# IL1B rs1143634 Polymorphism, Cigarette Smoking, Alcohol Use, and Lung Cancer Risk in a Japanese Population

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*IL1B* rs1143634 polymorphism, cigarette smoking, alcohol use, and lung cancer risk in

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**Background:** Interleukin 1B (IL1B) is involved in pulmonary inflammation induced by environmental or occupational toxins. Chronic inflammation has been implicated in the development of lung cancer.

**Methods:** We evaluated the role of *IL1B* (rs1143634, 3954C>T) in a case-control study comprised of 462 lung cancer cases and 379 controls in a Japanese population. Logistic regression was used to assess the adjusted odds ratios (OR) and 95% confidence intervals (95% CI).

**Results and Discussion:** Individuals with a history of smoking and at least one T allele (adjusted OR = 5.45, 95% CI = 2.75 – 4.42, P<0.01) presented a higher risk of lung cancer than those with the CC genotype (adjusted OR = 2.86, 95% CI = 2.02 – 4.05, P<0.01) as compared to never-smokers with the CC genotype (reference). The adjusted attributable proportion due to interaction between the *IL1B* rs1143634 genotypes and smoking was estimated to be 0.45 (95% CI = 0.08 – 0.83, P = 0.02), indicating that 45% of the excess risk for lung cancer in ever-smokers with at least one T allele was due to additive interaction. Subjects with excessive alcohol intake and at least one T allele had a significantly higher risk (OR = 2.48, 95% CI =1.36 – 4.54, P<0.01) than drinkers with appropriate intake and the CC genotype. There was no interaction between the polymorphism and alcohol intake.

**Conclusions:** Our findings indicate the possible association of the T allele carriers of the *IL1B* rs1143634 polymorphism with higher risk of lung cancer especially among smokers. Additional studies are warranted to confirm the *IL1B* rs1143634-smoking interaction suggested in the present study.

**Key words:** alcohol, IL1B, interaction, polymorphism, smoking

# INTRODUCTION

Pulmonary inflammation is induced from the effects of environmental or occupational exposure to toxins. Chronic inflammation has been implicated in the development of several human malignancies, including lung cancer.[1-4] In the lung, a considerable fraction of the carcinogenic process involves chronic inflammation, particularly in the promotion and progression stages. Pulmonary inflammation may promote tumor formation by the generation of reactive nitrogen and oxygen species and secretion of cytokines, chemokines and pro-angiogenic factors.[5, 6] However, many of the cellular and molecular mechanisms involved in the relationship between inflammation and the development of lung cancer are still to be explored.

The interleukin-1 (IL1) family of cytokines is produced by several cell types and has multiple biological effects. IL1B is a pro-inflammatory cytokine mainly produced by blood monocytes and tissue macrophages and has been implicated in mediating both acute and chronic inflammation.[7] IL1B regulates the expression of several genes involved in inflammation.[8, 9] Thus, IL1B may play an essential role in the carcinogenic process. Several single nucleotide polymorphisms (SNPs) have been described in the *IL1B* gene to date.[10] In particular, three polymorphisms, T>C at position-511 (rs16944), C>T at position -31 (rs1143627) and C>T at position +3954 (rs1143634), of the *IL1B* gene have been intensively studied. These variants have been found to be associated with several inflammatory diseases as well as some cancers.[11-13] The rs16944 SNP has been correlated with increased intracellular IL1B levels.[14] As for the rs1146327 polymorphism, the shift from T to C mediates a change from TATAAA to CATAAA and a potential disruption of the TATA box.[15] In

addition, several transcription factors such as the CCAAT-enhancer binding protein beta (C/EBPβ, also called NF-IL6) and spleen focus forming virus proviral integration oncogene spi1 (SPI1, also known as PU.1) have been shown to bind in the region nearby to this polymorphism.[16]    Even though the regulation of the *IL1B* gene has been extensively studied, the mechanisms for the involvement of these regulatory SNPs have not been elucidated.   A possible mechanism may involve differential binding of proteins (C/EBPβ and SPI1) to the polymorphic variants.[12, 17]   On the other hand, the rs1143634 SNP is a coding SNP but is also synonymous (silent).   Synonymous SNPs can cause inactivation of the native splicing donor site, which results in a premature stop codon or exon skipping, yielding a shorter mRNA.[18]    The shorter mRNA results in a truncated protein that is likely to be rapidly degraded or functionally inactive.[19] However, *in vitro* studies have shown that the TT genotype of the rs1143634 SNP up-regulates production of IL1B levels.[20, 21]    Studies of the association between promoter SNPs (rs16944 and rs1143627) and lung cancer risk has shown mixed results[10, 11, 22, 23] while the rs1143634 SNP has been shown to be marginally associated with lung cancer in two Caucasian studies.[10, 24]

Cigarette smoking is an established risk factor of lung cancer development but there is conflicting evidence regarding the effects of alcohol consumption.   Several studies have demonstrated that cigarette smoking and alcohol drinking may influence the production of cytokines.[25, 26]   Lung cancer is a common disease that results from a complex interplay of genetic and environmental risk factors just like other common multifactorial diseases, such as cardiovascular disease, diabetes mellitus and autoimmune disease.   Smokers (established high risk population)/drinkers (suspected

high risk population) with a genotype promoting greater cytokine production may be more susceptible to lung cancer than expected from the independent effects of the two (smoking/drinking and genetic) separate factors.    As smoking and drinking may interact with cytokine genotypes to enhance lung inflammation, we conducted a case-control study of lung cancer in a Japanese population with special reference to the interaction between the *IL1B* rs1143634 polymorphism and either cigarette smoking or alcohol drinking.

## MATERIALS AND METHODS

### Study subjects and data collection

Subjects with histologically confirmed primary lung cancer were recruited from 1996 to 2008 at the Kyushu University Hospital (Research Institute for Diseases of the Chest, Kyushu University).    Histological types were categorized into four major types according to the International Classification of Diseases for Oncology (ICD-O), second edition[27]: adenocarcinoma (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8560, 8570–8572), squamous cell carcinoma (8050–8076), small cell carcinoma (8040–8045) and large cell carcinoma (8012–8031, 8310).    Three hundred and seventy nine potential controls with no prior history of cancer were recruited on a voluntary basis at the Fukuoka Prefectural Government and the Kyushu University during the same period.    Judging from the basis of the study subject's family name, all subjects were possibly unrelated ethnic Japanese.    Information on self-reported details of smoking, alcohol drinking, years of education and environmental tobacco smoke exposure from spouses, which have been identified as independent or contributing risk

factors for lung cancer,[28] was gathered from both patients and controls.

The study protocol was approved by our institutional review board, and all participants provided written informed consent.

**Genetic analysis**

Genomic DNA was extracted from blood samples.    Genotyping was conducted with blinding to case/control status.    The genotyping of the *IL1B* rs1143634 SNP was done with Taqman assay (genotyping protocols supplied centrally by IARC). For quality control, both assays were repeated on a random 5% of all samples and the replicates were 100% concordant.

**Statistical analysis**

Comparisons of means, proportions and medians were based on unpaired *t* test, chi-square test and Wilcoxon rank-sum test, respectively.    The distribution of the *IL1B* rs1143634 genotypes in controls was compared with that expected from Hardy-Weinberg equilibrium (HWE) by the chi-square (Pearson) test.    Unconditional logistic regression was used to compute the odds ratios (ORs) and their 95% confidence intervals (CIs), with adjustments for several covariates.    Subjects were considered current smokers if they had smoked or stopped smoking less than one year before either the date of diagnosis of lung cancer or the date of completion of the questionnaires (controls).    Never-smokers were defined as those who had never smoked in their lifetime.    Former smokers were those who had stopped smoking one or more years before either the date of diagnosis of lung cancer or the date of completion of the

questionnaires (controls).    Based on "Healthy Japan 21" (National Health Promotion in the 21st Century), heavy drinkers were defined as those who drank alcohol more than 60g per day.[29]    As "Healthy Japan 21" has emphasized the drinking of an appropriate volume of alcohol (20g of alcohol per day), appropriate drinkers were defined as those who did not exceed 20g of alcohol intake per day.    The appropriate volume of alcohol use may have a protective effect on life expectancy and morbidity.[30]    Moderate drinkers were defined as those who drank alcohol more than 20g per day but not exceeding 60g per day.    Unlike cigarette smoking, ingested alcohol is eliminated from the body by various metabolic mechanisms and the alcohol elimination process begins almost immediately.    Significant relationships between excessive drinking and lung cancer have been reported while appropriate drinking has not shown the same effects.[31] In terms of alcohol consumption, the subjects were classified into the following two groups based on their intake for at least one year: those who drink more than 20g of alcohol per day (excessive drinkers) and those who drink less than 20g of alcohol per day (appropriate drinkers).    To test for statistical (multiplicative) interactions between the gene and smoking/drinking, we entered interaction terms (reflecting the product of gene-smoking/drinking status into the logistic models.    In a logistic regression model, interaction is a departure from multiplicativity.    If multiplicative interaction measure is statistically different from one, there is evidence of an interaction.    In such a situation, the OR ($OR_{EG}$) associated with both the environmental factor E and the genetic factor G is greater than the product of the ORs ($OR_E$ and $OR_G$, greater than 1) associated with each factor separately ($OR_{EG} > OR_E \times OR_G$) as in Tables 3 and 4.    Thus, lung cancer risk may be significantly increased by the exposure in the presence of the susceptible genotype but

not by the susceptible genotype alone.    Rothman has argued that interaction estimated as

a departure from additivity better reflects biologic (additive) interaction.[32]    Additive

interaction is measured in epidemiological studies primarily using the difference of

disease rates.    The difference of disease rates cannot be estimated from case-control

studies although it    can easily be accomplished in cohort-studies.    Alternative

measures of interaction on the additive scale are based on OR.        Three measures for

additive interaction as departure from additivity, namely the relative excess risk due to

interaction (RERI), attributable proportion due to interaction (AP) and synergy index

(SI), were calculated by the method described by Andersson et al.[33]    The RERI [$OR_{EG}$ -

$OR_E$ - $OR_G$ + $OR_{00}$ (= 1)] is the excess risk due to interaction relative to the risk without

factor.    AP (RERI / $OR_{EG}$) refers to the attributable proportion of disease which is due

to interaction among persons with both factors.    SI {($OR_{EG}$ - $OR_{00}$) / [($OR_E$ - $OR_{00}$) +

($OR_G$ - $OR_{00}$)]} is the excess risk from factor (to both factors) when there is interaction

relative, to the excess risk from factor (to both factors) without interaction.[34]    Additive

interaction is absent if the RERI and AP are equal to zero and SI is equal to one.

All statistical analyses were performed using the computer program STATA

Version 10.1 (STATA Corporation, College Station, TX).    All *P* values were

two-sided, with those less than 0.05 considered statistically significant.

## RESULTS

The distributions of selected characteristics among subjects are summarized in

Table 1.    Our analysis included 462 lung cancer patients (242 with adenocarcinoma,

131 with squamous cell carcinoma, 69 with small cell carcinoma, and 20 with large cell

carcinoma).    There were significant differences between cases and controls in terms of age, sex ratio, smoking status, drinking habits, pack-years of smoking and years of education.

As shown in Table 2, the frequencies of CC (ancestral, Human SNP ancestral alleles are determined by comparison with primate DNA, so in general, they're based on chimpanzee sequence[35]), CT and TT genotypes of the *IL1B* rs1143634 SNP were 82.9 %, 15.2 % and 2.0 % in cases and 88.1 %, 11.1 % and 0.8 % in controls, respectively.    Genotype distribution was consistent with HWE among controls. Genotypic distributions of the *IL1B* rs1143634 were statistically different between cases and controls (P = 0.02).    As the TT genotype has not been separated due to a low prevalence of the rare T allele in this study, we combined the CT genotype with the TT genotype.    The CT and TT genotypes combined were significantly associated with an increased risk of lung cancer (crude OR = 1.53, 95% CI = 1.03 − 2.27, P = 0.03) but this association was attenuated after adjustment for smoking and other confounding factors (adjusted OR = 1.45, 95% CI = 0.93 − 2.26, P = 0.11).    Based on these results, we designated the allele (T allele) that is presumed to increase the risk of lung cancer as the "at-risk" allele.    Subjects with at least one "at-risk" allele were bundled in one group for subsequent analysis.    Although we examined associations between the polymorphism and histological types, associations were similar across histological types (data not shown).

Table 3 shows the modifying effect of the *IL1B* rs1143634 genotypes on the association of smoking with lung cancer risk.    After adjustment for age, sex, education and drinking, current smoking (crude OR = 3.70, 95% CI = 2.44 − 5.60, P <0.01;

adjusted OR = 4.42, 95% CI = 2.78 – 7.04, P <0.01) and former smoking (crude OR =

2.10, 95% CI = 1.54 – 2.84, P <0.01; adjusted OR = 2.73; 95% CI = 1.92 – 3.89, P

<0.01) were associated with an increased risk of lung cancer (data not shown).    To

achieve adequate statistical power, current and former smokers were combined

(ever-smokers).    After adjustment for age, sex, education and drinking, ever-smoking

was associated with an increased risk of lung cancer (crude OR =2.48, 95% CI = 1.88 –

3.29, P <0.01; adjusted OR = 3.17; 95% CI = 2.28 – 4.39, P <0.01) (data not shown).

Generally, the reference category is the absence of exposure (risk factor).    Smokers

with at least one "at-risk" allele (adjusted OR = 5.45, 95% CI = 2.77 – 10.69, P <0.01)

had a higher risk of lung cancer than those with the CC genotype (adjusted OR = 2.86,

95% CI = 2.02 – 4.05, P <0.01), relative to non-smokers with the CC (non-risk)

genotype (reference,).    The multiplicative interaction between the *IL1B* rs1143634

genotypes and smoking was far from significant.    Assessment of additive interaction

measures was also carried out.    Adjusted measure of RERI was not statistically

significant (2.47, 95% CI = -1.05 – 6.00, P = 0.18).      Adjusted SI was marginally

significant (2.23, 95% CI = 0.91 – 5.60, P = 0.08).    Meanwhile, the adjusted AP

between the *IL1B* rs1143634 genotypes and smoking was estimated to be 0.45 (95% CI

= 0.08 – 0.83, P = 0.02), indicating that 45% of the excess risk for lung cancer in

smokers with at least one "at-risk" allele was due to additive interaction.

       Table 4 shows the modifying effect of the *IL1B* rs1143634 genotypes on the

association of alcohol drinking with lung cancer risk.    After adjustment for age, sex,

education and smoking status, excessive drinking was associated with an increased risk

of lung cancer (crude OR = 1.86, 95% CI = 1.41 – 2.45, P <0.01; adjusted OR = 1.75;

95% CI = 1.27– 2.41, P < 0.01) (data not shown).    Among excessive drinkers,

individuals with at least one "at-risk" allele (OR = 2.48, 95% CI = 1.36 – 4.54, P < 0.01)

presented a higher risk of lung cancer than those with the CC genotype (OR = 1.73,

95% CI = 1.22 – 2.45, P < 0.01), relative to appropriate drinkers with the CC genotype.

All interaction measures (multiplicative interaction, RERI, AP and SI) were far from

statistically significant.

## DISCUSSION

The *IL1B* rs1143634 genotypes were determined in 462 cases of lung cancer

and 379 controls.    The frequency of the C allele of the IL1B rs1143634 was 0.937 in

controls and the genotype distribution was consistent with HWE (Table 2).    According

to the HapMap SNP database,[35] the C allele frequency is most common among Han

Chinese (97.8 %) and least common among Caucasians (74.2 %) with Japanese

(88.9 %) and Yorubas (a West African ethnic group, 88.3 %) intermediate between these

groups.    The frequency of the C allele in our study was somewhat lower than the

HapMap SNP database but similar to other Japanese populations (92.8 – 96.9 %).[36, 37]

The T allele carriers of the *IL1B* rs1143634 were marginally associated with a

1.45-fold (95% CI = 0.93 – 2.26, P = 0.11) increase in the risk of lung cancer (Table 2).

Although the rs1143634 SNP is a synonymous change (Phe105Phe), an allelic dosage

effect on secretory capacity was observed after lipopolysaccharide stimulation.[20]    The

first Caucasian study reported that the carriers with the T allele had an increased risk of

lung cancer (OR = 1.27, 95% CI = 1.10 – 1.47, P<0.01).[10]    The association presented a

low false-positive report probability, indicating that the finding was unlikely due to

chance.    The second Caucasian study reported that the TT genotype was associated with an increased risk of lung cancer in former smokers (OR = 1.74, 95% CI = 1.07 – 2.85, P = 0.03) and in men (OR = 1.80, 95% CI = 1.04 – 3.11, P = 0.03).[24]    The lack of an association seen in the current smokers may be due to insufficient homozygous genotype numbers.

It is widely accepted that lung cancer development requires environmental factors acting on a genetically predisposed individual.    Because smoking is an established cause of lung cancer, we therefore evaluated whether an interaction existed between the *IL1B* rs1143634 SNP and smoking (Table 3).    A gene-environment interaction was suggested, with a combination of at least one "at-risk" allele and smoking conferring significantly higher risk (OR = 5.45, 95% CI = 2.77- 10.69, P<0.01), compared with the CC genotype and no history of smoking.    However, no multiplicative interaction of smoking and the *IL1B* rs1143634 with lung cancer was observed (the effect of the T allele did not differ between ever-smokers and never-smokers (crude and adjusted, 1.51 and 1.11, respectively) and ever-smokers (crude and adjusted, 1.67 (4.13/2.47) and 1.87(95% CI = 0.98 – 3.60, P = 0.06, respectively; data not shown).    Thus, the significantly high OR of 5.45 was attributed largely to the effect of ever-smoking (OR = 3.17, P<0.01).    Similarly, P-values for smoking-genotype interaction (multiplicative) were not significant.[10, 24]    The AP between *IL1B* rs1143634 genotypes and smoking was estimated to be 0.45 (95% CI = 0.08 – 0.83, P=0.02).    This measure was not equal to zero, suggesting the existence of an additive interaction.    To the best of our knowledge, no lung cancer studies on additive interaction between the *IL1B* rs1143634 SNP and smoking have been

previously reported.

The relationship between alcohol use and lung cancer risk remains controversial. While an association has been observed in many studies, it is often presumed to be due to residual confounding from smoking. A pooled analysis found that a slightly greater risk of lung cancer was associated with the consumption of ≥30 g alcohol per day than with no alcohol consumption.[38] It is unknown what biologic mechanism may be responsible for a harmful effect of alcohol, though several have been proposed.[38-41] The epidemiological evidence is suggestive of an increased lung cancer risk associated with drinking alcohol, particularly beer.[31, 39] Excessive drinking was significantly associated with a 1.75-fold (95% CI = 1.27 − 2.41, P < 0.01) increased risk of lung cancer in the present study (data not shown). According to the 132st National Tax Agency Annual Statistics Report,[42] beer, including low-malt beer (sparking liquor) is the most popular alcoholic beverage in Japan. A recent study reported that heavy drinkers of beer faced a 1.46-fold (95% CI = 1.07 − 1.98, P= 0.02 ) increased risk of lung cancer.[31] Beer has much higher levels of nitrosamines than any other alcoholic beverage.[43] These chemicals are formed during the process of production of the different alcoholic beverages. Because production techniques vary over time, different levels of these chemicals over time and in different geographical areas can be anticipated. This could explain, at least partly, some of the discrepancies when comparing epidemiological investigations of our relationship. Moreover, the appropriate volume of Japanese (<20g/day)[29] is relatively lower than that of Caucasians (15-30g/day).[44] Japanese may be genetically more susceptible to an alcohol consumption effect on cancer compared to Caucasians due to differences in alcohol

metabolism efficiency .[45]    It can be hypothesized that the effects of the genotype promoting greater cytokine production would be stronger among excessive drinkers. However, the *IL1B* rs1143634 SNP did not modify lung cancer risk in relation to alcohol use.    Significantly high OR of 2.48 was attributed largely to the OR (1.75) of excessive drinking.    Significant interaction can be seen when accurate categorization of alcohol use is employed instead of a binary variable.

In conclusion, our study suggested an interaction between the *IL1B* rs1143634 polymorphism and smoking on the risk of lung cancer among Japanese, but the current sample size may prevent any conclusive inference.    Future studies involving larger control and case populations and better exposure histories will undoubtedly lead to a more thorough understanding of the role of *IL1B* in lung cancer development.

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Table 1. Selected characteristics of lung cancer cases and controls

| Characteristics | Cases (n = 462) | Controls (n = 379) | P-value† |
|---|---|---|---|
| Age (year), median (IQR) | 68 (62 – 73) | 58 (48 – 65) | <0.01 |
| Male, n (%) | 287 (62.1) | 283 (74.7) | <0.01 |
| Smoking status, n (%) | | | <0.01 |
| Current smoker | 198 (42.9) | 129 (34.0) | |
| Former smoker | 111 (24.0) | 41 (10.8) | |
| Never smoker | 153 (33.1) | 209 (55.2) | |
| Pack-years, median (IQR) | 38 (0 – 58) | 0 (0 – 34) | <0.01 |
| Moderate/heavy drinkers, n (%) | 284 (61.5) | 175 (46.2) | <0.01 |
| Exposure to environmental tobacco smoke among non-smokers, n (%) | 99 (64.7) | 135 (64.6) | 0.98 |
| Education, median (IQR) | 12 (12 – 16) | 16 (12 – 16) | <0.01 |
| Histology, n (%) | | | |
| Adenocarcinoma | 242 (52.4) | | |
| Squamous cell carcinoma | 131 (28.4) | | |
| Small cell carcinoma | 69 (14.9) | | |
| Large cell carcinoma | 20 (4.3) | | |

IQR, interquartile range

†P for $\chi^2$ test.

Table 2. Association between the *IL1B* rs1143634 (3954C>T) polymorphism and risk of lung cancer

| | Number (%) of | | OR (95% CI) | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | Cases | Controls | Crude | P | Adjusted* | P |
| CC (ancestral**) | 383 (82.9) | 334 (88.1) | 1.0 (reference) | | 1.0 (reference) | |
| CT | 70 (15.2) | 42 (11.1) | 1.45 (0.96 – 2.19) | 0.07 | 1.34 (0.84 – 2.13) | 0.21 |
| TT | 9 (2.0) | 3 (0.8) | 2.62 (0.70 – 9.74) | 0.15 | 3.31 (0.71 – 15.30) | 0.13 |
| | P[†]= 0.02 | P[‡] = 0.20 | P-trend = 0.02 | | P-trend = 0.06 | |
| CT + TT | 79 (17.2) | 45 (11.9) | 1.53 (1.03 – 2.27) | 0.03 | 1.45 (0.93 – 2.26) | 0.11 |
| Prevalence of C allele | 0.905 | 0.937 | | | | |

*Adjusted for age, sex, education, smoking status and drinking.

**Defined by National Center for Biotechnology Information SNP database.

[†]P for $\chi^2$ test ($\chi^2$ = 5.2080, df = 1).

[‡]P for Hardy-Weinberg equilibrium test among controls.

Table 3. Interaction of the *IL1B* rs1143634 (3954C>T) polymorphism and cigarette smoking

| Genotype | Smoking* | Cases/Controls | | OR (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| | | | | Crude | P | Adjusted** | P |
| CC | Never | 125/182 | $OR_{00}$ | 1.0 (reference) | | 1.0 (reference) | |
| CT + TT | Never | 28/27 | $OR_G$ | 1.51 (0.85 – 2.68) | 0.16 | 1.11 (0.59 – 2.08) | 0.74 |
| CC | Ever | 258/152 | $OR_E$ | 2.47 (1.82 – 3.35) | <0.01 | 2.86 (2.02 – 4.05) | <0.01 |
| CT + TT | Ever | 51/18 | $OR_{EG}$ | 4.13 (2.30 – 7.39) | <0.01 | 5.45 (2.77 – 10.69) | <0.01 |
| Multiplicative interaction measure | | | | 1.10 (0.49 – 2.49) | 0.81 | 1.71 (0.68 – 4.26) | 0.25 |
| Additive interaction measure | | | | | | | |
|     Relative excess risk due to interaction (RERI) | | | | 1.14 (-1.62 – 3.91) | 0.42 | 2.47 (-1.05 – 6.00) | 0.18 |
|     Attributable proportion due to interaction (AP) | | | | 0.28 (-0.24 – 0.79) | 0.29 | 0.45 (0.08 – 0.83) | 0.02 |
|     Synergy index (SI) | | | | 1.58 (0.59 – 4.22) | 0.36 | 2.23 (0.91 – 5.60) | 0.08 |

* Current and former smokers were combined (ever-smokers).

** Adjusted for age, sex, education and drinking.

Table 4. Interaction of the *IL1B* rs1143634 (3954C>T) polymorphism and alcohol drinking

| Genotype | Alcohol drinking* | Cases/Controls | | OR (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| | | | | Crude | P | Adjusted** | P |
| CC | Appropriate | 231/151 | $OR_{00}$ | 1.0 | | 1.0 | |
| CT + TT | Appropriate | 53/24 | $OR_G$ | 1.49 (0.81 – 2.75) | 0.20 | 1.37 (0.69 – 2.74) | 0.37 |
| CC | Excessive | 152/183 | $OR_E$ | 1.84 (1.37 – 2.48) | <0.01 | 1.73 (1.22 – 2.45) | <0.01 |
| CT + TT | Excessive | 26/21 | $OR_{EG}$ | 2.66 (1.57 – 4.51) | <0.01 | 2.48 (1.36 – 4.54)) | <0.01 |
| Multiplicative interaction measure | | | | 0.97 (0.43-2.17) | 0.94 | 1.04 (0.42 – 2.60) | 0.92 |
| Additive interaction measure | | | | | | | |
|    Relative excess risk due to interaction (RERI) | | | | 0.33 (-1.53 – 2.18) | 0.73 | 0.38 (-1.50 – 2.26) | 0.69 |
|    Attributable proportion due to interaction (AP) | | | | 0.12 (-0.54 – 0.76) | 0.71 | 0.15 (-0.55 – 0.86) | 0.67 |
|    Synergy index (SI) | | | | 1.25 (0.35 – 4.48) | 0.73 | 1.35 (0.29 – 6.15) | 0.70 |

* Appropriate drinking and excessive drinking.

** Adjusted for age, sex, education and smoking status.