models after controlling for age, gender, alcohol drinking and betel quid chewing

The "-"in the table indicates missing data or values that were not calculated due to unmet statistical conditions

[a] $P=0.047$

[b] $P=0.049$

lung cancer selected a total of 32 SNPs localized in genes related to N-glycosylation, and found that rs34944508 SNP might modulate the risk for lung cancer by influencing the expression of MGAT5 [19]. But this SNP had not been found the association with lung cancer in our study. Additionally, it was worth noting that after stratified by smoking and alcohol drinking, ST6Gal-I rs2239611 AA exerted stronger risk effects lead to lung cancer development in our study. The disease-associated effects varied significantly by smoking or alcohol drinking status, which indicates that environmental factors might significantly regulate gene effects [37]. Furthermore, ST6GAL-I rs2239611 point polymorphisms in promoters or in 3' untranslated regions might result in subtle changes in their expression levels by modulating transcription factor or miRNA binding affinities, thus affecting the susceptibility to lung cancer.

Different stages and types of lung cancer might have different sensitivity and responsiveness to different treatment methods. The research progress of stages and types was of great significance for the development of individualized treatment strategies. The relevant study showed that Globo H, which is another glycan product of FUT2, might be shed from cancer cells through microvesicles, resulting in enhanced angiogenic activity [38]. The presence of TT genotype of rs1047781 resulted in associations with decreasing clinical stage III or IV and with less lymph node metastasis for individuals with lung cancer in our study.

It was well known that the development of cancer was a multistep process, including the accumulation of multiple genetic alterations and environmental influences [39]. Evidence showed that among 1255 smokers who carried genotype T in rs1047781, the susceptibility of chewing betel nut to oral cancer showed a synergistic effect of environmental factors (betel nut and smoking) in a Taiwanese case–control study [40]. In our study, the synergistic effects of behavial factors (cigarette smoking and betel quid chewing) and FUT2 rs1047781, ST6Gal-I rs2239611 polymorphisms on the risk of lung

Table 5 Effect of FUT2 rs1047781 polymorphism on clinical statuses in 428 lung cancer patients

Variable	FUT2 rs1047781						
	AA ($n=133$), *n* (%)	AT ($n=221$), *n* (%)	TT ($n=74$), *n* (%)	AT *vs.* AA *OR (95% CI)*	AT *vs.* AA OR_{adj} *(95% CI)*	TT *vs.* AA *OR (95% CI)*	TT *vs.* AA OR_{adj} *(95% CI)*
Clinical stage							
Stage I + II	34(25.6)	74(33.5)	35(47.3)	1.000	1.000	1.000	1.000
Stage III + IV	99(74.4)	147(66.5)	39(52.7)	0.892(0.446,2.409)	0.769(0.315,2.250)	**0.492(0.297,0.831)**[a]	**0.552(0.327,0.990)**[b]
Lymph node metastasis							
No	47(35.3)	119(53.8)	43(58.1)	1.000	1.000	1.000	1.000
Yes	86(64.7)	102(46.2)	31(41.9)	**0.468(0.301,0.730)**[c]	**0.514(0.322,0.821)**[d]	**0.394(0.220,0.706)**[e]	**0.461(0.249,0.856)**[f]
Histological type							
Adenocarcinoma	99(74.4)	162(73.3)	59(79.7)	1.000	1.000	1.000	1.000
Squamous carcinoma	19(14.3)	36(16.3)	9(15.1)	1.193(0.638,2.231)	1.112(0.626,5.249)	1.036(0.301,2.799)	1.052(0.191,2.598)
Small cell carcinoma	15(11.3)	23(10.4)	6(8.1)	0.926(0.458,1.873)	0.829(0.382,1.797)	0.686(0.342,1.376)	0.527(0.193,1.427)

OR_{adj} were estimated by multiple logistic regression models after controlling for age, gender, smoking, alcohol drinking and betel quid chewing

[a] $P=0.006$

[b] $P=0.047$

[c] $P<0.001$

[d] $P=0.005$

[e] $P=0.002$

[f] $P=0.014$

cancer were well demonstrated. Notably, the effect of FUT2 rs1047781 alone on lung cancer is not significant. According to previous studies, convincing evidence has been provided, indicating that various SNPs may remain silent on disease susceptibility, but together with environmental factors, they may further promote the development and progress of diseases [41]. Exposure to cigarette smoke containing high concentrations of reactive oxygen species (ROS) will activate respiratory epithelial cells to synthesize pro-inflammatory mediators, such as IL-8 and IL-1b [42]. In moderate and heavy drinkers, the levels of Galbeta1, 4GlcNAc alpha2, 6-sialyltransferase messenger RNA decreased by 70%, causing glycosylation defects [43]. Besides, areca nut chewing process can produce a large number of reactive oxygen species and many angiogenic factors such as VEGF, TNF-α and IL-1, which have genotoxicity and mutagenicity, thereby contributing to the development of cancer [44]. Rs1047781 polymorphism in FUT2 is the missense mutation, which may inactivate its function. Inactivated FUT2 might weaken the respiratory mucus barrier, and synergize with high-risk behavioral factors to exacerbate lung inflammation. Collectively, these effects might contribute to the development of lung cancer.

Our research had some limitations. First of all, the modest sample size, coupled with the fact that only participants from Hainan were included, China, represents a notable constraint. In addition, whether chewing betel nut was related to lung cancer was still relatively unknown. Therefore, the universality of our research results might be limited to people with similar ethnic backgrounds and geographical areas. Meanwhile, expanding the sample size, including different population groups. Secondly, our data were collected from only one medical center, and there might be selection bias. Therefore, future research could collect data from multiple hospitals to verify our current data. Thirdly, the questionnaire about the behavior factors of betel nuts, tobacco and alcohol use did not comprehensively analyzing the historical data such as behavior duration and daily average consumption. In addition, there were still uncontrollable potential confounding factors in this study, such as diet or occupational exposure. More demographic characteristics, clinical and experimental data were needed to verify and expand the observed association, so as to promote a more comprehensive understanding of the complex interaction between genetic susceptibility and environmental exposure in the pathogenesis of lung cancer.

Future efforts will focus on integrating environmental exposure data, studying the effects of Gene × Environment on lung cancer and the intermediary effect of

Table 6 Associations of the combined effect of FUT2, FUT3, ST6Gal-I and MGAT5 gene polymorphisms and behavior factors with the susceptibility to lung cancer

Variable	Cases(428)		Controls(428)		*OR*(95%*CI*)	*P*	OR_{adj}(95%*CI*)	P_{adj}
	n	%	n	%				
FUT2 rs1047781								
Model 1: AT Genotype or TT Genotype with Cigarette smoking	171	40.0	110	25.7	2.933(1.946,4.421)	**< 0.001**	3.757(2.383,5.923)	**< 0.001**
Model 2: AT Genotype or TT Genotype with Cigarette smoking with Alcohol drinking	55	12.9	110	25.7	1.918(1.139,3.227)	**0.014**	2.561(1.218,5.383)	**0.013**
Model 3:AT Genotype or TT Genotype with Cigarette smoking with Alcohol drinking with betel quid chewing	8	1.9	3	0.7	5.091(1.286,20.157)	**0.020**	5.877(1.460,23.650)	**0.013**
FUT2 rs601338								
Model 1: GA Genotype or AA Genotype with Cigarette smoking	3	0.7	1	0.2	4.821(0.497,46.715)	0.175	7.630(0.754,77.245)	0.085
Model 2:GA Genotype or AA Genotype with Cigarette smoking with Alcohol drinking	1	0.2	0	0	-	-	-	-
Model 3:GA Genotype or AA Genotype with Cigarette smoking with Alcohol drinking with betel quid chewing	0	0	0	0	-	-	-	-
FUT3 rs28362459								
Model 1: AC Genotype or CC Genotype with Cigarette smoking	136	31.8	81	18.9	2.467(1.663,3.659)	**< 0.001**	2.899(1.887,4.455)	**< 0.001**
Model 2:AC Genotype or CC Genotype with Cigarette smoking with Alcohol drinking	56	13.1	42	9.8	1.878(1.136,3.104)	**0.014**	3.454(1.781,6.700)	**< 0.001**
Model 3:AC Genotype or CC Genotype with Cigarette smoking with Alcohol drinking with betel quid chewing	6	1.4	2	4.6	4.304(0.844,21.959)	0.079	4.534(0.881,23.332)	0.071
FUT3 rs3745635								
Model 1: CT Genotype or TT Genotype with Cigarette smoking	62	14.5	41	9.6	2.194(1.396,3.449)	**< 0.001**	2.628(1.612,4.283)	**< 0.001**
Model 2:CT Genotype or TT Genotype with Cigarette smoking with Alcohol drinking	25	5.8	22	5.1	1.608(0.886,2.988)	0.131	3.171(1.647,6.499)	**0.002**
Model 3:CT Genotype or TT Genotype with Cigarette smoking with Alcohol drinking with betel quid chewing	2	0.5	0	0	-	-	-	-
ST6Gal-I rs2239611								
Model 1: GA Genotype or AA Genotype with Cigarette smoking	122	28.5	72	16.8	2.683(1.821,3.953)	**< 0.001**	3.402(2.201,5.259)	**< 0.001**
Model 2:GA Genotype or AA Genotype with Cigarette smoking with Alcohol drinking	49	11.4	32	7.5	2.212(1.315,3.721)	**0.003**	5.328(2.613,10.864)	**< 0.001**
Model 3:GA Genotype or AA Genotype with Cigarette smoking with Alcohol drinking with betel quid chewing	3	0.7	1	0.2	4.46(0.457,43.637)	0.198	9.861(1.039,103.719)	**0.047**
MGAT5 rs34944508								
Model 1: CT Genotype or TT Genotype with Cigarette smoking	73	17.1	31	7.2	3.453(2.148,5.549)	**< 0.001**	4.264(2.566,7.085)	**< 0.001**
Model 2:CT Genotype or TT Genotype with Cigarette smoking with Alcohol drinking	19	4.4	15	3.5	1.726(0.844,3.531)	0.135	2.970(1.314,6.578)	**0.007**
Model 3:CT Genotype or TT Genotype with Cigarette smoking with Alcohol drinking with betel quid chewing	2	0.5	1	0.2	2.83(0.254,31.660)	0.572	4.229(0.360, 49.653)	0.251

Model 1:Compared with the wild-type non-smokers; OR_{adj} andP_{adj}were estimated by multiple logistic regression after adjustment by age , gender, alcohol drinking and betel quid chewing

Model 2:Compared with the wild-type and non-alcohol drinking and non-smoking participants; OR_{adj} andP_{adj}were estimated by multiple logistic regression after adjustment by age , gender and betel quid chewing

Model 3:Compared with the wild-type and non-alcohol drinking and non-smoking and non-betel quid chewing participants; OR_{adj} andP_{adj}were estimated by multiple logistic regression after adjustment by age , gender

The "-"in the table indicates missing data or values that were not calculated due to unmet statistical conditions

epigenetics; Polygenic risk score (PRS) is constructed by integrating a large number of SNP effects, which is used for lung cancer risk prediction and stratified medical care; As an advanced machine learning technology, Reinforcement Learning (RL) has the potential to optimize decision-making through interactive learning with the

environment [45], so it may have a broad application prospect in the applied research of environmental exposure on lung cancer.

Conclusion

In conclusion, the ST6Gal-I rs2239611 AA genotype was associated with an elevated risk of lung cancer in the Chinese population, particularly among smokers or alcohol consumers. Additionally, FUT2 rs1047781 might influence the clinical characteristics of lung cancer. Notably, tobacco, alcohol, and betel nut use in individuals carrying both ST6Gal-I rs2239611 and FUT2 rs1047781 variants further amplified lung cancer susceptibility in this population. These findings highlighted a novel gene-environment interaction in lung cancer. Further large-scale, multi-ethnic studies would be warranted to validate and extend these observations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14088-x.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements
We sincerely thank the staff of the Hainan Medical University and those involved in data collection in particular, including Hainan General Hospital and the First Affiliated Hospital of Hainan Medical University.

Authors' contributions
SK and XP proposed the idea of the article. XS and XP drafted and reviewed the article. JZ, LL, NL, YD, PL and CZ completed the investigation and analysis of the data. All authors reviewed the manuscript.

Funding
This study was supported by Hainan Province Science and Technology Special Fund (ZDYF2025SHFZ046, ZDYF2021SHFZ086).

Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
The study was ethically conducted in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of Hainan Medical University (HYLL-2021–187). All participants provided informed consent.

Competing interests
The authors declare no competing interests.

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Received: 19 January 2025 Accepted: 4 April 2025
Published online: 30 April 2025

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