行政院國家科學委員會補助專題研究計畫成果報告

國人肺癌之分子致病機轉-子計畫一 臺灣地區女性肺腺癌之分子流行病學研究（3/3）

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Materials and Methods

Study subjects

The **s**tudy subjects were recruited from National Taiwan University Hospital, Taipei, Taiwan. National Taiwan University Hospital is the leading teaching hospital in Taiwan, and is the most important referral center in Taiwan. Subjects were mostly from great Taipei area; however, some of them were referred from other area from other hospitals. Eligible cases were newly diagnosed and histologically (pathology or cytology) confirmed primary lung adenocarcinoma by experienced pathologists or chest specialists. A total of 301 eligible cases were recruited between July 1996 and March 2001. Among them, 30 subjects were proved to be not lung cancer, including tuberculosis, ovary cancer, breast cancer, or other benign tumors; 4 subjects were of unknown diagnosis, and 263 subjects were proved to lung cancer. Among 263 lung cancer patients, 200 subjects were adenocarcinoma, and 63 of them were non-adenocarcinoma lung cancer, including squamous cell, small cell, large cell, and adenosquamous cell carcinoma. About 76 % of lung cancer patients were adenocarcinoma. Among adenocarcinoma, 16 subjects had no questionnaires due to either too ill to response, discharged, or expired. The response rate was 92%. Among the 184 subjects, 167 of them had blood sample, and 17 subjects had no blood sample due to discharge, expire, or refusal. The control group was recruited from

two stages. The first stage was between 1997 July and 1998 January. Hospital controls were recruited from National Taiwan University Hospital health examination department. A total of 279 controls were recruited. We did not perform individual matching because of administrative consideration. However, the control group was younger and receiving higher education than cases. In order to improve the power and efficiency, we stared a secondary stage of control recruitment. This time, controls were recruited from Taipei Municipal Chung-Hsiao hospital in 2001. Female older than 65 years receiving free health examination provided by Bureau of National Health Insurance, Taiwan was eligible controls. A total of 73 controls were recruited. Among the total 352 controls, only 2 subjects refused interview, and 10 subjects refused to provide blood samples. Only 277 controls and 148 cases had received genotyping for phase I ,2 xenobiotics-metabolizing enzymes, estrogen metabolizing and receptor gene , and DNA repair genes polymorphism.

The catchments areas of the controls were from the great Taipei city. However, the catchments areas of cases, though mostly were from great Taipei city, were from the whole Taiwan in fact. We did not use proxy responder information in our study.

Data specification

Two trained interviews conducted personal interviews to collect risk factors data. Data on demographic characteristics, menstrual and pregnancy history, tobacco

exposure status including the smoking status of the patient and her spouse, parents, and co-workers, individual medical condition, incense smoke, dietary history, alcohol consumption, occupational exposure, a family history of lung cancer and cooking fume exposure were obtained from structured questionnaires. **Cooking habit** before 40 was defined as cooking daily for at least 6 months before 40-year-old. **Cooking fume exposure** was defined as those who had cooking habit before 40-year-old and no ventilator was used when she was cooking. Subjects who had no cooking habits or used ventilator when cooking were defined as **no cooking fume exposure**. Other cooking related items, such as Cooking fuels, including electricity, natural gas, charcoal, wood, and coal, cooking oils, including lard oil or vegetable oils (soybean, peanut, sunflower, and other vegetable oils), age at starting cooking, total cooking years before 40, and fume extractor in kitchen (as dichotomous variable) were also interviewed and analyzed. **Ever smoker** was defined as having smoked daily for at least 6 months during her lifetime. **Nonsmoker** was defined as never having smoked daily for at least 6 months during her lifetime. Smoking duration (in years), and cumulative smoking amount (in pack-year) were stratified to four levels to test the dose-response relationship. As to the environmental tobacco smoke exposure, smoking status of father, mother, spouse, and co-workers were inquired. Spouse smoking duration (in years) and cumulative

smoking amount (in pack-years) were stratified into four levels to test the dose-response relationship. **Tobacco smoke exposure** was defined as ever smokers or spouse smoking nears her.

Hormone-related risk factors included age at menarche, age at menopause, menstruation regularity, menstrual cycle length, length of menstrual period, number of gestation, parity, spontaneous abortion, and total duration of breast-feeding. External source of sex hormone included oral contraceptives and hormone replacement therapy, and some Chinese herb drug for menstruation-regulation.

Period of hormone exposure was defined as (age of recruitment – age of menarche) × 12-10 × times of full term delivery- 5× times of abortion when she was not menopausal, and was defined as (age of menopause – age of menarche) × 12-10 × times of full term delivery- 5× times of abortion when she was menopausal. Body mass index was calculated by body weight six months before diagnosis in kilogram divided by square of body height in meter.

Interviewer also asked about the history of pulmonary tuberculosis, chronic obstructive airway disease (emphysema, chronic bronchitis), asthma, and history of hysterectomy, oophorectomy, and family history of lung cancer.

Laboratory methods

After obtaining the letter of consent from study subjects, we collected 10 ml of

venous blood for genotype analysis. Genomic DNA sample were extracted from peripheral lymphocytes using a Puregene DNA isolation kit (Gentra System, Lnc., Minneapoils, MN, USA). After extraction, DNA was dissolved in a hydration solution and stored at 4℃ until further analysis. Genotypes were detected using a PCR-RFLP technique as the following condition:

Phase I xenobiotics-metabolizing enzymes genotyping

CYP1B1 **(Codon 432)**

Primer:

5'-GTG GTT TTT GTC AAC CAG TGG-3'

5'-GCC TCT TGC TTC TTA TTG GCA-3'

Condition:

94℃ 4 mins → (94℃ 40" → 55℃ 30" → 72℃ 40") → 72℃ 10 mins

35 cycles

Exon3, codon 432 (Val→Leu) 1294 G→C

PCR product: 390 bp, create Eco57I site

G/G: 390 bp, C/C: 330+60 bp

CYP1B1 **(Codon 48)**

Primer:

5'-TAC GGC GAC GTT TTC CAG AT-3'

5'-CGT GAA GAA GTT GCG CAT CA-3'

Condition:

94℃ 4 mins → (94℃ 40" → 55℃ 30" → 72℃ 40") → 72℃ 10 mins

35 cycles

PCR product: 230 bp; codon 48 Ala→Ser (G→T)

Create Ahd1 site, G/G bp: 230; T/T: 110+120 bp

CYP1A1**-exon7 (Codon 462)**

Primer:

5'-GAACTGCCACTTCAGCTGTCT-3'

5'-GAAAGACCTCCCAGCGGTCA-3'

Condition:

94 °C 4 min → (94 °C 40" →60°C 25" →72 °C 30") →72°C 10min

35 cycles

Codon 462 Ile→ Val (ATT→GTT)

PCR product 187 bp, A-G mutation create HincII site, Ile: 139+48, Val: 120+48+19 bp

***CYP1A1*-Msp1 (3'-flanking region)**

C44: 5'-TAGGAGTCTTGTCTCATGCCT-3'

C47: 5'-CAGTGAAGAGGTGTAGCCGCT-3'

94 °C 4 min → (94 °C 40" →60°C 30" →72 °C 30") →72°C 10min

35 cycles

PCR product 340 bp

3'-flanking T→C mutation create Msp1 site, wt/wt: 340, mt/mt 205+135

CYP2E1-Rsa1

Primer:

5'-CCAGTCGAGTCTACATTGTCA-3'

5'-TTCATTCTGTCTTCTAACTGG-3'

Condition:

PCR product 412 bp, Rsa1, wt/wt: 366+46, mt/mt: 412

CYP1A2 (-2964)

Primer:

5'-GCT ACA CAT GAT CGA GCT ATA C -3'

5'-CA GGT CTC TTC ACT GTA AAG TTA-3'

94℃ 4 mins → (94℃ 40" → 56℃ 30" → 72℃ 40") → 72℃ 10 mins

35 cycles

G→ A at position-2964, create *BslI*

Size of PCR product: 596 bp

G:/G: 343 +132+ 93+ 28

A/A: 475+ 93+ 28

CYP2C19 m1

Primer:

5'-AATTACAACCAGAGCTTGGC -3'

5'-TATCACTTTCCATAAAAGCAAG-3'

Condition:

94 °C 4 min → (94 °C 40" →52°C 30" →72 °C 30") →72°C 10min

35 cycles

PCR product: 169 wt/wt: 120+49 mt/mt: 169

Phase II xenobiotics-metabolizing enzymes genotyping

COMT (Val158Met)

5'-TCGTGGAC GCCGTGATTCAGG-3'

5’-AGGTCTGAC AAC GGGTCAGGC-3’

94℃ 4 mins → （94℃ 40” → 55℃ 30” → 72℃ 30”）→ 72℃ 10 mins

35 cycles

Size of PCR product: 217bp

A→G loss of an NlaIII site

Met/Met: 40+96+81bp, Val/Val: 136+81bp.

GST T1M1:

M1:G5 5’-GAAC TCCCTGAAAAGCTAAAGC-3’

G6 5’-GTTGGGCTCAAATATAC GGTGG-3’

T1: T1-R 5’-TCAC CGGATCATGGCCAGCA-3’

T1-F 5’-TTCCTTAC TGGTCCTCAC ATCTC-3’

B-globin: CAAC TTCATCCAC GTTCAC C

GAAGAGCCAAGGAC AGGTAC

PCR condition:

94 °C 4 min → (94 °C 40” →55°C 30” →72 °C 40”) →72°C 10min

35 cycles

2.5 % agarose electrophoresis

GSTP1 (Ile105Val)

P105F 5’-ACC CCA GGG CTC TAT GG-3’

P105R 5’-TGA GGG CAC AAG AAG CCC CT-3’

94 °C 4 min → (94 °C 40” →60°C 25” →72 °C 30”) →72°C 10min

35 cycles

PCR product: 176bp, Ile/Ile: 176 bp, Val/Val: 91+85 bp

The Alw26I site created by the A→G mutation at codon105

NAT2

N4: 5’-TCT AGC ATG AAT CAC TCT GC-3’

N5: 5’-GGA AC A AAT TGG AC T TGG-3’

94 °C 4 min → (94 °C 40” →52°C 30” →72 °C 90”) →72°C 10min

35 cycles

PCR product: 1093 M1 (Kpn1) C/C: 660+433bp, T/T: 1093bp

M2 (Taq1) G/G: 380+317+226+170, A/A: 396+380+317

M3 (BamH1) G/G: 811+282, A/A: 1093

NAT1

N1323 5’-TAAAAC AATCTTGTCTATTTG-3’

N1536NR 5’-ATAAC CAC AGGCCATCTTTAGAA-3’

94 °C 4 min → (94 °C 40” →52°C 30” →72 °C 40”) →72°C 10min

35 cycles

ACCESSION: X17059

SNP site: *4/*4:1528T/T; 1535:C/C.

*3/*3:1528T/T; 1535:A/A

*10/*10:1528A/A; 1535:A/A

*11/*11:1520-1528 deleted;

Run cycle-sequence to distinguish ***3**/4*/10/*11

EH (Tyr113His)

5’-TGT CCT TCC CAT CCC TCT CAA CTT-3’

5’-CCT TCA ATC TTA GTC TTG AAG TGA CGG T-3’

94 °C 4 min → (94 °C 40” →55°C 30” →72 °C 40”) →72°C 10min

35 cycles

C→ T mutation loss of an Asp1 site.

PCR product 228bp, Tyr/Tyr: 201+ 27bp, His/His: 228bp.

EH (His139Arg)

5’-AAC AC CGGGCCCAC CCTTGGC-3’

5’-GGGGTAC CAGAGCCTGAC CGT-3’

94 °C 4 min → (94 °C 40” →60°C 25” →72 °C 30”) →72°C 10min

35 cycles

A→G mutation create a Rsa1 site

PCR product: 357 bp, His/His: 299+58 bp, Arg/Arg: 177+122+58 bp

2%agarose electrophoresis’

Estrogen metabolizing and receptor gene polymorphism genotying

COMT (Val158Met)

5’-TCGTGGACGCCGTGATTCAGG-3’

5’-AGGTCTGACAACGGGTCAGGC-3’

94 4 mins → （94 40” → 55 30” → 72 30”）→ 72 10 mins

35 cycles

Size of PCR product: 217bp

A→G loss of an NlaIII site

Met/Met: 40+96+81bp, Val/Val: 136+81bp

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CYP17

5’-CATTCGCACTCTGGAGTC-3’

5’-AGGCTCTTGGGGTACTTG-3’

94 °C 4 min → (94 °C 40” →57°C 30” →72 °C 40”) →72°C 10min

35 cycles

SNP located at 34 bp upstream from the initiation of translation

T-C mutation create a MspA1I site,

PCR product: 419, wt/wt: 419, mt/mt: 295+124

***CYP19* (TTTA)n in Intron 5**

5’-GTC TAT GAA TAT GCC TTT TT-3’

5’-GTT TGA CTC CGT GTG TTT GA-3’

PCR product: 291-320 bp

94 4 mins → （94 40” → 55 30” → 72 30”）→ 72 10 mins

for 35 cycles

***ESR* (Codon 325)**

5’-GCC CGC TCA TGA TCA AAC G-3’

5’-GGA TCA TAC TCG GAA TAG AGA AT-3’

94 4 mins → （94 40” → 55 30” → 72 30”）→ 72 10 mins

for 35 cycles

Size of PCR product: 120 bp

Codon 325 CCC→ CCG create Hinf1

CCC (120bp) →CCG (98+21 bp)

***CYP1A1* (exon 7)**

5’-GAACTGCCACTTCAGCTGTCT-3’

5’-GAAAGACCTCCCAGCGGTCA-3’

94 °C 4 min → (94 °C 40” →60°C 25” →72 °C 30”) →72°C 10min

35 cycles

Codon 462 Ile→ Val (ATT→GTT)

PCR product 187 bp, A-G mutation create HincII site, Ile: 139+48, Val: 120+48+19 bp

DNA repair enzyme genotying

Genotypes were examined using polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) assays. Primers for XRCC1 exon 6 were 5’-CGA GTC TAG GTC TCA ACC CTA CTC ACT-3’ and 5’-GTT CCG TGT GAA GGA GGA GGA-3’, which amplified a 138

bp DNA fragment. Primers for XRCC1 exons 9 and 10 were 5'-TTG ACC CCC AGT GGT GCT AA-3' and 5'-GGC TGG GAC CAC CTG TGT T-3', which amplified an 861 bp DNA fragment. Primers for XRCC3 exon 7 were 5'- TCG CCT GGT GGT CAT CGA CTC-3' and 5'-GCA TCC TGG CTA AAA ATA CGA GC-3', which amplified a 207 bp DNA fragment. Primers for hMLH1 5'-flanking region were 5'-AGT AGC CGC TTC AGG GA-3' and 5'-CTC GTC CAG CCG CCG AAT AA-3', which amplified a 259 bp DNA fragment. Primers for XPD exon 23 were 5'-AGG ATC AGC TGG GCC TGT CCC TGC-3' and 5'-TGT GGA CGT GAC AGT GAG AAA T-3', which amplified a 220 bp DNA fragment. All PCRs were under the same condition as follows: a 50μL reaction mixture containing 2μL of genomic DNA, 1μL each dNTPS, 0.5 unit Tag (Promega, Madison, WI), and 1X PCR buffer. PCR program was consisted of an initial melting step of 94℃ for 4 minutes, followed by 35 cycles of 40 seconds at 94℃and 30 second at 55℃. The products were electrophoresed using 2% agarose gel and visualized by ethidium bromide.

The restriction enzyme Pvu II was used to distinguish the 26304 polymorphism of XRCC1 exon 6 in which the gain of a Pvu II restriction site occurred in the polymorphic allele. The Arg/Arg, Arg/Trp, and Trp/Trp genotypes for codon 194 resulted in 138 bp; 138 bp, 63 bp and 75 bp; and 63 bp and 75 bp digestion products, respectively. The restriction enzyme Rsa I was used to distinguish the 27466 polymorphism of XRCC1 exon 9. The Arg/Arg, Arg/His, and His/His genotypes for codon 280 resulted in 63 bp, 201 bp and 597 bp; 63 bp, 201 bp, 597 bp and 660 bp; and 660 bp and 201 bp digestion products, respectively. The restriction enzyme Msp I was used to distinguish the 28152 polymorphism of XRCC1 exon 10. The Arg/Arg, Arg/Gln, and Gln/Gln genotypes for codon 399 resulted in 115 bp, 285 bp and 461 bp; 115 bp, 285 bp, 461 bp and 576 bp; and 285 bp and 576 bp digestion products, respectively. The restriction enzyme Nla III was used to distinguish the 18067 polymorphism of XRCC3 exon 7. The Thr/Thr, Thr/Met and Met/Met genotypes for codon 241 resulted in 207 bp; 207 bp, 103 bp and 104 bp; and 103 bp and 104 bp, respectively. The restriction enzyme Mob II was used to distinguish the 35931 polymorphism of XPD exon 23. The Lys/Lys, Lys/Gln, and Gln/Gln genotyps for codon 751 resulted in 80 bp and 140 bp; 80 bp, 140 bp and 220 bp;

and 220 bp, respectively. The restriction enzyme Pvu II was used to distinguish the polymorphism at position -93nt of hMLH1 5'-flanking region. The G/G, G/A, and A/A alleles resulted in 125 bp and 134 bp; 125 bp, 134 bp and 259 bp; and 259 bp digestion products, respectively.

Statistical analysis

In the case-control study, odds ratios and their 95% confidence intervals were used as estimates of relative risk. Univariate logistic regression model was applied to test the potential risk factors mentioned above. The significant risk factors identified in univariate logistic regression model were put into multiple logistic regressions. All the models were adjusted for age and education levels. Stratified analysis was done for evaluating the interactive effect of tobacco smoke exposure and cooking exposure, tobacco smoke exposure and family history, and hormone exposure period and BMI. All univariate and multivariate logistic regressions were adjusted for age, education level. All non-smoking related risk factors analysis was adjusted for smoking exposure. All p values were obtained by two-tail test.

The genotype-genotype interaction effect was divided into four groups: individuals with three, two, one, and no putative high-risk genotypes of phase I metabolizing genes, phase II metabolizing genes, and estrogen metabolizing enzymes. The gene dosage effect was evaluated by p value obtained from test for trend method. The genotype-environment interaction effect was divided into four groups: individuals

with three, two, one, and no putative high-risk factors among tobacco smoke exposure, cooking fume exposure, and three putative high-risk genotypes. The gene-environment dosage effect was evaluated by p value obtained from test for trend method. All p values were from two-tailed tests.

Results

We showed demographic characteristics in Table 1-1. Among cases, the peak incidence was among 60-69 years group (26.6%), which was consistent with previous finding. And we found a small plateau over 40-60 years (comprised of more than 40% cases). It seemed that more female adenocarcinoma occurring at younger age than male. The mean age was 60.33 among case group, and was 56.27 among control group; the mean schooling year was 7.4 years among case group, and 9.72 years among control group. Overall, the control group was younger and receiving higher education than cases. So, in the following analysis, we all adjusted for age and education levels. As to the ethnic groups, we found no significant difference among cases and controls. More than three fourth of the subjects were Fukienese.

In Table 1-2, we showed the smoking-related risk factors in association with lung adenocarcinoma. The ever-smoker possessed a 2.4-folds significant risk compared with nonsmoker. Only 8.2% female adenocarcinoma were an ever smoker, which was the lowest compared to previous study (4). The risk increased when the smoking duration and cumulative smoking amount increased, showing a significant trend. Those who smoked more than 25 pack-years possessed a 6.3-folds risk compared with nonsmoker. Table 1-3 showed the passive cigarette smoke related

factors. Spouse smoking exposure only carried a 1.2-folds non-significant risk; however, if her husband smoked just besides her, the risk increased to 1.5-folds. We stratified the cumulative amount of spouse smoking exposure into four levels to test the dose-response relationship; however, there were no significant trend. We also found that if more than 10 coworkers were ever smoker, the risk would be up to 2.8-folds. We categorized the subjects who were ever-smokers or her spouse smoked just besides her as having “tobacco smoke exposure”, and found that it carried a 1.7-fold (95%CI=1.1-2.5) significant risk.

Table 1-4 showed cooking-related risk factors before 40. Almost all subjects (>90 % cases and controls) cooked daily before 40, which is consistent with traditional Chinese women daily practice. The odds ratio for cooking habit did not show significant association with lung adenocarcinoma (OR=0.6) because almost all subjects had the exposure. However, if we compared those who had cooking habit and did not have fume extractor in kitchen with those who did not cook or cooked but had fume extractor in kitchen, we see a non-significant increased risk (OR=1.3, 95%CI= 0.8- 2.2). And then, we categorized those who did not cook or cooked but had fume extractor in kitchen as no cooking fume exposure, and those who had cooking habit and did not have fume extractor in kitchen as having cooking fume exposure. Age at starting cooking did not show significant trend with the

development of lung adenocarcinoma. However, total duration of cooking before 40 showed a mild, but non-significant trend in association with the development of lung adenocarcinoma. As to the cooking oils, we found that lard oils possessed a 2.1-folds (95%CI=1.2-3.8) of significant risk compared with no cooking fume exposure. Vegetable oils did not show significant risk (OR=0.7, 95% CI=0.4-1.3). As to the cooking fuels, we found that coal, wood and charcoal possessed a 1.6-folds (95%CI=1.0-2.8) of significant risk compared with no cooking fume exposure. Electricity and natural gas did not show significant risk (OR=0.6, 95% CI=0.2-1.6). We concluded that those who cooked, had no fume extractor, and used lard oils as cooking oils or used coal, wood, and charcoal as cooking fuels possessed higher risk for lung adenocarcinoma.

Table 1-5 showed hormone-related risk factor in association with lung adenocarcinoma. Late onset of menarche (>=15 years) showed a borderline significant risk for developing lung adenocarcinoma compared with early onset of menarche. The earlier menopause the subjects were, the higher risk for lung adenocarcinoma they would have, showing a significant trends. Those who were menopausal carried a 6.6-folds risk (95%CI=2.9-14.7) compared with those who were not yet menopausal, adjusting for age and education levels. Longer menstruation period (>6 days) (OR=1.6, 95%CI=1.0-2.5), longer menstruation cycle

(>=25 days) (OR=2.3, 95%CI=1.0-5.3) showed higher risk compared with shorter menstruation period (<=6 days) and shorter menstruation cycle (<25 days). As the numbers of gestation and parity increased, the risk for lung adenocarcinoma increased simultaneously, and it showed a significant trend (p for trend <0.05). Breast-feeding more than 18 months carried a 1.7-folds significant risk (95%CI=1.0-2.8) compared with less than 18 months or no breast-feeding. As to the external source of sex hormone, history of oral contraceptives and hormone replacement therapy carried a borderline significantly protective effect (OR=0.6, 0.7, respectively). And the protective effect increased as the duration of usage increased, all showed a significant trend (p for trend <0.05). In those taking more than 1 year compared with subjects never using, the ORs were 0.3, and 0.4 respectively for oral contraceptives and HRT. Taking Chinese herb drug for menstruation-regulation possessed a 1.2-folds significant risk (95%CI=1.0-1.5). BMI was inversely associated with lung adenocarcinoma risk, and the more obese the women were, the more unlikely she contracted lung cancer (p for trend =0.01). BMI >22.5 had a 0.6-fold significantly protective risk compared with BMI <=22.5. Hormone exposure period (>=30 years) had no association with lung adenocarcinoma. (OR=1.1, 95%CI=0.7-1.7). Overall, many hormone-related items were associated with lung cancer risk.

Table 1-6 showed personal medical history and family history of lung cancer in association with lung adenocarcinoma. Pulmonary tuberculosis had a 2.3-folds significant risk for lung adenocarcinoma. COPD, asthma, hysterectomy, and oophorectomy were not associated with lung adenocarcinoma. As to the family history, we found mother contracting lung cancer carried an 8.9-folds significant risk for lung adenocarcinoma. Sibling contracting lung cancer also carried a 5.6-folds significant risk for lung adenocarcinoma. Father contracting lung cancer was not associated with lung adenocarcinoma. If we included all first-degree relatives, we found 1.9-folds significant risk for lung adenocarcinoma. If we exclude father, all first-degree relatives showed a 4.9-flods (95%CI=1.7-14.1). Table 1-7 showed the results of hormone-related risk factors in multiple logistic regression models. The analysis was adjusted for age, education levels, and smoking exposure. We found that oral contraceptives (OR=0.6), hormone replacement therapy (OR=0.2), BMI (OR=0.4), menopause (OR=9.0), and longer menstruation period (OR=1.7) showed significant association with lung adenocarcinoma. However, “breast feeding longer than 18 months” showed borderline significance (OR=1.8). Other items, including shorter menstruation cycle length, menstruation regularity, age at menarche, and Chinese herb drug did not show association with lung adenocarcinoma. In Table 1-8, we put all putative risk factors derived from univariate logistic regression into

multiple logistic regression models. The analysis was adjusted for age and education levels. We found that cooking oil with lard (OR=2.0), tobacco smoke exposure (OR=2.0), oral contraceptives (OR=0.6), hormone replacement therapy (OR=0.2), BMI (OR=0.5) and menopause (OR=9.8) showed significant association with lung adenocarcinoma. However, longer menstruation period (OR=1.7) showed borderline significance. Other items, including lung cancer history of first-degree relatives (OR=3.0), and pulmonary tuberculosis (OR=0.9) did not show association with lung adenocarcinoma.

Tables 1-9 to 1-13 showed the interactive effect of tobacco smoke exposure and cooking fume exposure, tobacco smoke exposure and cooking oil, tobacco smoke exposure and cooking fuels, tobacco smoke exposure and, and BMI and hormone exposure period in relation to lung adenocarcinoma. We found **multiplicative** patterns in “tobacco smoke exposure” and “cooking fume exposure”, “tobacco smoke exposure” and “cooking oils”, “tobacco smoke exposure” and “cooking fuels”, and “tobacco smoke exposure” and “family history of lung cancer”. We investigated the modifier effect with regard to BMI in association with lung adenocarcinoma. In shorter hormone exposure period, the ORs for lung adenocarcinoma were 1, 0.6, 0.6 respectively for those BMI<=22.5, 22.5-25, and BMI>25. However, in longer hormone exposure period, the ORs for lung

adenocarcinoma were 1, 0.5, 0.4 respectively, for those BMI<=22.5, 22.5-25, and BMI>25. It seemed no modifying among BMI and hormone exposure period.

Table 2-1 presents the overall distribution of cases and controls and adjusted ORs and 95% CI s by genotypes of phase I genes. The *CYP1A1* Ile/Ile genotype had 1.8-folds (95% CI=1.1-2.9) increased risk of developing lung adenocarcinoma (compared with Ile/Val and Val/Val genotype as the referent group). The *CYP1A2* G/G or G/A genotype had 3.9-folds (95% CI=1.4-11.3) increased risk of developing lung adenocarcinoma (compared with A/A). Other phase I gene, i.e. *CYP1A1* MspI polymorphism (TT/TC vs. CC, OR= 1.4, 95% C.I.= 0.7-2.5), *CYP2E1* RsaI polymorphism (c1c1/ c1c2 vs. c2c2, OR= 1.4, 95% C.I= 0.4-4.3), *CYP2E1* DraI polymorphism (DD/ DC vs. CC, OR=1.5, 95% C.I= 0.5-3.9), *CYP2C19* exon 5 (GG/GA vs. AA, OR= 1.3, 95% C.I.= 0.6-2.98), *CYP1B1* codon 48 (Ala/Ala vs. Ala/Ser, Ser/Ser, OR= 1.1, 95% C.I= 0.6-2.0), *CYP1B1* codon 432 (Val/Val vs. Val/Leu, Leu/Leu, OR= 1.4, 95% C.I= 0.7-2.5), did not show significant association with lung adenocarcinoma.

To avoid gene-gene confounding effect, we put all phase I genes into multiple logistic regression model. Because the *CYP1A1* MspI and Ile/Val polymorphism, and the *CYP2E1* RsaI and DraI polymorphisms all showed strong linkage disequilibrium, only *CYP1A1* Ile/Val polymorphisms and *CYP2E1* RsaI

polymorphism were included in the model. *CYP1A1* Ile/Val polymorphism was chosen due to their greater risk in the simple logistic regression. *CYP2E1* RsaI polymorphism was chosen because its phenotypic implication is more evident than DraI polymorphisms in previous studies. As to *CYP1B1*, only codon 432 polymorphism was included in the model due to their greater risk in the simple logistic regression than *CYP1B1* codon 48. The results are showed in table 2-2: only *CYP1A2* 5' flanking region polymorphism (GG/GA vs. AA) showed a 6.5-folds risk of developing female lung adenocarcinoma (95% C.I 1.6-29.2), *CYP2E1* RsaI polymorphism (c1c2/c1c1 vs. c2c2) had a 1.3-folds risk; however, it did not reach statistical significance. Table 2-3 presents the gene dosage effect. *CYP1A1* Ile/Val, *CYP1A2* 5' flanking region, and *CYP2E1* RsaI polymorphisms were combined into a four-level model of risk. A borderline significantly dose-response relationship was noted between the numbers of putative high-risk genotype and the risk of lung adenocarcinoma (p=0.06). OR=1 for those with three risk genotype (referent group), adjusted OR=0.9 (95% CI=0.5-1.5) for those with two putative high-risk genotype, adjusted OR=0.5 (95% CI=0.2-1.0) for those with one putative high-risk genotype, and adjusted OR=0.2 (95% CI=0.02-1.3) for those with zero putative high-risk genotype. Table 2-4 presents the gene-environment dosage effect. Tobacco exposure, cooking fume exposure, and phase I gene were combined into a four-level model of

risk. We categorized phase I gene into two groups: one group having less than three putative high-risk genotypes, the other group having three putative high-risk genotypes. We assigned those with neither risk factor as referent group. Having one putative high-risk factor (including any one of tobacco smoke exposure, cooking fume exposure, or three putative high-risk genotypes) is associated with a 1.4-folds increased risk for developing lung adenocarcinoma. Having two putative high-risk factors (including any two of tobacco exposure, cooking fume exposure, or three putative high-risk genotypes) is associated with a significantly higher risk of lung adenocarcinoma (OR=3.0; 95% CI=1.4-6.2). Women who had three putative high-risk factors (those who exposed to tobacco, cooking fume, and having three putative high risk genotypes) had a strong associated with lung adenocarcinoma (OR=20.8; 95% CI =2.4-179.3). And it showed strong linear trend in our analysis ($p<0.0001$).

Table 3-1 presents the overall distribution of cases and controls and adjusted ORs and 95% CI s by genotypes of phase II genes. The *GSTM1* null genotype has 1.5-folds (95% CI=0.9-2.5) borderline significantly increased risk for developing lung adenocarcinoma (compared with non-null genotype). The *COMT* Val/Met, Met/Met genotype has 1.7-folds (95% CI=1.1-2.8) increased risk for developing lung adenocarcinoma (compared with Val/Val). Other phase II gene, such as *GSTT1*

(null vs. non-null, OR= 0.9, 95% CI=0.5-1.4), *GSTP1* $^{Ile}105^{Val}$ polymorphism (Ile/Ile vs. Ile/Val and Val/Val, OR= 1.3, 95% CI=0.8-2.1), *NAT1* (slow acetylator vs. rapid acetylator, OR=1.2, 95% CI=0.7-2.4), *NAT2* (slow acetylator vs. rapid acetylator, OR=1.2, 95% CI= 0.6-2.3), *Epoxide hydrolase* $^{Tyr}113^{His}$ (His/His, Tyr/His vs. Tyr/Tyr, OR=1.4, 95% CI=0.9-2.3), *Epoxide hydrolase* $^{His}139^{Arg}$ (Arg/Arg, Arg/His vs. His/His, OR=1.2, 95% CI =0.7-2.3), do not show significant association with female lung adenocarcinoma.

To avoid gene-gene confounding effect, we put all phase II genes into multiple logistic regression models. The results are showed in Table 3-2. *COMT* $^{Met}158^{Val}$ (Met/Met, Met/Val vs. Val/Val) shows a 2.2-folds increased risk for developing female lung adenocarcinoma (95% C.I 1.2-4.0). *Epoxide hydrolase* $^{Tyr}113^{His}$ (Tyr/His, His/His vs. Tyr/Tyr) shows a 2.0-folds increased risk (95% CI =1.1-3.7), and *GSTM1* null genotype shows borderline significantly association with female lung adenocarcinoma compared with *GSTM1* non-null genotype (OR=1.7, 95% CI =0.9-3.1). In order to see the gene dosage effect, *GSTM1*, *EH* $^{Tyr}113^{His}$, and *COMT* $^{Met}158^{Val}$ polymorphisms are combined into a model of four-level risk. The results are shown in Table 3-3: OR=1 for those with zero putative high-risk genotype (referent group), adjusted OR=3.1 (95% CI =0.9-10.3) for those with one putative high-risk genotype, adjusted OR=4.1 (95% CI =1.2-13.5) for those with two putative

high-risk genotype, and adjusted OR=11.7 (95% CI =3.0-45.5) for those with three putative high-risk genotype. A significantly dose-response relationship is noted between the numbers of putative high-risk genotype and the risk of lung adenocarcinoma (test for trend p<0.001). Table 3-4 presents the gene-environment dosage effect. Tobacco exposure, cooking fume exposure, and phase II gene are combined into a model of four-level risk. We categorize phase II gene into two groups: one group has less than three putative high-risk genotypes; the other group has three putative high-risk genotypes. OR=1 is for those with neither risk factor (referent group), adjusted OR=2.9 (95% CI=1.3-6.6) is for those with one putative high-risk factor (including any one of tobacco exposure, cooking fume exposure, or three putative high-risk genotypes). Having two putative high-risk factors (including any two of tobacco exposure, cooking fume exposure, or three putative high-risk genotypes) is associated with a significantly higher risk for lung adenocarcinoma (OR=6.0; 95% CI=2.6-13.8). Having two putative high-risk factors (those who exposed to tobacco, cooking fume, and having three putative high risk genotypes) is strongly associated with lung adenocarcinoma (OR=13.5, 95% CI =4.7-38.4). And a significantly dose-response relationship is noted between the numbers of putative high-risk factors and the risk of lung adenocarcinoma (test for trend p<0.001). Table 3-5 shows the combined effect of *NAT1* and *NAT2* genetic polymorphisms. The

subject possessing one or two rapid acetylator shows an 8.4-folds significantly increased risk for developing lung adenocarcinoma, compared with the slow/slow acetylator combination. Table 3-6 shows the combined effect of *GSTM1*, *GSTT1*, and *GSTP1*. We found that the subjects possessing three putative high-risk genotypes have a 2.2-folds increased risk for developing lung adenocarcinoma, compared with those who have none putative high-risk genotype. And the subjects possessing one or more than one putative high-risk genotype have a 1.9-folds of increased risk compared with those who have none putative high-risk genotype, but all do not reach statistical significance.

Table 4-1 presents the overall distribution of cases and controls and adjusted ORs and 95%CIs by genotypes of hormone-related genes. The *CYP17* A2A2 genotype has 2.2-folds (95%C.I.=1.1-4.5) significantly increased risk for developing lung adenocarcinoma (compared with A1A1 genotype). The *COMT* Val/Met, Met/Met genotype has 1.7-folds (95% CI=1.1-2.8) increased risk for developing lung adenocarcinoma (compared with Val/Val). Other hormone-related gene, such as *CYP19* microsatellite number and *ESR* codon 325 polymorphisms do not show statistically significant association with lung adenocarcinoma.

To avoid gene-gene confounding effect, we put all hormone-related genes into multiple logistic regression models. The results are showed in table 4-2. In model 1,

we put all the hormone related genes into the model. In model 2, only CYP17, CYP19, and COMT are put into the model. In model 2, *COMT* (Met/Met, Met/Val vs. Val/Val) shows a 1.7-folds increased risk for developing female lung adenocarcinoma (95% C.I=1.0-2.9), and *CYP17* A2A2 shows a 1.7-folds increased risk for developing female lung adenocarcinoma (95% C.I=1.0-3.0). *CYP19* and *ESR* codon 325 do not show statistical significance with lung adenocarcinoma. In order to see the synthesis gene and metabolizing gene interactive effects stratified analysis of *CYP17* and *COMT* in relation to lung adenocarcinoma is shown in table 4-3. Those who possess *CYP 17* A2/A2 and *COMT* Met carrier have a 4.2-folds risk compared with those who possess *CYP17* A1/A1 and *COMT* Val/Val. In table 4-4, we show that the synthesis gene and metabolizing gene interactive effect is modified by BMI of the subjects. Those who possess *CYP17* A2/A2 and *COMT* Met carrier have a 6.7-folds significantly increased risk compared with those who possess *CYP17* A1/A1 and *COMT* Val/Val among thinner subjects (BMI<=23), but only 2.5-folds non-significant risk among fatter subjects (BMI>23). In table 4-5, we show that the synthesis gene and metabolizing gene interactive effect is modified by hormone exposure period of the subjects. Those who possess *CYP17* A2/A2 and *COMT* Met carrier have a 10.4-folds significantly increased risk compared with those who possess *CYP17* A1/A1 and *COMT* Val/Val among shorter hormone

exposure period group (<=363 months), but only 1.1-folds non-significant risk among longer hormone exposure period group (>363 months). In order to see the three genes gene-dosage effect, *CYP17*, *CYP19*, and *COMT* polymorphisms are combined into a model of four-level risk. The results are shown in table 4-6: OR=1 for those with three putative high-risk genotypes (referent group), adjusted OR=0.5 (95%CI=0.3-0.9) for those with two putative high-risk genotypes, adjusted OR=0.4 (95%CI=0.2-0.8) for those with one putative high-risk genotype, and adjusted OR=0.2 (95%CI=0.01-2.3) for those with zero putative high-risk genotype. A significantly dose-response relationship is noted between the numbers of putative high-risk genotype and the risk of lung adenocarcinoma (test for trend $p<0.002$). Table 4-7 shows four genes gene-dosage effect. *CYP1A1*, *CYP17*, *CYP19*, and *COMT* polymorphisms are combined into a model of five-level risk. OR=1 for those with four putative high-risk genotypes (referent group), adjusted OR=0.4 (95%CI=0.4-0.7) for those with three putative high-risk genotypes, adjusted OR=0.2 (95%CI=0.1-0.5) for those with two putative high-risk genotypes, and adjusted OR=0.3 (95%CI=0.1-0.9) for those with one putative high-risk genotype. No any cases possess zero high-risk genotype. A significantly dose-response relationship is noted between the numbers of putative high-risk genotype and the risk of lung adenocarcinoma (test for trend $p<0.005$).

Table 5-1 compares the genetic polymorphisms of four DNA-repair enzymes between cases and controls. Cases had higher percentages of Arg/Arg and Arg/Trp genotypes of XRCC1 codon 194, Gln/Gln genotype of XRCC1 codon 399, Thr/Met genotype of XRCC3 codon 241, Lys/Gln and Gln/Gln genotypes of XPD codon 751, and GA and AA genotypes of hMLH1 at -95 nucleotide. Cases and controls had similat genotype frequency of XRCC1 codon 280. The age-adjusted OR (95% CI) of developing lung adenocarcinoma was 5.6 (1.2-26.2) for Arg/Arg and Arg/Trp genotypes of XRCC1 codon 194 compared with Trp/Trp genotype as the referent; 2.2 (1.1-4.6) for Gln/Gln genotype of XRCC1 codon 399 compared with Arg/Arg and Arg/Gln genotypes; 2.8 (1.0-7.8) for Thr/Met genotype of XRCC3 codon 241 compared with Thr/Thr genotype; 2.7 (1.5-4.8) for Lys/Gln and Gln/Gln genotypes of XPD codon 751 compared with Lys/Lys genotype; and 2.9 (1.2-7.1) for GA and AA genotypes of hMLH1 compared with GG genotype.

There was significant correlation with genotype of XRCC1 codon 399 for genotypes of XRCC1 codon 194 and codon 280. The percentages of Trp/Trp genotype of XRCC1 codon 194 and His/His genotype of XRCC1 codon 280 were less than 2%. Accordingly, only the genotype of XRCC1 codon 399 was included in the further multiple regression analysis as shown in Table 5-2. Genetic polymorphisms of all four DNA-repair enzymes remained to be significant risk factors for lung

adenocarcinoma after adjustment for age, exposures to tobacco smoke and cooking fume, and genotypes of other DNA-repair enzymes. The multivariate-adjusted ORs for high-risk genotype of these DNA-repair enzymes ranged from 2.5 to 3.1. Table 5-3 presents the association with lung adenocarcinoma for the combination of high-risk genotypes of four DNA repair enzymes. Neither cases nor controls had high-risk genotypes of all four enzymes. There were more cases had a higher number of high-risk genotypes than controls. A significant dose-response relationship was observed between the risk of lung adenocarcinoma and the number of high-risk genotypes of DNA-repair enzymes ($p<0.0001$ for trend). Compared with those who had no high-risk genotype as the referent group, the multivariate-adjusted ORs (95% CI) were 4.3 (1.0-19.67), 11.8 (2.5-54.8) and 18.9 (3.1-115.8) for those who had one, two and three high-risk genotypes, respectively. The dose-response relationship remained statistically significant in the stratification analyses by exposures to tobacco smoke and cooking fume. Table 5-4 shows the effects of combination of genetic and environmental factors on the development of lung adenocarcinoma. We categorized DNA repair gene into two groups. A significantly increased risk of lung adenocarcinoma was observed with the number of both environmental and genetic risk factors showing a dose-response relationship ($p<0.0001$ for trend).

Discussion

The cause of female lung adenocarcinoma in Taiwan remained unknown. Our case-control study was conducted to elucidate the possible risk factors, including active smoking, passive smoking, cooking fume exposure, hormone-related risk factors, and personal and family history. We focused on female lung adenocarcinoma in Taiwan, where had the lowest sex ratio of lung cancer incidence, relatively low smoking prevalence among female lung cancer, higher proportion of adenocarcinoma among lung cancer, and the most rapid increased rate of lung cancer during past fifty years in the world. To the best of our knowledge, this was the first study focusing on lung adenocarcinoma conducted in Taiwanese women. In our study, a total of 184 lung adenocarcinoma (histologically proved) and 350

controls were recruited. The response rate in cases was 92%; only 8% of the cases did not received interview due to too ill, death, and discharge. The response rate in controls was 99.4% (350/352); only 2 eligible controls refuse to be interviewed. The causes for not participating the study were not associated with risk factors we intended to investigate in our study; so, it did not influence the accuracy of our results. In our study, we did not use proxy responders in both cases and controls to avoid information bias. The catchments area of cases was slightly different from the catchments area of controls. However, we compared the ethnicity for cases and controls, we found no significant difference. Our control group was selected from health examinees. The risk factors we intended to investigate (such as smoking, cooking, hormone-related factors) were not associated with the characteristics of the health examinees. So, the selection bias may be limited. As to recall bias, it is common problem in case-control study. However, the cooking habits and smoking habits of herself or her coworker and co-inhabitants were so consistent and unchangeable in her life, so the effects of recall bias were also limited. As to the sample size, our study is adequate for OR=1.5, under the assumption of α level=0.05, β level =0.8, exposure p=0.5, 1: 2 match. In most of risk factors we investigated, the sample size was adequate.

In our study and cancer registry data conducted in Taiwan (1), we found that female

lung adenocarcinoma occurred at younger age than male lung cancer. A small plateau was noted between 40-60 years, and most of them were nonsmokers. Chinese cooking style was considered as important risk factors in previous studies (2, 3-6). The cooking related items, such as cooking frequency, cooking oils, cooking fuels, fume extractor and ventilation device were considered as important factors for lung cancer (3-6). There were some debates as to cooking fume exposure being the major determinants for female lung adenocarcinoma. Firstly, the use of fume extractor in Taiwan now is very popular, but the incidence of female lung adenocarcinoma remains steadily increased; secondly, Chinese women had cooked for thousands of years; however, the incidence rate of lung cancer increased for about 8-folds during past thirty years, and 50-folds during past fifty years (1). Ko (5) had proposed several reasons: fume extractors are not positioned properly, modern housing is small, vegetable oils were increasingly used, cohort effect and longer life expectancy, and other risk factors (such as passive smoking, air pollution) interacted with the mutagenicity of cooking oil fume. However, we did not think that the reasons could fully explain the discrepancy. In Ko study (5), using fume extractor had a more than 2-folds significant protective effect compared with no using fume extractor before age 40. In our study, we found a non-significant risk for those who cooked and no using fume extractor (OR= 1.3) before age 40. The fume extractor

might not be positioned properly; however, it was better than no using fume extractor. Till now, there is no consistent evidence showing vegetable oils more hazardous than lard oils. Cooking fume analysis showed mutagenicity and genotoxicity in both lard oils and vegetable oils (7-8). PAHs and other carcinogens were also found in both (7-8). And in our study, we showed much higher risk for using lard as cooking oils (OR=2.1), compared with using vegetable oils (OR=0.7). So, the increased usage of vegetable oils could not explain the increase of lung adenocarcinoma. As the life expectancy prolonged, other competing cause for lung cancer, such as other malignancy, cardiovascular disease, and cerebrovascular diseases did not show the same magnitude of increase as lung cancer. The only plausible reason was that modern housing is smaller than before due to the effect of urbanization and industrialization. So, more cooking fume was exposed during past thirty years. In our study, we found that cooking habit was not associated with lung adenocarcinoma, because more than 90% cases and controls had cooking habits before 40. So, the cooking habit was not the main determinant for cooking hazards. However, we categorized the subjects having no cooking habit or cooking but using fume extractor as “no cooking fume exposure”. Those who cooked and did not use fume extractor were considered as having “cooking fume exposure”. We found that cooking fume exposure had a 1.3-fold borderline significant risk for developing lung

adenocarcinoma. Then, we further stratified the subjects into three groups: no cooking exposure, using vegetable oils, and using lard oils. We found lard oils had a 2.1-folds risk compared to no cooking fume exposure. We also found that using coal or charcoal as cooking fuels possessed a 1.6-folds significant risk for developing lung adenocarcinoma. Age at starting cooking and total cooking duration before 40 did not show any significant trends for developing lung adenocarcinoma. Our results were slightly difference from previous studies. It seemed that cooking-related risk factors not so important in our study. The style of cooking (stir-frying, deep frying, and frying) and cooking frequency were also not associated with lung adenocarcinoma (not shown in our analysis). In Chinese studies, especially conducted in Shanghai, rapeseed oils seemed to be hazardous, and the component analysis and mutagenicity and genotoxicity assay all showed compatible results (9). However, in Taiwan, rapeseed oil was not used. Lard oils, soybeans oils, peanut oils, and sunflower oils were the most often used cooking oils. In the early decades, lard oils were not refined, and were frequently repeated used due to economic consideration. Chinese cooking style, including deep-frying, frying, stir-frying, might reach high temperature (250-300℃) while cooking. The unrefined lard oils repeated used in high temperature could produce large amount carcinogens. As to the cooking fuels, it had been reported that smoke from coal, wood, and charcoal

contains genotoxic PAHs (10). In China, Xuan Wei County had the highest lung cancer incidence in both male and female. However, the smoking rate was low in Xuan Wei. It was believed that the high incidence of lung cancer might be due to indoor air pollution from coal combustion (11). However, there were no reports for natural gas and electricity. So, our study showing that cooking fuels with coal, wood, or charcoal possessing higher risk for lung adenocarcinoma was biological plausible.

Passive smoking was a proved risk factor to lung cancer. Meta-analysis for 13 studies reported in NRC (12) showed a 1.34 (95%CI=1.18-1.53) significant risk for lung cancer. Hackshaw reported a meta-analysis recently conducted for 37 studies (13), and showed a 1.23-folds (1.13-1.34) significant risk. As we know, the major histological type of lung cancer related to cigarette smoking is SCC, and adenocarcinoma is weakly associated with cigarette smoking. In our study, we found that eve-smoker possessed only 2.4-folds of risk for lung adenocarcinoma. Some carcinogens, such as 4-aminobiphenyl, have higher concentration in side-stream smoke than in the mainstream smoke (up to 30 folds). One important limitation of studies investigating the relationship between passive smoking and lung cancer was that the true exposed amount of smoke is difficult to be measured, depending on number of ever-smoker exposed, duration of exposure per day, and whether the active smokers smoke just besides the subjects or not. Despite that urine cotinine

may be a useful markers, it is not yet widely used in researches. In our study, spouse smoking exposure carried a 1.2-folds non-significant risk; however, if the spouse smoked just besides her, the risk was increased to 1.5-folds ($p<0.05$). The hazard was slightly greater than previous studies (OR=1.23) (13). In Taiwan, the husbands often smoke just besides her wives, and the average living space is smaller than that in American. So, the higher risk for spouse smoking exposure in Taiwan is reasonable. In our study, we couldn't find significant trends in spouse smoking duration and cumulative smoking amounts, because the duration and cumulative smoking amount couldn't represent the true amount of smoke the subjects exposed. For more precisely estimating the total sources of passive smoking, we must evaluate the childhood passive cigarette smoke exposure (including father and mother smoking history) and workplace passive cigarette smoke exposure. The childhood passive cigarette smoke exposure is important because the early event in life may play an important role on cancer initiation. The workplace passive cigarette smoke exposure is important because one may spend more than 8-10 hours per day in workplace during her adulthood. In our study, we found maternal smoking status possessed 1.8-folds significant risk. Paternal smoking status did not possess higher risk. We also found "more than 10 coworkers were ever-smoker" carrying a 2.5-folds significant risk. So, the hazard of passive cigarette smoke is more than

hazard of spouse smoking. What role did the passive cigarette smoke play in the growing epidemics of female lung adenocarcinoma in Taiwan? In 1972, the smoking prevalence is about 30% in male, and 2-3% in female; the smoking prevalence changed to 55-60% in male, and 3-4% in female in 1996. However, the sex ratio was still about 2.0-2.3. The increased incidence rate of lung cancer in male might be due to smoking epidemics and urbanization in Taiwan since 1950. How to explain the simultaneous increase of female incidence rate? Could it be explained by simultaneous increase in passive smoking prevalence (increase smoking rate of her father, husband, and male co-workers during the thirty years) and the same urbanization effect? Risch had mentioned that females are more susceptible to smoking induced lung cancer (14). The most possible explanation was different genetic susceptibility between sexes. Taioli had mentioned that hormone-related factors were associated with lung cancer. He also found that smoking could interact with hormone to contract lung cancer (15). The interaction of passive smoking with hormone-related factors might be the possible contributor for the growing epidemics for lung adenocarcinoma in Taiwanese women.

The most amazing finding in our study was that hormone-related factors were associated with female lung adenocarcinoma. As we previously mentioned, hormone-related risk factors might play a role in lung adenocarcinoma. Previously,

sex hormone was considered as promoter effect; however, recently, estrogen was considered a complete carcinogen due to accumulated evidence for estrogen action in the breast cancer and endometrial cancer (16). However, sex hormone possessed bi-directional effect, in other words, pro-oxidant or anti-oxidant. It had been proposed that in lower concentration of catechol estrogen, its lipid peroxidation effect predominates and shows carcinogenic effect. In higher level, its free radical scavenging effect predominates, and shows protective effect (17). Many papers reported that estrogen or progesterone receptors expression in lung tumor tissues (18-23). In our study, we found that early menopause, late menarche, more gestation and parity, longer duration of breast-feeding all carried significant higher risk for lung adenocarcinoma. Oral contraceptives, hormone replacement therapy, and larger BMI all showed significant protective effect. Longer hormone exposure periods showed non-significant. Length of menstrual period (>6 days), longer menstrual cycle all showed significant risk for lung adenocarcinoma. What did the above results mean? We propose that: longer and higher estrogen exposure seemed to be protective in lung adenocarcinoma in Taiwan, so we obtained just opposite results to breast cancer. After menopause, estrogen was mainly from peripheral fat tissue conversion. The more obese the subjects are, the higher serum level of estrogen the subjects will have. So, larger BMI after menopause means higher serum estrogen

level, thus showing protective effect for lung adenocarcinoma. In our study, the number of cases who were not menopause was so small that we could not further stratify it to test the interaction between BMI and menopause status. It had been reported (24) that mean serum estrogen level in Chinese women is lower than that in American. The results may be due to dietary factors (low fat and cholesterol), less obesity, and genetic components. So, among nonsmokers, the incidence rate of lung cancer in female is higher in Chinese women than in Caucasian women; however, the breast cancer incidence is much higher in Caucasian than in Chinese women. Taioli showed that smoking might interact with hormone to lung cancer (15). So, the baseline higher incidence of lung adenocarcinoma in Chinese women might be due to lower mean level of estrogen compared with Caucasian, and the growing epidemics of female lung adenocarcinoma in Taiwan might be due to interaction of passive smoking, cooking fumes with sex hormone. What is the precise mechanism of interaction? We know that some CYP enzymes, such as *CYP1A1*, *CYP1A2*, and *CYP1B1* were all responsible for metabolizing catechol estrogen. And the CYPs enzymes expression was modulated by Ah receptor, which is in induced by many inducers, such as dioxin, or some substances from tobacco smoke. In other word, tobacco smoke and dioxin may induce CYPs enzymes expression, thus influencing the metabolizing of catechol estrogen. So, the hypothesis is biological plausible. We

know that Taiwan is an area of heavy industrial pollution, and dioxin is especially notorious. Another study will be needed to elucidate the impact of environmental hormone.

If the sex hormone acted opposite roles among lung adenocarcinoma and breast cancer; as the western life style becoming more popular, the breast cancer incidence will be increased, and we can infer that: the incidence of lung adenocarcinoma will be decreased in the future. In Taiwan, the breast cancer incidence increased rapidly in recent decades; however, the incidence of lung adenocarcinoma did not decrease recently. However, some trend was still noted: the sex ratio increased gradually (1962-66, sex ratio= 1.6; 1987-1991, sex ratio=2.3) (25). In other words, the female adenocarcinoma increased more slowly than male in past thirty years. We proposed that the incidence rate of female lung adenocarcinoma in Taiwan might be decrease in the future.

Personal medical history was considered as risk factor for lung cancer in previous studies. Among them, pulmonary tuberculosis was most important. Cohort study (26) and case-control studies (27) all showed pulmonary tuberculosis associated with lung cancer, especially adenocarcinoma. Pulmonary tuberculosis is associated with lung cancer in several aspects: pulmonary tuberculosis is the risk factor for lung cancer; pulmonary tuberculosis may co-exist with lung cancer; pulmonary

tuberculosis is the competing cause of death for lung cancer; pulmonary tuberculosis may be misdiagnosed as lung cancer; and lung cancer may be misdiagnosed as tuberculosis. In Taiwan, the age-adjusted mortality rate of tuberculosis per 100,000 person was 88.6 for male, 46.6 for female in 1960, and 18.7 for male, 5.0 for female in 1991, decreased about 5-folds in male and 9-folds in female during past thirty decades (25), largely contributed to nutrition status improvement and widely use of anti-TB drug. However, in Taiwan, drug compliance was so poor that the tuberculosis often was not completely treated and relapsed frequently. Persistent inflammatory lung condition may provide the adequate environment for tumor formation. And according to the competing cause of death theory: if two diseases had the same etiology, as the one mortality decreased, the other one mortality increased simultaneously. This phenomenon might explain why female lung adenocarcinoma increased rapidly during the thirty years. Indirect evidence can support the hypothesis: in Taiwan, Aborigine had the highest smoking rate among different ethnicity; however, the lung cancer rate was lowest. And the pulmonary tuberculosis mortality rate was highest among different ethnic group. In our study, we found a 2.4-folds of risk for tuberculosis to develop lung adenocarcinoma. However, in multiple logistic regression analysis, the association became non-significant. It may be due to inadequate sample size to estimate too any

variables. The possibility of inaccurate recall of tuberculosis history existed. However, tuberculosis is a major event of life, and needs to take drug for a long duration. So, the possibility of recall bias was in limited range. Several studies had been conducted to evaluate the association of chronic obstructive pulmonary disease (chronic bronchitis and emphysema) with lung cancer (28-29), and the results mostly supported the association between lung cancer and COPD. However, in our study, we did not find any association with lung adenocarcinoma. COPD is highly correlated with cigarette smoking; however, in Taiwanese cohort study (30), the association of cigarette smoking with COPD was not so strong as that in western population. In Taiwan, COPD was frequently misdiagnosed as asthma or congestive heart failure. Thus, no association of COPD with lung adenocarcinoma might be the result of misclassification bias. In this situation, a medical record was more reliable than questionnaire interview. Other personal history, such as asthma, hysterectomy, and oophorectomy were also not associated with lung adenocarcinoma. Wu (31) had found the association of hysterectomy with lung cancer, and he proposed that pelvic thrombus during hysterectomy which might produce multiple showers of small emboli in the lungs, resulting in localized proliferative changes in the bronchial epithelium, thus causing lung cancer. We think that the hypothesis has too many assumptions and has little biological plausibility. In our study, we found no

association of hysterectomy with lung adenocarcinoma, because hysterectomy did not influence the hormone status. As to oophorectomy, we did not classify the age (pre-menopausal or post-menopausal), the causes (incidental or for cancer treatment), and the methods (unilateral or bilateral). So we could not accurately estimate the effect of oophorectomy on lung adenocarcinoma.

As to family history, previous studies (32-33) had shown that first-degree relatives carried a two to five folds risk for developing lung cancer. In our study, we found that the risk of family history differs between sexes. Among parents, mother contracting lung cancer carried an 8.9-folds significant risk, but father contracting lung cancer did not have any increased risk (OR=1.1). Sibling contracting lung cancer had a 5.6-folds significant risk for lung adenocarcinoma, however, the sisters contracting lung cancer possessing higher risk compared with brother (not shown here). According to our results, we found that: all first-degree relatives excluding father had a 4.9-folds for developing lung adenocarcinoma. Combined with the finding that hormone-related factors were associated with lung adenocarcinoma, we propose that: the hormonal factors related to lung adenocarcinoma were genetic inherited, and were transmitted among female relatives. So, hormone-related gene and X chromosome may be the target for linkage analysis in the future family study.

In our study, we had the following conclusions. Active smoking and passive

smoking were still important risk factors for lung adenocarcinoma in Taiwan. Higher prevalence of passive smoking among Taiwanese women may be the contributor to female lung adenocarcinoma epidemics during the fifty years. Cooking fume exposure was also the contributors for the lung adenocarcinoma; however, its importance was limited. Hormone-related risk factors were important determinants for lung adenocarcinoma. Higher and longer estrogen exposure had lower risk for lung adenocarcinoma, just opposite to the results found in breast cancer. The interaction between sex hormone and tobacco smoke may be the major contributors to lung adenocarcinoma epidemics. Family history carried a high risk for lung adenocarcinoma, especially female first-degree relatives. The decline of tuberculosis mortality during the thirty years might be another contributor to lung adenocarcinoma. Further studies for evaluating the genetic contribution for lung adenocarcinoma were needed. Family study and genome-wide scan for major genes or large-scale genetic association study for candidate genes approaches might be the future directions.

References

1. Department of Health, Executive Yuan, Republic of China: Health Statitics. Vol II, Vital Statistics, 1981-1997, Taipei, Department of Health, 1982-1997.
2. MacLennan R, Da Costa J, Day NE, et al. Risk factors for lung cancer in Singapore Chinese, a population with high female with high female incidence rate. Int J Cancer, 20: 854-860, 1977.
3. Law CH, Day NE, Shanmugaratnam K. Incidence rates of specific histological types of lung cancer in Singapore Chinese dialect group and their etiological significance. Int J Cancer, 17: 304-309, 1976.
4. Liu ZY, He XZ, Chapman RS. Smoking and other risk factors for lung cancer in Xuan Wei, China. Int J Epidemiol, 20: 26-31, 1991.
5. Ko YC, Lee CH, Chen MJ, et al. Risk factors for primary lung cancer among non-smoking women in Taiwan. Int J Epidemiol, 26: 24-31, 1997.
6. Gao YT, Blot WJ, Zheng W, et al. Lung cancer among Chinese women. Int J Cancer, 40: 604-609, 1987.
7. Wu PF, Chiang TA, Ko YC, Lee H. Genotoxicity of fumes from heated cooking oils produced in Taiwan. Environ Res Section A, 80: 122-126, 1999.
8. Wu PF, Chiang TA, Wang LF, Chang CS, Ko YC. Nitro-polycyclic aromatic hydrocarbon contents of fumes from heated cooking oils and prevention of mutagenicity by cetechin. Mutat Res, 403: 29-34, 1998.
9. Zhong LJ, Goldberg MS, Gao YT, Jin F. Lung cancer and indoor air pollution arising from Chinese-style cooking among nonsmoking women living in Shanghai, China. Epidemiol, 10: 488-494, 1999.
10. Oanh NTK, Reutergårdh LB, Dung NT, Emission of polycyclic aromatic hydrocarbons and particulate matter from domestic combustion of selected fuels. Environ Sci Technol, 33: 2703-2709, 1999.
11. Chuang JC, Wise SA, Cao S, Mumford J. Chemical characterization of mutagenic fractions of particles from Indoor Coal Combustion: A study of lung cancer in Xuan Wei, China. Environ Sci Technol, 26 (5): 999-1004, 1992.
12. National Research Council Committee On Passive Smoking Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects, Washington, DC, National Academy Press, 1986.
13. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. Brit Med J, 315: 980-988, 1997.
14. Risch HA, Howe GR, Jain M, et al. Are female smokers at higher risk for lung cancer male smokers? Am J Epidemiol, 138: 281-293,1993.
15. Taioli E, Wynder EL. Endocrine factors and adenocarcinoma of the lung in

women. J Natl Cancer Inst, 86: 869-870, 1994.
16. Huang CS, Chern HD, Chang KJ, Cheng CW, Hsu SM, Shen CY. Breast cancer risk associated with genotype polymorphism of the estrogen-metabolizing genes *CYP17*, *CYP1A1*, and *COMT*: A multigenic study on cancer susceptibility. Cancer Res, 59: 4870-4875, 1999.
17. Dabrosin C, Hammer M, Olinger K. Impact of oestradiol and progesterone on antioxidant activity in normal human breast epithelial cells in culture. Free Radic Res, 28: 241-249, 1998.
18. Beattle CW, Hansen NW, Thomas PA. Steroid receptors in human lung cancer. Cancer Res, 45: 4206-4214, 1985.
19. Cagle PT, Mody DR, Schwartz MR. Estrogen and progesterone receptors in bronchogenic carcinoma. Cancer Res, 50: 6632-6635, 1990.
20. Ollayos CW, Riodan GP, Rubin JM. Estrogen receptor detection in paraffin sections of adenocarcinomas of colon, pancreas, and lung. Arch Pathol Lab Med, 118: 630-632, 1994.
21. Canver CC, Memoli VA, Vanderveer PL, et al. Sex hormone receptors in non-small cell lung cancer in human beings. J Thorac Cardiovas Surg, 108: 153-157, 1994.
22. Su JM, Hsu HK, Chang H, et al. Expression of estrogen and progesterone receptors in non-small cell lung cancer: immunohistochemical study. Anticancer Res, 16: 3803-3806, 1996.
23. Kaiser U, Hofmann J, Schilli B, et al. Steroid-hormone receptors in cell lines and tumor biopsies of human lung cancer. Int J Cancer, 67: 357-364, 1996.
24. Bernstein L, Yuan JM, Rose RK, et al. Serum hormone levels in pre-menopausal Chinese women in Shanghai and white women in Los Angels: results from two breast cancer case- control studies. Cancer Causes control, 1: 51-58, 1990.
25. Department of Health, Executive Yuan, Republic of China: Health Statitics. Vol II, Vital Statistics, 1960-1991, Taipei, Department of Health, 1961-1991.
26. Hinds MW, Cohen HI, Kolonel LN. Tuberculosis and lung cancer risk in nonsmoking women. Am Rev Respir Dis, 125: 776-778, 1982.
27. Zheng W, Blot WJ, Liao ML, et al. Lung cancer and prior tuberculosis infection in Shanghai. Br J Cancer, 56: 501-504, 1987.
28. Wu AH, Fontham ETH, Reynolds P, et al. Previous lung disease and risk of lung cancer among lifetime nonsmoking women in the United States. Am J Epidemiol, 141: 1023-1032, 1995.
29. Alavanja MCR, Brownson RC, Boice JD, Hock E. Preexisting lung disease and lung cancer among nonsmoking women. Am J Epidemiol, 136: 623-632, 1992.

30. Liaw KM, Chen CJ. Mortality attributable to cigarette smoking in Taiwan: a 12-year follow-up study. Tob Control, 7:141-148, 1998.
31. Wu AH, Yu MC, Thomas DC, Pike MC, Henderson BE. Personal and family history of lung disease as risk factors for adenocarcinoma of the lung. Cancer Res, 48: 7279-7284, 1988.
32. Wu AH, Fontham ETH, Reynolds P, et al. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. Am J Epidemiol, 143: 535-542, 1996.
33. Osann KE. Lung cancer in women: The importance of smoking, family history of cancer, and medical history of respiratory disease. Cancer Res, 51: 4893-4897, 1991.

Table 1-9. Interactive effect of tobacco smoke exposure and cooking exposure in relation to female lung AC patients

Tobacco smoke exposure	Cooking exposure	Case No	Controls No	OR1 (95%CI)	OR2 (95%CI)	P
-	-	56	173	1	1	
-	+	33	58	1.3 (0.8-2.3)	1.4 (0.9-2.3)	
+	-	38	68	1.5 (0.9-2.5)		
+	+	50	50	2.2 (1.2-4.0)	2.3 (1.2-4.1)	<0.05

Adjusted for age, education level

Table 1-10. Interactive effect of tobacco smoke exposure and cooking oil in relation to female lung AC patients

Tobacco smoke exposure	Cooking oil	Case No	Controls No	OR1 (95%CI)	OR2 (95%CI)	P
-	No cooking exposure or vegetable oils	65	204	1	1	
-	Lard oils	23	27	2.2 (1.1-4.4)	1.6 (1.1-2.5)	<0.05
+	No cooking exposure or vegetable oils	49	94	1.5 (0.9-2.4)		
+	Lard oils	38	24	4.2 (2.1-8.1)	4.0 (2.1-7.6)	<0.05

Adjusted for age, education level

Table 1-11. Interactive effect of tobacco smoke exposure and cooking fuels in relation to female lung AC patients

Tobacco smoke exposure	Cooking oil	Case No	Controls No	OR1 (95%CI)	OR2 (95%CI)	P
-	No cooking exposure, electricity, natural gas	58	186	1	1	
-	Coal, wood , charcoal	31	45	1.7 (1.0-2.6)	1.6 (1.0-2.5)	<0.05
+	No cooking exposure, electricity, natural gas	41	75	1.6 (0.9-3.3)		
+	Coal, wood, charcoal	46	42	2.8 (1.5-5.3)	2.7 (1.5-5.1)	<0.05

Adjusted for age, education level

Table 1-12. Interactive effect of tobacco smoke exposure and family history in relation to female lung AC patients

Tobacco smoke exposure	Family history of lung cancer *	Case No	Controls No	OR1 (95%CI)	OR2 (95%CI)	P
-	-	80	227	1	1	
+	-	76	110	1.7 (1.1-2.5)	1.8 (1.2-2.7)	<0.05
-	+-	7	2	8.0 (1.6-39.6)		
+	+	7	3	5.2 (1.3-21.1)	5.2 (1.3-21.1)	<0.05

*: all first degree of relatives excluding father
Adjusted for age, education level

Table 1-13. Interactive effect of BMI and hormone exposure in relation to female lung AC patients

Hormone exposure period		**Body mass index**		
		<22.5	22.5-25	>=25
<30 years	Cases	27	26	17
	Controls	47	27	28
	OR	**1**	**0.7 (0.2-1.9)**	**0.5 (0.2-1.3)**
	OR1	***1***	***0.6 (0.3-1.0)***	***0.6 (0.3-1.0)***
>=30 years	Cases	47	27	28
	Controls	89	73	59
	OR	**1.5 (0.6-3.6)**	**0.9 (0.4-2.3)**	**0.9 (0.3-2.1)**
	OR1	*1*	*0.5 (0.2-1.3)*	*0.4 (0.2-1.0)*

Adjusted for age, education level

Table 2-3: Phase 1 gene dosage effect model

CYP1A1 Ile-Val	CYP1A2	CYP2E1Rsa1	Adenocarcinoma	Control	OR (95%CI)	p
+	+	+	52(38.0%)	78(36.6%)	1	
-	+	+	23(16.8%)	44(20.7%)		
+	-	+	0(0%)	1(0.5%)	0.9(0.5-1.5)	0.64
+	+	-	38(27.7%)	40(18.8%)		
-	-	+	6(4.4%)	13(6.1%)		
-	+	-	14(10.2%)	30(14.1%)	0.5(0.2-1.0)	0.06
+	-	-	0(0%)	0(0%)		
-	-	-	4(2.9%)	7(7.3%)	0.2(0.02-1.3)	0.09

All ORs were adjusted for age, education, cooking fume exposure, and tobacco smoke exposure
p test for trend =0.06
+: putative high-risk genotype
-: putative low-risk genotype

Table 2-4: Gene-environmental dosage effect model

Tobacco smoke exposure	Cooking fume exposure	Numbers of putative high risk gene	Cases	Control	OR (95%CI)
-	-	2	19(16.8%)	79(37.6%)	1
+	-	2	11(9.7%)	28(13.3%)	
-	+	2	14(12.4%)	14(6.7%)	1.4(0.7-2.7)
-	-	3	15(13.3%)	53(25.2%)	
+	+	2	22(19.5%)	12(5.7%)	
+	-	3	11(9.7%)	16(7.6%)	3.0*(1.4-6.2)
-	+	3	10(8.8%)	7(3.3%)	
+	+	3	11(9.7%)	1(0.5%)	20.8*(2.4-179.3)

All ORs were adjusted for age, education
p test for trend <0.001

Table 3-3: Phase II gene dosage effect

GSTM1	EH 113	COMT	Adenocarcinoma (%)	Control (%)	OR (95%CI)	p
+	+	+	4.1	12.3	1	
-	+	+	10.7	14.0		
+	-	+	9.9	15.7	3.1(0.9-10.3)	0.07
+	+	-	12.4	8.5		
-	-	+	20.7	18.2		
-	+	-	15.7	13.1	4.1*(1.2-13.5)	0.02
+	-	-	9.9	10.6		
-	-	-	16.5	7.6	11.7*(3.0-45.5)	0.0004

All ORs were adjusted for age, education, cooking fume exposure, and tobacco smoke exposure
test for trend $p<0.001$. *: $p<0.05$

Table 3-4: Gene-environmental dosage effect

Tobacco smoke exposure	Cooking fume exposure	Numbers of putative high risk gene	Adenocarcinoma (%)	Control (%)	OR (95%CI)	p
-	-	<=2	6.3	26.1	1	
+	-	<=2	4.2	9.8		
-	+	<=2	4.9	3.3	2.9*(1.3-6.6)	0.01
-	-	3	22.5	33.3		
+	+	<=2	10.6	3.6		
+	-	3	16.2	12.0	6.0*(2.6-13.8)	0.0001
-	+	3	15.5	8.0		
+	+	3	19.7	4.0	13.5*(4.7-38.4)	0.0001

All ORs were adjusted for age, education.
test for trend p <0.001. *: p<0.05

Table 3-5. Interaction of *NAT1* and *NAT2* in relation to female lung adenocarcinoma

NAT1	NAT2	Case (%)	Control (%)	OR (95%C.I)	
Slow	Slow	1.9	6.0	1	1
Rapid	Slow	14.0	11.9	6.1 (0.7-57.1)	
Slow	Rapid	21.5	22.6	7.1(0.8-64.4)	8.4*(1.0-69.1)
Rapid	Rapid	62.6	59.9	6.4(0.8-55.0)	

All ORs were adjusted for age, education, cooking fume exposure, and tobacco smoke exposure
*: $p<0.05$

Table 3-6: Interaction of GSTM1, GSTT1 and GSTP1 in relation to female lung adenocarcinoma

GSTM1	GSTT1	GSTP1	Adenocarcinoma (%)	Control (%)	OR (95%CI)	OR (95%CI)
Non-null	Non-null	Ile/Ile	10.09	13.0	1	1
Null	Non-null	Ile/Ile	15.9	13.4		
Non-null	Null	Ile/Ile	15.2	16.0	1.6(0.7-3.7)	
Non-null	Non-null	Ile/Val, Val/Val	5.1	7.4		
Null	Null	Ile/Ile	23.2	26.4		1.9(0.9-4.2)
Null	Non-null	Ile/Val, Val/Val	10.9	5.6	1.6(0.7-3.6)	
Non-null	Null	Ile/Val, Val/Val	7.2	8.2		
Null	Null	Ile/Val, Val/Val	11.6	10.0	2.2(0.8-6.1)	

All ORs were adjusted for age, education, cooking fume exposure, and tobacco smoke exposure
test for trend p <0.06

Table 4-3. ORs for female lung adenocarcinoma with combined genotypes

Genotype	**COMT WW**			**COMT WV/VV**		
	CYP17 A1A1	**CYP17 A1A2**	**CYP17 A2A2**	**CYP17 A1A1**	**CYP17 A1A2**	**CYP17 A2A2**
Case	9	33	23	10	28	36
Control	39	73	39	20	49	38
OR (95% C.I)	**1**	**1.7 (0.6-4.5)**	**2.5(0.9-6.9)**	**2.2(0.7-7.2)**	**2.2(0.8-6.1)**	**4.2*(1.6-11.4)**

Table 4-4. ORs for female lung adenocarcinoma with combined genotypes, stratified by BMI status

BMI<=23

Genotype	COMT W/W			COMT WV/VV		
	CYP17 A1A1	**CYP17 A1A2**	**CYP17 A2A2**	**CYP17 A1A1**	**CYP17 A1A2**	**CYP17 A2A2**
Case	3	21	11	10	16	25
Control	16	31	12	10	26	21
OR(95% C.I)	**1**	**4.0(0.7-23.4)**	**6.2(0.9-43.6)**	**4.3(0.6-29.0)**	**2.9(0.5-18.1)**	**6.7*(1.1-40.1)**

BMI >23

Genotype	COMT W/W			COMT WV/VV		
	CYP17 A1A1	**CYP17 A1A2**	**CYP17 A2A2**	**CYP17 A1A1**	**CYP17 A1A2**	**CYP17 A2A2**
Case	6	12	12	0	12	11
Control	23	42	27	10	23	17
OR(95% C.I)	**1**	**0.7 (0.2-2.5)**	**1.3(0.4-4.6)**	**-**	**1.6(0.5-5.5)**	**2.5(0.7-9.0)**

Table 4-5. ORs for female lung adenocarcinoma with combined genotypes, stratified by hormone exposure period

Hormone exposure period <=363 months

Genotype	**COMT W/W**			**COMT WV/VV**		
	CYP17 A1A1	**CYP17 A1A2**	**CYP17 A2A2**	**CYP17 A1A1**	**CYP17 A1A2**	**CYP17 A2A2**
Case	6	22	14	4	17	31
Control	22	43	21	10	32	18
OR(95% C.I)	**1**	**1.5(0.4-5.4)**	**2.3(0.6-9.4)**	**2.2(0.4-12.3)**	**1.9(0.5-7.2)**	**10.4*(2.7-39.3)**

Hormone exposure period >363 months

Genotype	**COMT W/W**			**COMT WV/VV**		
	CYP17 A1A1	**CYP17 A1A2**	**CYP17 A2A2**	**CYP17 A1A1**	**CYP17 A1A2**	**CYP17 A2A2**
Case	6	19	13	7	17	17
Control	19	31	19	10	17	23
OR(95% C.I)	**1**	**1.5 (0.4-5.3)**	**1.6(0.4-6.2)**	**2.1(0.5-9.4)**	**1.8(0.5-6.9)**	**1.1(0.3-4.5)**

Table 4-6: Gene dosage effect model, with CYP17, CYP19, COMT

Genotype			Case	Control	OR(95%CI)	OR(95%CI)
CYP17	CYP19[+]	COMT	No (%)	No (%)		
A1A1	WW	WW	1(0.7)	5(2.0)	1	0.2(0.01-2.3)
A1A2/A2A2	WW	WW	7(5.0)	20(8.0)		
A1A1	WM/MM	WW	8(5.8)	33(13.2)	1.7(0.1-20.1)	0.4*(0.2-0.8)
A1A1	WW	WM/MM	1(0.7)	5(2.0)		
A1A2/A2A2	WM/MM	WW	49(35.3)	91(36.4)		
A1A2/A2A2	WW	WM/MM	5(3.6)	13(5.2)	2.6(0.2-28.3)	0.5*(0.3-0.9)
A1A1	WM/MM	WM/MM	9(6.5)	14(5.6)		
A1A2/A2A2	WM/MM	WM/MM	59(42.4)	69(27.6)	4.9(0.4-55.1)	1

[+]: M: Microsatellite number <=8
W: Microsatellite number >8
*: $p<0.05$
Test for trend $p<0.002$

Table 4-7 Gene dosage effect model, with CYP17, CYP19, COMT, CYP1A1

Genotype				Case	Control	OR(95%CI)
CYP1A1	CYP17	CYP19	COMT	No(%)	No(%)	
-	-	-	-	0	2(0.8)	-
+	-	-	-	3(2.2)	7(2.8)	
-	+	-	-	4(2.9)	10(4.0)	
-	-	+	-	1(0.8)	1(0.4)	0.3*(0.1-0.9)
-	-	-	+	1(0.7)	3(1.2)	
+	+	-	-	1(0.7)	36(14.6)	
+	-	+	-	19(13.8)	6(2.4)	
+	-	-	+	4(2.9)	13(5.3)	
-	+	+	-	4(2.9)	9(3.6)	0.2*(0.1-0.5)
-	+	-	+	4(2.9)	22(8.9)	
-	-	+	+	4(2.9)	4(1.6)	
+	+	+	-	13(9.4)	33(13.4)	
+	+	-	+	29(21.0)	53(21.5.)	
+	-	+	+	1(0.7)	7(2.8)	0.4*(0.2-0.7)
-	+	+	+	5(3.6)	5 (2.0)	
+	+	+	+	46(33.3)	36(14.6)	1

Test for trend $p<0.005$

Table 1-1. Distribution of selected demographic characteristics between 184 female adenocarcinoma and 350 controls

Variables	Cases No (%)	Controls No (%)
Age (years)		
<40	9(4.9)	33(9.4)
40-49	31(16.8)	72(20.6)
50-59	47(25.5)	110(31.4)
60-69	49(26.6)	72(20.6)
70+	48(26.1)	63(18.0)
Schooling years		
None	54(29.5)	48(13.7)
1-6	45(24.6)	92(26.3)
7-9	49(26.8)	102(29.1)
9+	35(19.1)	108(30.9)
Ethnic group of father		
Aborigine	1(0.6)	0(0)
Fukienese	145(80.1)	265(75.5)
Hakkas	14(7.7)	34(9.7)
China mainlanders	21(11.6)	51(14.6)
Ethnic group of mother		
Aborigine	2(1.1)	1(0.3)
Fukienese	147(81.2)	266(76.0)
Hakkas	15(8.3)	37(10.6)
China mainlanders	17(9.4)	46(13.1)

Table 1-2. ORs of Tobacco smoke related items in association with female lung adenocarcinoma patients

Variable	Cases N (%)	Controls N (%)	OR (95% C.I)
Smoking habit			
Nonsmoker	169 (91.8)	340 (97.1%)	1
Ever smoker	15 (8.2)	10 (2.9)	2.4*(1.0-5.6)
Smoking duration (years)			
Nonsmoker	169 (91.8)	340 (97.1%)	1
<=10	2 (1.1)	3 (0.9)	1.5 (0.2-9.2)
10-19	1 (0.5)	1 (0.3)	1.7 (0.1-28.6)
>19	12 (6.5)	6 (1.7)	3.0*(1.1-8.2)
Cumulative smoking amount (pack-years)			
Nonsmoker	169 (91.8)	340 (97.1%)	1
<=10	3 (1.6)	7 (0.8)	0.8 (0.2-3.0)
10-25	3 (1.6)	1 (0.3)	5.1 (0.5-50.6)
>25	9 (4.9)	2 (0.6)	6.3*(1.3-30.2)

Adjusted for age, education level

* $p<0.05$

Table 1-3. ORs of Environmental tobacco smoke related items in association with female lung adenocarcinoma patients

Variable	Cases N (%)	Controls N (%)	OR (95% C.I)
Paternal smoking status			
Nonsmoker	85 (50.3)	159 (43.5)	1
Ever-smoker	84 (49.7)	195 (56.5)	0.8 (0.6-1.2)
Maternal smoking status			
Nonsmoker	158 (88.8)	323 (93.1)	1
Ever-smoker	20 (11.2)	24 (6.9)	1.7 (0.9-3.1)
Spouse smoking status			
Nonsmoker	70 (39.3)	172 (49.3)	1
Ever-smoker	108 (60.7)	177 (50.7)	1.2 (0.8-1.8)
Spouse smoking years			
Never	70 (41.4)	172 (50.3)	1
<20	32 (18.9)	62 (18.1)	1.2 (0.7-2.0)
20-35	23 (13.6)	54 (15.8)	0.9 (0.5-1.6)
>35	44 (26.0)	54 (15.8)	1.3 (0.8-2.3)
Spouse smoking pack-years			
Never	70 (41.4)	172 (50.4)	1
<20	21 (12.4)	67 (19.6)	0.7 0.4-1.2)
20-50	53 (31.4)	70 (20.5)	1.5 (0.9-2.3)
>=50	25 (14.8)	32 (9.4)	1.4 (0.8-2.6)
Spouse smoke just besides her			
No	95 (53.4)	214 (67.0)	1
Yes	83 (46.6)	115 (33.0)	1.5*(1.0-2.2)
Workplace smoking exposure			
No	134 (76.6)	210 (60.9)	1
Yes	41 (23.4)	135 (39.1)	0.6 (0.4-1.0)
Numbers of co-worker ever-smoker			
0	134 (82.2)	210 (68.2)	1
0-10	22 (13.5)	93 (30.2)	0.5 (0.3-0.9)
>10	7 (4.3)	5 (1.6)	2.8 (0.9-9.2)
Tobacco smoke exposure			
No	91 (49.5)	232 (66.3)	1
Yes	93 (50.5)	118 (33.7)	1.7*(1.1-2.5)

Tobacco smoke exposure: ever smokers or spouse smoking just besides her

All analysis adjusted for age, education level

* $p<0.05$

Table 1-4. ORs of cooking-related risk factors before 40 years in association with female lung adenocarcinoma patients

Variable	Cases N (%)	Controls N (%)	OR (95% C.I)
Cooking habit			
No	17 (9.4)	27 (7.7)	1
Yes	164 (90.6)	323 (92.3)	0.6 (0.3-1.1)
Fume extractor in kitchen			
Yes or no cooking habit	94 (53.1)	241 (69.1)	1
No	83 (46.9)	108 (30.9)	1.3 (0.8-2.2)
Age at starting cooking			
No cooking fume exposure	94 (53.1)	241 (69.1)	1.0
<19	28 (15.9)	37 (10.6)	1.2 (0.6-2.4)
19-25	36 (20.5)	41 (11.7)	1.4 (0.8-2.7)
>25	18 (10.2)	30 (8.6)	1.3 (0.6-2.5)
Total duration of cooking before 40			
No cooking fume exposure	94 (53.4)	241 (69.3)	1
>17	21 (11.9)	36 (10.3)	1.2 (0.6-2.3)
17-25	43 (24.4)	53 (15.2)	1.3 (0.7-2.4)
>=25	18 (10.2)	18 (5.2)	1.6 (0.8-3.6)
Cooking oils			
No cooking fume exposure	94 (53.7)	241 (69.1)	1.0
Vegetable oil	20 (11.4)	57 (16.3)	0.7 (0.4-1.3)
Lard oil	61 (34.9)	51 (14.6)	2.1*(1.2-3.8)
Cooking fuels			
No cooking fume exposure	94 (53.4)	241 (69.3)	1.0
Electricity, natural gas	5 (2.8)	20 (5.7)	0.6 (0.2-1.6)
Coal, charcoal, wood	77 (43.8)	87 (25.0)	1.6*(1.0-2.8)

* $p<0.05$

All analysis adjusted for age, education level, and tobacco smoke exposure

Table 1-5. ORs of hormone-related risk factors in association with female lung adenocarcinoma patients

Variable	Cases N (%)	Controls N (%)	OR (95% C.I)	OR (95%CI)
Age at menarche				
<15	50 (29.9)	150 (43.1)	1	
>=15	117 (70.1)	197 (56.8)	1.4 (0.9-2.3)	
Age at menopause				
No	10 (6.4)	110 (31.7)	1	1
>51	40 (25.5)	78 (22.5)	5.0 (2.1-12.3)	
47-51	60 (38.2)	88 (25.4)	6.6 (2.8-15.5)	6.6*(2.9-14.7)
<=47	47 (29.9)	71 (20.5)	7.3 (3.1-16.9)	
Is menstrual cycle regular				
Yes	145 (84.3)	301 (86.7)	1	
No	27 (15.7)	46 (13.3)	1.3 (0.8-2.3)	
Length of menstrual period (day)				
<4	44 (27.7)	98 (28.3)	1	1
4-6	68 (42.8)	108 (52.0)	1.0 (0.6-1.7)	
>6	47 (29.6)	68 (19.7)	1.6 (1.0-2.8)	1.6*(1.0-2.5)
Menstrual cycle length (day)				
<25	7 (4.5)	37 (10.8)	1	1
25-31	135 (87.7)	269 (78.2)	2.4 (1.0-5.5)	
>31	12 (7.8)	38 (11.0)	1.6 (0.6-3.5)	2.3*(1.0-5.3)
No of gestation				
None	11 (6.1)	22 (6.3)	1	
<5	81 (44.8)	160 (45.7)	1.5*(1.0-2.3)	
>=5	89 (49.2)	168 (48.0)	2.3 (0.6-5.4)	
No of parity				
None	15 (8.3)	23 (6.6)	1	
<5	106 (58.6)	251 (71.7)	0.9 (0.5-1.4)	
>=5	60 (33.1)	76 (21.7)	1.9 (0.7-4.6)	*
No of spontaneous abortion				
None	142 (78.9)	23 (6.6)	1	
<3	35 (19.4)	251 (71.7)	1.0 (0.6-1.6)	
>=3	3 (1.7)	76 (21.7)	1.2 (0.3-5.4)	
Total duration of breast feeding (month)				
None	34 (19.1)	104 (29.8)	1	1
<18	46 (25.8)	124 (35.6)	1.1 (0.6-1.8)	
>=18	98 (55.1)	121 (34.7)	1.8 (1.0-3.2)	1.7*(1.0-2.8)

History of oral contraceptives				
No	153 (85.5)	273 (78.4)	1	
Yes	26 (14.5)	75 (21.6)	0.6 (0.4-1.1)	
Total duration of taking oral contraceptives				
None	153 (87.4)	273 (78.9)	1	1
<=1	17 (9.7)	37 (10.7)	0.8 (0.4-1.5)	
>1	5 (2.9)	36 (10.4)	0.3	0.6*(0.4-0.9)
History of hormone replacement therapy				
No	146 (81.6)	262 (75.1)	1	
Yes	33 (18.4)	87 (24.9)	0.7 (0.4-1.1)	
Total duration of hormone replacement therapy				
None	146 (82.0)	262 (76.4)	1	1
<=1	24 (13.5)	41 (12.0)	1.0 (0.6-1.8)	
>1	8 (4.5)	40 (11.7)	0.4 (0.2-0.9)	0.4*(0.2-0.9)
Taking Chinese herb drug during menstruation				
No	120 (67.4)	247 (70.8)	1	
Yes	58 (32.6)	102 (29.2)	1.2 (1.0-1.5)	
Body mass index				
<=22.5	67 (41.9)	107 (35.8)	1	1
22.5-25	44 (27.5)	97 (32.4)	0.6 (0.4-1.0)	
>=25	49 (30.6)	95 (31.8)	0.5 (0.3-0.9)	0.6*(0.4-0.9)
Hormone exposure period (years)				
<30	56 (34.1)	92 (26.7)	1	
>=30	108 (65.9)	252 (73.3)	1.1 (0.7-1.7)	

Hormone exposure period: definition sees text

* p for trends <0.05

Adjusted for age, education, tobacco smoke exposure

Table 1-6. ORs of other personal and family history in association with female lung adenocarcinoma patients

Variable	Cases N (%)	Controls N (%)	OR (95% C.I)
History of pulmonary TB			
No	165 (91.2)	335 (96.0)	1
Yes	16 (8.8)	14 (4.0)	2.3*(1.1-5.0)
History of COPD			
No	173 (96.6)	341 (98.0)	1
Yes	6 (3.4)	7 (2.0)	1.4 (0.4-4.4)
History of hysterectomy			
No	156 (87.2)	297 (85.1)	1
Yes	23 (12.8)	52 (14.9)	0.8 (0.5-1.4)
History of oophorectomy			
No	169 (95.4)	317 (91.6)	1
Yes	8 (4.5)	29 (8.4)	0.6 (0.3-1.4)
History of asthma			
No	170 (94.4)	330 (94.6)	1
Yes	10 (5.6)	19 (5.4)	0.9 (0.4-2.0)
Father contracted lung cancer			
No	163 (94.8)	327 (95.1)	1
Yes	9 (5.2)	17 (4.9)	1.1 (0.5-2.5)
Mother contracted lung cancer			
No	168 (97.1)	343 (99.7)	1
Yes	5 (2.9)	1 (0.3)	8.9*(1.0-77.8)
Sibling contracted lung cancer			
No	168 (94.4)	341 (99.1)	1
Yes	10 (5.6)	3 (0.9)	5.6*(1.5-21.1)
Offspring contracted lung cancer			
No	174 (98.9)	348 (99.7)	1
Yes	2 (1.1)	1 (0.3)	4.4 (0.4-50.2)
All first degree relatives contracted lung cancer			
No	146 (88.0)	320 (93.9)	1
Yes	20 (12.0)	21 (6.1)	1.9*(1.0-3.7)
All first degree relatives excluding father contracted lung cancer			
No	156 (91.8)	337 (98.5)	1
Yes	14 (8.2)	5 (1.5)	4.9*(1.7-14.1)

Adjusted for age, education, and tobacco smoke exposure

* $p<0.05$

Table 1-7. ORs and 95% C.I of Hormone-related risk factors of female lung adenocarcinoma in multiple logistic regression models

Variables	OR	95% CI
Age at menarche >=15 y vs <15 y	1.4	0.7-2.5
Menstruation regularity no vs yes	0.5	0.2-1.4
Menstrual cycle length >=25 vs <25	2.2	0.7-7.0
Length of menstrual period> 6d vs <=6d	1.7*	1.0-3.1
Breast feeding >=18 m vs <18m or no	1.8	0.9-3.5
Taking oral contraceptives > 1 y vs <=1y or no	0.6*	0.4-1.0
Hormone replacement therapy >1y vs <=1y or no	0.2*	0.1-0.6
BMI >22.5 vs BMI <=22.5	0.4*	0.2-0.7
Menopause yes vs no	9.0*	3.1-26.2
Chinese herb drug taking during menstruation yes vs no	1.1	0.8-1.4

Adjusted for age education level

* $p<0.05$

Table 1-8. ORs and 95% C.I of putative risk factors of female lung adenocarcinoma in multiple logistic regression models

Variables	OR	95% CI
Tobacco smoke exposure vs no exposure	2.0*	1.2-3.4
Cooking oil with lard oil vs no cooking exposure or cooking with vegetable oils	2.0*	1.0-4.0
Length of menstrual period> 6d vs <=6d	1.7	0.9-3.0
Taking oral contraceptives > 1 y vs <=1y or no	0.6*	0.4-1.0
Hormone replacement therapy >1y vs <=1y or no	0.2*	0.1-0.7
BMI >22.5 vs BMI <=22.5	0.5*	0.3-0.8
Pulmonary TB history	0.9	0.3-2.7
Lung cancer history of first degree relatives°	3.0	0.7-12.0
Menopause yes vs no	9.8*	3.4-28.1

° excluding father, * $p<0.05$

Adjusted for age, education level

Table 2-1: The association of phase1 gene polymorphisms and female lung adenocarcinoma

Genotype	Adenocarcinoma (%)	Control (%)	OR (95% CI)	p
CYP1A1 MspI				
CC	18.9	18.4	1	
TC/TT	81.1	81.6	1.4(0.7-2.5)	0.35
CYP1A1 Ile-Val				
Val/Val, Ile/Val	34.2	42.6	1	
Ile/Ile	65.8	57.4	1.8(1.1-2.9)	0.02
CYP1A2				
AA	7.1	10.2	1	
GG/GA	92.9	89.8	3.9(1.4-11.3)	0.01
CYP2E1 DraI				
CC	6.8	6.2	1	
DD/DC	93.2	93.8	1.5(0.5-3.9)	0.46
CYP2E1 RsaI				
c2c2	4.7	3.8	1	
c1c1/c1c2	95.3	96.2	1.4(0.4-4.4)	0.59
CYP2C19				
m1m1	7.4	13.0	1	
m1w/ww	92.6	87.0	1.3(0.6-2.9)	0.52
CYP1B1 codon 48				
Ala/Ser, Ser/Ser	33.3	34.0	1	
Ala/Ala	66.7	66.0	1.1(0.6-2.0)	0.74
CYP1B1 codon 432				
Val/Leu, Leu/Leu	20.9	23.7	1	
Val/Val	79.1	76.3	1.4(0.7-2.5)	0.35

All ORs were adjusted for age, education, tobacco smoke exposure, and cooking fume exposure

Table 2-2: ORs and 95% CI of phase I genes related to female lung adenocarcinoma in multiple logistic regression model

Genotype	OR (95% CI)	p
CYP1A1 Ile-Val		
Val/Ile, Val/Val	1	
Ile/Ile	1.2(0.7-2.2)	0.59
CYP1A2		
AA	1	
GG/GA	6.5(1.6-29.2)	0.009
CYP2E1 RsaI		
c2c2	1	
c1c1/c1c2	1.3(0.8-2.4)	0.32
CYP2C19		
m1m1	1	
ww/wm1	1.2(0.5-2.9)	0.71
CYP1B1 codon 432		
Val/Leu, Leu/Leu	1	
Val/Val	1.2(0.6-2.4)	0.57

All ORs were adjusted for age, education, tobacco smoke exposure, and cooking fume exposure

Table 3-1: The association of phase II gene polymorphisms and female lung adenocarcinoma

Genotype	Adenocarcinoma (%)	Control (%)	OR (95%C.I.)
GSTM1			
Non-null	55(37.9)	121(44.6)	1
Null	90(62.1)	150(55.4)	1.5†(0.9-2.5)
GSTT1			
Non-null	63(43.4)	107(39.4)	1
Null	82(56.6)	164(60.6)	0.9(0.5-1.4)
GSTP1			
Ile/Ile	90(65.2)	187(69.0)	1
Ile/Val, Val/Val	48(34.8)	84(31.0)	1.3(0.8-2.1)
NAT1			
Slow acetylator	25(22.9)	75(28.8)	1
Rapid acetylator	84(77.1)	185(71.2)	1.2(0.7-2.4)
NAT2			
Slow acetylator	25(17.5)	45(17.5)	1
Rapid acetylator	118(82.5)	212(82.5	1.2(0.6-2.3)
EH codon 113			
Tyr/His, His/His	65(45.1)	130(48.1)	1
Tyr/Tyr	79(54.9)	140(51.9)	1.4(0.9-2.3)
EH codon 139			
His/Arg, Arg/Arg	25(19.2)	49(19.8)	1
His/His	105(80.8)	199(80.2)	1.2(0.7-2.3)
COMT codon 158			
Val/Val	64(46.7)	151(58.1)	1
Val/Met, Met/Met	73(53.3)	107(41.5)	1.7*(1.1-2.8)

ORs were all adjusted for age, education, tobacco smoke exposure, and cooking fume exposure

†: $0.05<p<0.1$

*: $p<0.05$

The numbers are not the same between different genotypes due to genotyping failure in some subjects

Table 3-2: ORs and 95% CI of phase II genes related to female lung adenocarcinoma in multiple logistic regression model

Genotype	OR (95%C.I)	P
GSTM1		
Non-null	1	
Null	1.7(0.9-3.1)	0.08
GSTT1		
Non-null	1	
Null	1.3(0.7-2.5)	0.35
GSTP1		
Ile/Ile	1	
Ile/Val, Val/Val	0.9(0.4-1.6)	0.63
NAT1		
Slow acetylator	1	
Rapid acetylator	1.1(0.6-2.2)	0.72
NAT2		
Slow acetylator	1	
Rapid acetylator	1.1(0.5-2.4)	0.78
EH codon 113		
Tyr/His, His/His	1	
Tyr/Tyr	2.0(1.1-3.7)	0.03
EH codon 139		
His/Arg, Arg/Arg	1	
His/His	1.2(0.5-2.8)	0.63
COMT codon 158		
Val/Val	1	
Val/Met, Met/Met	2.2(1.2-4.0)	0.01

All ORs were adjusted for age, education, tobacco smoke exposure, and cooking fume exposure

Table 4-1: The association of hormone-related gene polymorphisms and female lung adenocarcinoma

Genotype	Case (148) No (%)	Control (267) No (%)	OR (95%CI)	OR (95%CI)
CYP17				
A1/A1	20(13.4)	60(22.6)	1	1
A1/A2	68(45.6)	126(47.4)	1.4(0.7-2.8)	1.8^{+}(0.9-3.3)
A2/A2	61(40.9)	80(30.0)	2.2*(1.1-4.5)	
CYP19				
MM	16(10.7)	42(16.7)	1	1
WM	64(43.0)	107(42.5)	1.3(0.6-2.8)	1.3(0.7-2.7)
WW	69(46.3)	103(40.9)	1.3(0.6-2.7)	
ESR codon 325				
CC	29(21.3)	69(27.0)	1	1
CG	67(49.3)	116(45.3)	1.2(0.6-2.2)	1.1(0.6-2.0)
GG	40(29.4)	71(27.7)	1.0(0.5-2.1)	
COMT				
Val/Val	65(46.4)	151(58.5)	1	1
Val/Met	60(42.9)	81(31.4)	1.8(1.1-3.0)	1.7*(1.0-2.8)
Met/Met	15(10.7)	26(10.1)	1.4(0.6-3.2)	

W: Microsatellite number <=8

M: Microsatellite number >8

* $p<0.05$, $^{+}$ $p<0.1$

Adjusted for age, education, smoking exposure, and cooking fume exposure

Table 4-2: ORs and 95% CI of hormone-related genes related to female lung adenocarcinoma in multiple logistic regression model

	Model 1		Model 2	
Genotype	OR (95%CI)	p	OR (95%CI)	p
CYP17				
A1A1	1.0		1.0	
A1/A2	1.3(0.6-2.8)	0.43	1.4(0.7-2.7)	0.4
A2A2	1.6(0.9-3.0)	0.11	1.7*(1.0-3.0)	0.06
CYP19				
MM	1.0		1.0	
WM/WW	1.5(0.7-3.3)	0.27	1.6(0.8-3.5)	0.19
ESR325				
CC	1.0			
CG/GG	1.1(0.6-2.0)	0.83		
COMT				
WW	1.0		1.0	
WV/VV	1.7(1.0-2.9)	0.06	1.7*(1.0-2.9)	0.03

W: Microsatellite number <=8

M: Microsatellite number >8

* $p<0.05$

Adjusted for age, education, smoking exposure, and cooking fume exposure

Table 5-1: Univariate analysis of genetic polymorphism of DNA repair gene

Genotype	Cases (n=160)	Controls (n=279)	OR(95%CI)	OR1(95%CI)
XRCC1-194				
Arg/Arg	51.6%	51.0%	1.0	1.0
Arg/Trp	46.9%	40.3%	1.14(0.68-1.90)	
Trp/Trp	1.6%	8.7%	0.19(0.04-0.92)	0.18(0.04-0.85)
XRCC1-280				
Arg/Arg	79.8%	76.7%	1.0	1.0
Arg/His	18.5%	21.3%	0.69(0.36-1.34)	
His/His	1.7%	1.9%	2.17(0.38-12.34)	2.32(0.41-13.12)
XRCC1-399				
Arg/Arg	51.3%	53.5%	1.0	1.0
Arg/Gln	31.1%	36.8%	1.11(0.62-1.99)	
Gln/Gln	17.6%	9.7%	2.33(1.10-4.95)	2.24(1.10-4.58)
XRCC3-241				
Thr/Thr	92.6%	95.8%	1.0	
Thr/Met	7.4%	4.2%	2.79(0.99-7.81)	
Met/Met	0.0%	0.0%		
XPD-751				
Lys/Lys	59.8%	82.1%	1.0	1.0
Lys/Gln	34.4%	17.1%	2.30(1.27-4.17)	
Gln/Gln	5.7%	0.8%	13.91(2.45-79.10)	2.72(1.54-4.80)
hMLH1				
GG	8.0%	18.5%	1.0	1.0
GA	53.6%	48.6%	2.97(1.19-7.42)	
AA	38.4%	32.8%	2.85(1.11-7.33)	2.92(1.20-7.10)

ORs[a] were adjusted for age, cooking fume exposure, and tobacco exposure

Table 5-2 Multivariate analysis for DNA reapir gene

Genotype	OR(95%CI)
XRCC1-399	
Arg/Arg+Arg/Gln	1.0
Gln/Gln	2.55(1.20-5.40)
XRCC3-241	
Thr/Thr	1.0
Thr/Met	3.10(1.06-9.09)
XPD-751	
Lys/Lys	1.0
Lys/Gln+Gln/Gln	2.53(1.39-4.60)
hMLH1	
GG	1.0
GA+AA	2.47(0.99-6.16)

ORs[a] were adjusted for age, cooking fume exposure, and tobacco exposure

Table 5-3 gene-gene interaction for lung AC

XRCC1-399	XRCC3-241	XPD-751	hMLH1	Case(n=160)	Control(n=279)	OR(95%CI)
Arg/Arg+Arg/Gln	Thr/Thr	Lys/Lys	GG	4.5%	14.1%	1.0
Arg/Arg+Arg/Gln	Thr/Thr	Lys/Lys	GA+AA	39.3%	57.6%	
Arg/Arg+Arg/Gln	Thr/Thr	Lys/Gln+Gln/Gln	GG	1.8%	2.7%	4.32(0.95-19.66
Arg/Arg+Arg/Gln	Thr/Met	Lys/Lys	GG	0.9%	0.4%	
Gln/Gln	Thr/Thr	Lys/Lys	GG	1.8%	1.2%	
Arg/Arg+Arg/Gln	Thr/Thr	Lys/Gln+Gln/Gln	GA+AA	28.6%	13.3%	
Arg/Arg+Arg/Gln	Thr/Met	Lys/Lys	GA+AA	3.6%	2.4%	
Gln/Gln	Thr/Thr	Lys/Lys	GA+AA	9.8%	5.1%	11.78(2.53-54.7
Arg/Arg+Arg/Gln	Thr/Met	Lys/Gln+Gln/Gln	GG	0.0%	0.0%	
Gln/Gln	Thr/Thr	Lys/Gln+Gln/Gln	GG	0.0%	0.0%	
Gln/Gln	Thr/Met	Lys/Lys	GG	0.0%	0.4%	
Gln/Gln	Thr/Met	Lys/Gln+Gln/Gln	GG	2.7%	0.4%	
Gln/Gln	Thr/Met	Lys/Lys	GA+AA	0.9%	0.8%	
Gln/Gln	Thr/Thr	Lys/Gln+Gln/Gln	GA+AA	6.3%	1.6%	18.93(3.09-115.
Arg/Arg+Arg/Gln	Thr/Met	Lys/Gln+Gln/Gln	GA+AA	0.0%	0.0%	
Gln/Gln	Thr/Met	Lys/Gln+Gln/Gln	GA+AA	0.0%	0.0%	

OR: adenoma adjusted age, tobacco exposure, and cooking fume exposure

trend<0.0001

Table 5-4. DNA repair gene and environmental interactive effect of female lung AC

tobacco exposure	cooking fume	repair gene	case	control	OR(95%CI)
no	no	0-1	10.8%	48.0%	1.0
no	no	2-3	17.2%	13.5%	
no	yes	0-1	7.5%	7.5%	4.65(2.11-10.24)
yes	no	0-1	12.9%	15.5%	
no	yes	2-3	16.1%	3.2%	
yes	no	2-3	6.5%	5.6%	9.37(3.96-22.16)
yes	yes	0-1	15.1%	4.9%	
yes	yes	2-3	14.0%	2.0%	18.96(5.21-69.04)

ORs were adjusted for age

trend<0.0001