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Review

Lung Adenocarcinoma in Never Smokers: Problems of Primary Prevention from Aspects of Susceptible Genes and Carcinogens

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Abstract. *Global statistics estimate that approximately 25% of patients with lung cancer are never smokers. We suggest that genes related to susceptibility to metabolic syndrome were present among those related to susceptibility to lung adenocarcinoma (AC) in never smokers. There are many questions concerning lung AC in never smokers, which is increasing in incidence, with female predominance, good prognosis, unique genes related to susceptibility and good response to treatment with specific agents. The purpose of this review was to investigate the carcinogenesis of lung AC in never smokers focusing on genes related to susceptibility to lung AC and carcinogens, including environmental factors. In order to clarify the carcinogenesis of lung AC in never smokers, the definition of never smokers, survey of environmental tobacco smoke, the presence of the physical characteristics of metabolic syndrome, and other carcinogens should be investigated for primary prevention of lung AC.*

Lung cancer was the leading cause of death in developed countries in 2012 in both males and females, and the leading cause in less developed countries in males and the second cause in females (1). Lung cancer is classified into two morphological groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC includes squamous cell lung cancer (SC) and adenocarcinoma (AC). Lung AC is on the rise in both sexes, especially women, although the number is not as high as among men, in both developed and developing countries (2). Lung AC is associated with life-style throughout the world (1, 3).

Islami *et al*. reported that global incidence and mortality rates of lung cancer are still closely associated with smoking prevalence (4). However, high-income countries have shown remarkable decrease in smoking in both males and females (4). Parkin *et al*. reported that 15% of lung cancer cases in men and 53% in women are not attributable to smoking, and approximately 25% of patients with lung cancer were never smokers, according to global statistics in 2002 (5). This was a very shocking report. A review article by Sun, *et al*. (6) and others (7-10) reported that never-smoker patients with lung AC were predominantly female (6, 10), were significantly younger (7, 8) and had better prognosis (6, 7, 10-12), with especially good response to treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (7, 13-15). Such patients were frequently Asian females (4, 16).

We previously wrote a review on genes related to susceptibility to lung AC in never smokers and demonstrated that genes associated with metabolic syndrome were present among these (17). Many questions arose, *e.g*. whether lung AC may be a different disease (6, 7), whether it may involve different genes (8), why female predisposition is present, whether the number of patients continues to increase (16), and why there are so many patients with AC among never smokers with NSCLC (6, 16, 18). For primary prevention, it is most important to clarify the mechanism of carcinogenesis, especially to identify carcinogens related to genes susceptibility to lung cancer. Moreover, it should also be elucidated whether and how metabolic syndrome plays a role in these patients (17).

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Concerning lung carcinogenesis in never smokers, environmental tobacco smoke (ETS) at home, work and other places have been supposed to be the cause of lung cancer in never smokers (4, 19-24). If never smokers have been exposed to ETS, it may act as a trigger, converting stem cells into cancer cells in the lung (25) with involvement of metabolic syndrome (26). Besides ETS, reported carcinogens include radon (27-29), cooking oil vapor (9, 30), indoor coal burning, hormonal factors (after hormonal replacement therapy) (6, 8, 9), occupational chemical exposure including asbestos/heavy metals (8), infectious factors (31, 32), and air pollution (8).

The purpose of the present study was to clarify the carcinogenesis of lung AC in never smokers from the viewpoints of both genes related to susceptibility, environmental factors and lifestyle. It is necessary to clarify why lung AC is increasing in Asian women never smokers (15, 29). Finally this review shows the interrelation between genes related to susceptibililty and suspected carcinogens from original articles on lung AC in never smokers, and discusses a primary prevention strategy for lung cancer in never smokers.

Selection of Bibliography

The articles cited in this review dated before 2000 were selected from review articles. Original articles after 2000 sought from PubMed were screened by us. The key words used in the search were as follows: lung cancer, lung AC, never smoker, NSCLC, incidence rate of global lung cancer, mortality rate of lung cancer, smoking prevalence, genes susceptible to lung cancer, and genes susceptible to lung AC. Of the articles published after 2000 we selected those we considered to be most important and appropriate for this study. The purpose of this review was to investigate the carcinogenesis of lung AC in never smokers focusing on genes related to susceptibility and suspected carcinogens, including environmental factors, in order to improve primary prevention of lung AC.

Original Articles on Genes Related to Susceptibility to Lung AC in Never Smokers

Thirty-one original articles listed in our previous review (17) were examined once again from the following standpoints: the hypothesis or purpose stated by the authors, the genes they had investigated, the study style used, the definition of never smokers, and the etiology of lung AC they analyzed such as ETS. Among these, the study hypothesis was considered the most important. If the authors had found genes related to susceptibility to lung AC and these genes were analyzed by the grade of heavy smoking but did not include discussion on never smokers, we deleted these articles from the list of originals in the present study. We focused more precisely on genes related to susceptibility to lung AC in never smokers (Table I).

1. Classical Genes

The hypothesis stated in the original articles on classical genes (20, 33-43) is as follows: exposure of never smokers to ETS resulted in lung AC, hence the genes affected in these cases are the same as those seen in the tobacco-related cases (33-36). The relative risk of the genes suspected in patients with lung AC exposed to ETS was higher than the frequency of suspected genes in patients with lung AC without exposure to ETS (Table I). The slow and the fast genotypes among the polymorphisms of *N*-acetyltransferase 2 (*NAT2*) were shown to be related to the risk of lung cancer among women never smokers (37). *NAT2* participates in the detoxification of aromatic amines. The authors took into consideration exposure to cooking oil fumes among never smoker women who developed lung cancer.

The tumor suppressor genes, *TP53* and, *TP63* may be involved in carcinogenesis of lung AC in female never smokers (38, 39), although *TP53* mutation has been reported in smokers with lung SC (17). These two reports (38, 39) did not describe the survey methods regarding ETS. Of course the authors understood the possibility of ETS, or other environmental risk factors, such as exposure to combustion products of indoor heating and cooking solid fuel and cooking oil fumes, as possible etiologies (38). Zhang *et al*. (39) introduced studies by Cianchi *et al*. (68) and Yao and Rahman (69), reporting that exposure to external carcinogens, including cigarette smoking, infectious agents, and dietary carcinogens, can result in inflammation and play a role in tumor development, but ETS in their cases was not analyzed because it was not their purpose. The purpose of their studies was to discover novel genes. DNA-repair genes were investigated in never smokers (40-43) and the authors strongly suggested the possibility of ETS (41, 42) or cooking oil fumes (40) as suspected carcinogens.

2. Susceptible Genes Found by Genome-wide Association Study (GWAS)

Nicotine acetylcholine esterase [cholinergic receptor nicotinic alpha (*CHRNA*)] genes found by GWAS for association with lung cancer reported by Amos *et al*. (70), Hung *et al*. (71) and Thorgeirsson *et al*. (72) indicated the association of chromosome 15q variants for *CHRNA* (rs16969968 and rs8034191) and risk of lung cancer with odds ratios (ORs) between 1.30 and 1.32. This was not found in patients with lung AC in Asia by Wu *et al*. (44), who identified four novel single-nucleotide polymorphisms (SNPs) for *CHRNA3* (rs2036534c>T, rs667282C>T,

rs12916984G>A, and rs6495309T>C) associated with significantly increased lung cancer risk and smoking behavior. Shiraishi *et al*. reported *CHRNA* SNPs to be associated with lung cancer susceptibility in a small subset of the Japanese population in a smoking-independent manner (45). These two reports from Asia did not focus on never smokers, and the results regarding smoking habits were very different between the reports, stressing the vital importance of the survey method used when analyzing smoking habits in patients as well as in controls (Table I). Wang *et al*. found no evidence of association between 6p21.33 or 15q25.1 variation and risk of lung AC in never smokers (47), and this finding was widely accepted in an article written by authors of 69 Institutions (73).

Telomerase reverse transpeptidase (*TERT*)–Cleft lip and palate transmembrane 1-like protein (*CLPTM1L*) variants may be involved in lung AC as a gene related to lung AC in never smokers (46-51) (Table I). The survey method regarding ETS was not described in this excellent and important article (Table I). The 5p15.33 region was associated significantly with lung AC in Asian female never smokers (48). Landi *et al*. revealed that 5p15.33 rs2736100 (*TERT*) was associated with risk of AC [odds ratio (OR)=1.23] (49). Jin *et al*. confirmed that 5p15.33, especially in the *TERT* gene, may also predispose to susceptibility to lung AC in Chinese female never smokers (50). Fine-mapping analysis of genetic variants in the 5p15.33 region conducted by Pande *et al*. revealed four SNPs associated with lung cancer risk (46): rs4975538, which is an intronic SNP in *TERT*, rs451360 and rs370348, which are intronic SNPs in *CLPTM1L*, and rs4975615, which is in the intergenic region between the two genes. However, these excellent articles did not discuss any association with ETS among never smokers.

Lan *et al*. made the extremely important finding that the strongest association signal, rs7086803 at 10q25.2, located at intron 7 of the vesicle transport through interaction with t-SNAREs homologue 1A gene (VTl1A) gene was implicated in lung carcinogenesis (52). VTl1A is involved in ACRP30-containing vesicles in adipocytes, and lower amounts of VTl1A in cultured adipocytes can inhibit adiponectin secretion (74). However, it is not clear how this international team defined the term never smokers or how several thousand cases and controls were surveyed for smoking habits.

Li *et al*. demonstrated a strong correlation between the transcription level of the gene glypican-5 (*GPC5*) and genotypes of the replicated SNP (rs2352028 at 13q31.3) in 77 non-tumor lung tissue samples, and the expression levels of GPC5 in the matched lung AC tissue were lower by half than in normal tissues (54). The main function of membrane-attached glypican is to regulate the signaling pathway of wingless transformation, hedgehog, fibroblast growth factors, and bone morphogenetic proteins (75). The authors showed that down-regulation of *GPC5* contributes to the development of lung cancer in never smokers. Their results were discussed from the viewpoints of former smokers and never smokers who had quit smoking (54) in relation to ETS exposure in never smokers (76). Landi *et al*. did not agree with this observation (55). However, the study by Li *et al*. (54) opened the way to a new epidemiological approach to clarify the interrelationships between the susceptible genes found by GWAS and carcinogens in ETS.

Tessema *et al*. reported that never smokers with primary AC had a significantly higher prevalence of methylation of tumor necrosis factor receptor superfamily member 10C (*TNFRSF10C*), basic helix-loop-helix (*bHLH*) transcription factor 5 (*BHLHB5*) and boule-like RNA-binding protein (*BOLL*) (regulating meiotic G_2/M transition) than current and former smokers (56). Genotypes of C3ORF21, which plays an important role in the formation of NOTCH EGF repeats, were nominally associated with a reduced risk of lung AC among never smokers (39). Another locus, 18p11.22, near the adenomatous polyposis coli down-regulated 1 (*APCDD1*), *N*-ethylmaleimide-sensitive factor attachment protein gamma (*NAPG*) and family with sequence similarity 38, member B (*FAM38B*) genes was reported in Korean never smokers with NSCLC by Ahn *et al*. (53). These findings for never smokers are very important, but the survey method of smoking was not sufficiently described.

3. Driver Genes

Driver genes are of interest as genes related to susceptibility to lung AC in Asian women never smokers from the standpoints of signal transduction for cell proliferation, survival migration and angiogenesis, as well as good treatment response to EGFR-TKIs if *EGFR* mutation was present (57-64) (Table I). Driver genes include mutations of *EGFR*, Kirsten rat sarcoma viral oncogene (*KRAS*), protooncogene B-Raf (*BRAF*), phosphatidylinositol-4,5-*bis*phosphate 3-kinase, catalytic subunit alpha (*PIK3CA*), and fusion of echinoderm microtubule-associated protein-like 4 (*EML4*) and the intracellular signaling portion of the anaplastic lymphoma kinase (ALK) protein (*EML4–ALK*).

Among never smokers with AC, the frequency of *EGFR* mutation was reported to be 42 ~50% in Asia (57, 58, 60), and 55% in those of European descent (63), while the frequencies of those with fusion of *EML4–ALK, PTEN, PIK3CA, c-MET, KRAS, STK11*, and *BRAF* were 9.3%, 9.1%, 5.2%, 4.8%, 4.5%, 2.7%, and 1.9%, respectively (57). Among smoker patients with AC, the frequency of *EGFR* mutation was reported to be 22.0% (57) or 10% to 20% (60), while the mutation frequency of *STK11* was 19.0%, and of *KRAS* was 12.0% (57). That is, never smokers with lung AC showed

Table I. *List of publications selected for the present review on genes related to lung adenocarcinoma (AC) in never smokers.*

Author(s) (Ref. no.)	Hypothesis (purpose)	Gene (cases/controls)	Country/ city/year	Definition of NS	ETS Consideration
1. Classical genes					
CYP1A1 polymorphisms					
Yoon *et al*. (33)	Low dose carcinogen exposure in never smokers	*CYP1B1* Leu432Val with *CYP1A1* Ile462Val (213/213) OR=2.16	Korea/2004-2005	Yes*	Smoking habits of family members, environmental factors obtained by a personal interview (trained personnel).
GST polymorphisms					
Bennett *et al*. (34)	Never-smoking women exposed to ETS	GSTM1 null (no ETS 55/ETS 51 in never smoker women) OR=2.6	Missouri/ 1992-1995	Yes*	Interview by trained personnel.
Wenzlaff *et al*. (20)	Low levels of household ETS exposure in never smokers.	GST M1 null (20 or years more household ETS in never smokers). OR=2.3	Missouri/Detroit/ 1990-2005	Lifetime never smokers.	Trained interviewer conducted telephone interview. Participants were asked about ETS exposure at home and workplace, including hours and years of exposure.
Hung *et al*. (35)	The role of *CYP1A1* and *GSTM1* in lung carcinogenesis might be more important at low levels of ETS exposure in never smokers.	*CYP1A1 Ile 462Val* (a pooled analysis 14 case-control studies, 302 cases/1631 controls) OR=2.99	USA, Norway, Finland, Sweden, Germany, Hungary, Slovakia, Poland, UK/1988-1997	Never smoked in their lives, varied slightly among the studies.	(Collected studies not described in detail)
Malats *et al*. (36)	The role of *GSTM1* and *GSTT1* in lung carcinogenesis might be more important at low levels of ETS exposure in never smokers.	*GSTM1**2(null) (122 nonsmoking cases/ 121 nonsmoking controls) OR=1.5 (ETS), OR=3.1 (indoor wood combustion)	Eight countries/?	Pure never smokers.	Information on demographics and environmental exposures was obtained through a personal interview using a standard questionnaire.
NAT2 fast acetylator genotype					
Chiou *et al*. (37)	A correlation between cooking oil fumes and female lung cancer has been revealed.	Polymorphisms of *NAT2* responsible for the metabolism of heterocyclic amines (162 cases/208 controls) OR=2.44	Veterans General Hospital-Taichung and Chung Shan Med. University Hospital/Taiwan/ before 2007?	Not described	Interview
Tumor suppressor genes: *TP53, TP63*					
Hosgood *et al*. (38)	To determine the risk of lung AC in Asian female never smokers.	*TP63* SNPs, rs10937405 (3,467/3,787) allelic risk 0.80	Taiwan, China, South Korea, Singapore/ before 2010?	Not described	Collected studies (not described)
Zhang *et al*. (39)	*TP63* SNPs and *C3orf21* SNPs were genes susceptible for lung AD in never smokers in China.	TP63 SNPs were not but C3ORF21 SNPs were associated with susceptibility to NSCLC in Chinese never smokers. *C3ORF21* and *TP63* (200/200) OR(*C3ORF21*)= 0.707 and OR (*TP63*) 1.227.	Zejiang Cancer Hospital/ China/?	Never smoked	Not described
DNA damage repair genes					
Shen *et al*. (40)	To clarify the role of ATM gene in lung AC in Chinese female non-smokers.	ATM rs189037 AA genotype compared with those carrying the GA or GG genotype (487 cases/ 516 controls) OR=1.89 (cooking oil fumes)	Liaoning Cancer Hospital, China/Jan. 2002-Nov. 2012	Yes*	Information on demographics and environmental exposures was obtained by trained interviewers.

Table I. *Continued*

Table I. *Continued*

Author(s) (Ref. no.)	Hypothesis (purpose)	Gene (cases/controls)	Country/ city/year	Definition of NS	ETS Consideration
Bock *et al*. (41)	Risk reduction due to procarcinogen activating of *NQO1*.	*NQO1 T* allele (161/173) OR=0.48 and OR=0.57 (ETS)	Detroit/diagnosed in 1984-87; after 1990	Yes*	The overall interview response rate for cases was 66.1%
Cohet *et al*. (42)	Second-hand smoke and repair of DNA damage in never smokers.	Exon 5 of the AGT gene (136/133) OR=2.05 and OR=1.95 (ETS)	Eight countries/ 1992-1944	Yes*	Not sufficient
Pulling *et al*. (43)	The prevalence for O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and K-ras mutation.	Promoter hypermethylation of *MGMT* (157 smokers/34 former uranium miners/ 46 never smokers)	New Mexico Tumor Registry/?	Yes*	Multi-center studies (not described)
2. Susceptible Genes Found by Genome-Wide Association Studies					
15q25: Nicotine acetylcholine esterase genes					
Wu *et al*. (44)	To identify other variants on 15q25 associated with lung cancer susceptibility in Chinese.	rs2036534C>T, rs667282C> T, rs12910984G>A, rs6495309T> C (576/576; 2,989/ 2,880; 2,221/2112) OR=1.42, and 1.40, respectively in never smokers.	Beijing/1997-2008; Jiangsu/2002-2008	Less than 1 cigarette per day and <1 y in their lifetime nonsmoker.	Through interviews
Shiraishi *et al*. (45)	To obtain further information on CHRNA SNPs in lung cancer risk.	Haplotype of minor alleles for three SNPs rs8034190, rs16969968 and rs1051730 (1250/936) OR=2.3 in Japanese.	Japan/2009.	Non-smokers were defined as those who had not smoking habit.	Smoking history was obtained *via* interview using a questionnaire. Smoking exposure was expressed in "pack-years".
5p15: TERT and CLPTM1L					
Pande *et al*. (46)	To analyze 215 SNPs across *TERT* and *CLPTM1L*.	215 SNPs at 5p15.33 (1,681/1,235) rs451360 OR=0.62 in never smokers.	Texas/1995-?	Not described	Not described
Wang *et al*. (47)	To examine if variation at 5p15.33 (*TERT-CLPTMIL*), 6p21.33 and 15q25.1 (*CHRNA5-CHRNA3*) influences the risk of lung cancer in never smokers.	5p15.33-*TERT* (rs2736100), 5p15.33-*CLPTMIL* (rs4975616), 6p21.33-BAT3 (rs317582), 15q25.1-*CHRNA3* (rs8042374), and 15q25.1-*CHRNA3* (rs12914385) (239/553)	Genetic Lung Cancer Predisposition Study (2008)	Yes*	Not described
Hsiung *et al*. (48)	To investigate 5p15.33 in lung cancer among never smoker Asian women by GWAS.	rs2736100 (1,164/1,736), Allelic risk 1.62	Seven studies/ Taiwan/?	Not described	Seven studies (not described)
Landi *et al*. (49)	A GWAS of lung cancer and its major histological types.	rs2736100 (*TERT*) (5739/5848) OR=1.3 in adenocarcinoma.	NCI GWAS/10 European studies /1985-2001	Not described	Eleven studies (not described)
Jin *et al*. (50)	To test TERT and CLPTM1L in a Chinese Population.	5p15.33 (rs402710C/T and rs2736100C) (1,221/1,344), OR=1.09, and 1.59, respectively.	Nanjing/2003-?	Not described	Face-to-face interviews to obtain exposure information (*e.g.* smoking status)
McKay *et al*. (51)	A GWAS of lung cancer detected two genes, *TERT* and *CLPTM1L*.	5p15.33 (rs402710 and rs2736100) (3,259/4159; 2,899/ 5,573) OR=1.25, and 1.15, respectively.	Toronto, HUNT2/ Tromsφ, CARET/?	Not described	The survey of ETS was not described? Suppl online

Table I. *Continued*

Table I. *Continued*

Author(s) (Ref. no.)	Hypothesis (purpose)	Gene (cases/controls)	Country/ city/year	Definition of NS	ETS Consideration
VTL1A					
Lan *et al*. (52)	To identify common genetic variants susceptible to lung cancer in never smoker Asian women.	10q25.2 (rs7086803) (5,510/4,544) OR=1.32	China, South Korea, Japan, Singapore, Taiwan and Hong Kong/before 2010?	Not described (online version?)	Not described (online?)
Other Genes Found by GWAS					
Zhang *et al*. (39)	Do environmental agents affect genetic polymorphisms ?	TP63 SNPs were not but *C3ORF21* SNPs were associated with susceptibility to NSCLC in a Chinese population. *C3ORF21* and *TP63* (200/200)	China/Zejiang/?	Not described	Not described
Ahn *et al*. (53)	To identify genetic loci associated with susceptibility of lung cancer in never smokers in Korea.	Among the 44 validation SNPs, two (rs11080466 and rs11663246) near *APCDD1, NAPG, FAM38B* (446/497)	Samsung Medical Center/2009	Yes*	Not described
Li *et al*. (54)	To unravel the genetic basis of lung cancer, *glypican-5*.	Among 44 top candidate SNPs, 13p31.3 (rs2352028) (377/377) OR=1.46	Rochester, Texas, Harvard/?	Yes*	Interview by trained personels.
Landi *et al*. (55)	To replicate glypican-5 study by Y. Li *et al*. (54) on 754 never smoker lung cancer cases and 10580 controls from seven GWAS studies.	13p31.3 (rs2352028) (754/10580) OR=1.04	USA, France, Germany, UK, Iceland/?	Not described	Not described
Tessema *et al*. (56)	To reveal the involvement of promoter hypermethylation in lung AD.	Prevalence of methylation of *TNFRSF10C, BHLHBS*, and *BOLL* (175 AD)	Johns Hopkins and Mayo Clinic/?	Not described	Not described
3. Driver Genes: *EGFR, KRAS, BRAF, PIK3CA*, and *EML4-ALK*					
An *et al*. (57)	The tyrosine kinase inhibitors targeting *EGFR* is the first line therapy for patients with *NSCLC* related with the mechanism of *EGFR* exon *20 T790M* mutation.	Driver gene alterations (524)	China/Guangdong (2007-2009)	Yes*	Not described
EGFR mutation					
Li *et al*. (58)	To reveal the prevalence of *EML4-ALK*, *EGFR* status and *KRAS* mutation.	208 NSCLC patients	China/Tianjin Medical University/?	Not described	Not described
Ren *et al*. (59)	To determine the distribution of known oncogenic driver mutation in female non-smoker Asian patients with lung AC.	396 Female non-smoker patients with AC; Oncogenic mutation (82.7%)	Shanghai/Tongi University/?	Yes*	Not described
Lee *et al*. (60)	To clarify the effect of ETS on *EGFR* mutation.	The nucleotide sequences of exons 18 to 21 on *EGFR* gene (179 cases) *EGFR* mutation (ETS 38.5% *vs*. Never 61.4%)	Yonsei University College of Med, Seoul/June 2006-Dec 2008	Yes*	Interviewed by trained interviewers.

Table I. *Continued*

Table I. *Continued*

Author(s) (Ref. no.)	Hypothesis (purpose)	Gene (cases/controls)	Country/ city/year	Definition of NS	ETS Consideration
Jou *et al*. (61)	Association of an *EGFR* intron 1 SNP with never-smoking female lung AC	SNP 8227G>A (rs763317) (730/730) OR=1.23 (for GA genotype), OR=3.52 (for AA genotype), OR=1.35 (adenocarcinoma). The rare alle of 8227G>A (haplotype) OR=2.81	Taiwan/ 2002-2004	Not described	If ETS exposure was present, mark 1, and if not, mark 0.
HER2					
Jo *et al*. (62)	To determine four polymorphisms (–3444C>T, –1985G>T, 1655A A>G and P1170A C>G) of *HER-2* gene.	814 Patients with lung cancer OR=2.65 (–3444C>T), and OR=2.38 (–1985G>T)	Seoul/Inha University/ 2001-2005	Not described	Smoking information was obtained using questionnaires by trained interviewers, but information on ETS was not described.
BRAF and PIK3CA					
Ren *et al*. (59)	To determine the distribution of known oncogenic driver mutation in female non-smoker Asian patients with lung AC.	396 Female non-smoker AD patients Driver mutations 1.90%BRAF, 1.0% PI3K.	Shanghai/ Tongi University/?	Yes*	Not described
EML4-ALK					
Jang *et al*. (63)	Oncogene fusion transcripts, *EZR-ROS1* and *KIF5B-RET* were identified between exons 1-9 of *SND1* and exons 2 to 3' end of *BRAF*.	Oncogene fusion transcripts by RNA-Seq (89 tumors)	Mayo Clinic/USA/ Jan 1997-Sep 2008	Yes*	Interviewed by trained interviewers.
Li *et al*. (58)	To reveal the prevalence of *EML4-ALK*, *EGFR* status and *KRAS* mutation.	208 NSCLC patients	China/Tianjin Medical University/?	Not described	Not described
HIF-2α					
Iwamoto *et al*. (64)	To reveal the association of *EPAS1* gene rs4953354 in lung cancer	*EPAS1* AG polymorphism (rs4953354) (346 patients/247 healthy controls) OR=3.31 (female never smokers)	Shimane University Hosp., Higashi-Hiroshima Med. Cent., Hiroshima University Hosp./2009-2012	Not described	Not described
4. Genes related to inflammation/innate immunity					
Kang *et al*. (65)	To identify genetic factors responsible for lung cancer.	*CSF1R* (rs10079250A>G), *TP63*, *C1R1* (181 cases/ 179 controls; 596/1194) OR=1.85 (rs10079250A>G)	Kyngpook National University Daegu, Korea/?	Yes*	Not described
Kiyohara *et al*. (66)	To evaluate the role of *IL1B* (rs1143634, 3954C>T) in lung cancer patients with a history of smoking.	*IL1B* (rs1143634, 3954C>T) (462/379) OR=2.62 (TT), and adjusted OR=3.31 (TT)	Kyushu University/ 1996-2008	Never smokers were defined as those who had never smoked in their lifetime.	As to ETS, interviewed by Kiyohara C.

Table I. *Continued*

Table I. *Continued*

Author(s) (Ref. no.)	Hypothesis (purpose)	Gene (cases/controls)	Country/ city/year	Definition of NS	ETS Consideration
Olivo-Marston *et al*. (67)	Children may be more susceptible to ETS, and this susceptibility may be exacerbated by alteration in inherited genetic variants in innate immunity genes.	*MBL2* (mannose binding lectin-2) gene (624 cases/ 348 controls; 172 cases/289 controls in never smokers) High MBL levels OR=2.52 (NCI-MD study), and OR=2.78 (Mayo Clinic study)	National Cancer Institute-Maryland Cancer (NCI-MD)/Mayo Clinic Study/ 1997-2001	Yes*	ETS during the past 30 years was examined in detail.

NS: Never smoker; AC, adenocarcinoma; ETS, environmental tobacco smoke; OR, odds ratio; *Yes: Indicates the definition that the never smoker had a lifetime exposure of fewer than 100 cigarettes.

increased *EGFR* mutation and *EML4–ALK* fusion protein. These mutations were at low frequency in smokers, but other mutations were seen in smokers with lung cancer (57). Although some cases showed overlap of *EGFR* and *KRAS* mutations, these were generally few in AC (57). The *EML4–ALK* fusion gene has been identified in a small subset of patients with lung AC (58). Ren *et al*. reported that 82.7% of lung AC in Asian female non-smokers showed well-known oncogenic mutations in *EGFR, KRAS, HER2, BRAF* and *PIK3CA*, and a majority of the mutations were mutually exclusive as noted above, except two with EGFR mutation and *BRAF* mutation, one with *EML4–ALK* fusion and *PIK3CA* mutation (59). Li *et al*. identified seven (among 208 cases; 3.37%) patients with the *EML4–ALK* fusion gene, of whom four had variant 3, two had variant 1, and one case had variant 1. Of these cases, six were non-smokers, and five were found among 33 cases of female non-smokers. *EML4–ALK* translocation was predominant in never smokers with AC (58).

Lung AC with *EGFR* mutation in never smokers showed somewhat good prognosis (57). The effect of ETS on *EGFR* mutation was reported in lung cancer in never smokers, and the rate of *EGFR* mutation among never smokers exposed to ETS was significantly low, as discussed below (60). Moreover, EGFR-TKIs, *e.g*. gefitinib and erlotinib, have been reported to be associated with high sensitivity to AC in Asian women non-smokers (57-61, 77, 78). Activating *EGFR* mutation, including 19 in-frame deletions and exon 21 L858R substitutions, have been shown to be the most potent biological predictors of sensitivity to EGFR-TKIs (60). Jou *et al*. found significant frequency of *EGFR* intron 1 SNP in Asian female never smoker patients with lung AC, as shown in Table I (61).

Other driver genes, human epidermal growth factor receptor type 2 (*HER2*) and *BRAF*, have been reported in female never smokers with AC (62, 63). Jo *et al*. found that three SNPs of *HER2* (-3444C>T, -1985G>T and P1170A C>G) were significantly frequent in Asian female non-smokers and nondrinker patients with lung AC (62). Suzuki *et al*. examined *HER2* gene mutation in 1,275 patients (1,055 ACs, 146 SCs, and 74 others) and detected *HER2* gene mutation in 46 (3.6%) of all cases. Mutation-positive cases were all ACs, comprising 4.3% of ACs (79). These positive cases were younger never smokers, with smaller tumor size (79).

Jang *et al*. found novel fusion transcript formed between exon 1-9 of staphylococcal nuclease domain-containing protein 1 (*SND1*) and exons 2 to 3' end of *BRAF* (63). This was observed in 3/89 tested tumors and 2/64 never-smoker lung ACs (63). *BRAF* mutations and their fusion transcripts lead to constitutive activation of Ser/Thr kinase activity and are located downstream of the RAF/MEK/ERK pathway in lung, melanoma, thyroid and colon cancer (63). SND1 is a component of the RNA-induced silencing complex and plays a role as a regulator for transcription of specific mRNAs by mediating RNA interference reported in colon, prostate and liver cancer (63).

4. Genes Related to Inflammation and Natural Immunity

Kang *et al*. used an Affymetrix custom-made GeneChip for finding novel genes related to susceptibility to lung cancer in female never smokers, and found three SNPs involved: colony stimulating factor 1 receptor (*CSF1R*) rs10079250 A>G, *TP63* rs7631358G> A and core-pressor interacting with *RBPJ 1 (C1R1)* rs130090791 (65). *CSF1R* rs10079250 A>G exhibited an increased level of phosphorylated c-Jun NH(2)-terminal kinase (JNK), a downstream molecule of the CSF1-CSF1R signaling pathway. They did not analyze genes

from the viewpoint of ETS. Kiyohara *et al*. reported that an association of *IL1B* (rs1143634, 3954 C>T) polymorphism with lung cancer was seen in never smokers (OR=1.11); higher risk was of course observed for smokers (OR=2.48) (66). Olivo-Marston, *et al*. reported that ETS exposure during childhood is associated with increased lung cancer risk among never smokers, especially never smokers with the haplotype mannose-binding lectin-2 (*MBL2*) (OR=2.52), suggesting alteration in inherited genetic variants of innate immunity genes (67). In these reports, the authors described in detail their surveys of smoking habits.

Definition of Never Smoker and Survey Methods for Smoking Habits

We sent e-mails with a questionnaire regarding the ETS exposure of never smokers to authors who had published original articles on genes and lung AC among never smokers in December of 2015. Very few responses were received. The reason for this is easily understandable because the hypothesis or purpose of the original articles was not to clarify carcinogenesis but focus on novel genes. Then, we examined the original articles listed in Table I again.

It is globally accepted that the definition of never smoker is as follows: a never smoker is an individual who has had a lifetime exposure of fewer than 100 cigarettes (University of California at Los Angeles, Harvard, Mayo, and International Agency for Research on Cancer studies) (24). This definition is the same as that of World Health Organization nomenclature (80).

Other definitions such as the Hawaii study (those who smoked fewer than 180 cigarettes in their lifetime), the Seoul study (those who smoked fewer than 200 cigarettes in their lifetime), the Liverpool study (those who never smoked more than 10 cigarettes per week regularly), the CREST study (those who either smoked less than 400 cigarettes in their lifetime or less than one cigarette per day for one year), the Aichi and GenAir studies (those who reported they had never smoked) have been reported (24).

We checked the definitions of never smoker described in original articles on novel susceptibility genes for lung AC in never smokers as shown in Table I, and found that most described never smokers as individuals with a lifetime exposure of fewer than 100 cigarettes.

Regarding the method used to survey the smoking habits of the patients, most authors described that a trained interviewer administered the questions regarding smoking. ETS at home, work or other places has been reported to be the cause of lung cancer in never smokers (19-24; Figure 1). De Andrade *et al*. showed that from 1997 to 2001, 810 women with lung cancer were interviewed to obtain data including the source, intensity, and duration of ETS exposure (76). In this descriptive study, relationships between smoking history, ETS exposure, and lung cancer histological subtypes were analyzed. Among the 810 patients, 773 (95.4%) reported personal smoking or ETS exposure, including 170 out of 207 (82%) never smokers. Among the never smokers with a history of ETS exposure, the mean years of exposure were 27 from smoking spouses, 19 from parents, and 15 from co-workers. For each major subtype of lung cancer (AC, SC, unclassified NSCLC, small cell, or carcinoids) among never smokers, 75-100% of patients had ETS exposure. Trends for AC, SC and small cell carcinoma were found to be statistically significant using the Cochran-Armitage Test for Trend I ($p<0.001$) among never smokers without ETS exposure, never smokers with ETS exposure, former smokers, and current smokers.

Kurahashi *et al*. reported a population-based prospective study (Cohort I in 1990 and Cohort II in 1993) including 28,414 nonsmoking women aged 40-69 years old, 28,414 nonsmoking women with exposure to ETS from their husband, at the workplace and during childhood (21). Over 13 years of follow-up, 109 cases with lung cancer were diagnosed. Among them 82 had lung AC. The hazard ratio (HR) in women with smoker husbands compared to those with never-smoker husbands was 1.34, and an association with lung AC had an HR of 2.03, with a dose–response relationship with the husbands' smoking. Tse *et al*. demonstrated an association between ETS on lung cancer in nonsmokers using a population-based, case-referent study in Hong Kong during 2004-2006, including 132 Chinese male nonsmoker cases with lung cancer and 536 nonsmoking community referents (22). They found a weak association between lung cancer and ETS exposure from household/workplace with OR of 1.11, and an increased risk of lung AC with OR of 1.68.

A recent report by the International Lung Cancer Consortium (ILCCO) in 2014 (24) is valuable in understanding the situation of ETS exposure among never smokers; it includes eight studies in North America, four studies in Europe and six studies in Asia/Oceania. The data comprise 12,688 lung cancer cases and 14,452 controls of which 2,504 cases and 7,276 controls were never smokers. This study showed that exposure to ETS increased risk of lung cancer among both ever smokers and never smokers. The association between ETS exposure and lung cancer development among never smokers was follows: OR=1.35 in males, OR= 1.27 in females; OR=1.56 in those ≥65 years old, OR=1.10 in those<65 years old. The adjusted OR comparing SCLC with NSCLC was 1.28 in the overall population and 2.11 in never smokers.

Clinical Features of Lung AC in Never Smokers

As noted above, global statistics estimate that 15% of lung cancer in men and 53% in women are not attributable to smoking, indicating that worldwide approximately 25% of

Figure 1. *Several scenarios showing sources of exposure to environmental tobacco smoke (ETS). Upper right image shows the possibility of ETS at the workplace. Lower image shows ETS at unidentified places. Upper left shows ETS at the home.*

patients with lung cancer are never smokers (5). Moreover, never smoker patients with lung cancer with AC were female, younger and had a better prognosis (6, 7, 10-12), although Pallis *et al*. noted that a correlation between younger age in never smoker lung cancer and the severity of cases was doubtful (9). NSCLC in never smokers is currently on the rise (16, 18, 22) and there is a question as to whether it may not be a different disease altogether (23, 24). Moreover, lung AC harboring an *EGFR* mutation responds to EGFR-TKIs, while that without *EGFR* mutation does not (85, 86). *HER2* amplification was an unfavorable prognostic factor, but HER2 phosphorylation was a favorable prognostic factor (79).

Histopathology of Lung Cancer in Never Smokers

Incidence of lung AC in men surpassed the incidence of lung SC in the 1960s and 1970s in the USA and Europe, and in the 1980s and 1990s in Japan (3). The report of the International Association for the Study of Lung Cancer (IASLC) noted imbalance with respect to gender and histology: among 2,341

Table II. *Genes related to susceptibility to metabolic syndrome resembling genes related to susceptibility to lung adenocarcinoma (AC) in never smokers.*

Gene	Evidence (Ref. no.)	Related signal pathways/comments	Gender
VTL1A	10q25.2 (rs7086803) OR=1.32 (5,510 female never smokers/4,510) (52).	*VTL1A* is involved in ACRP 30-containing vesicles in adipocytes. Lower levels in adipocytes can inhibit adiponectin secretion.	Female
TNFRSF10C *BHLHB5* *BOLL*	The methylation of these three genes are significantly more higher frequency in patients with lung AC among never smokers than those in smokers (56).	*TNFRSF10C* is TNF receptor family member.	Both
C3ORF21	rs(952481) OR=0.785 (200/200 Chinese) (39).	*C3ORF21* encodes a UDP-xylose: α-xylosided, 3-xylosyl-transferase, which plays an important role in the formation of notch epidermal growth factor (NOTCH EGF) repeats.	Both
EGFR	*EGFR* mutation in females (females 47.5% *vs*. males 15.0%) (208 Chinese patients with NSCLC) (58).	*EGFR* mutation and estrogen receptor (ER) α and β, crosstalk between membranous ER α and *EGFR* mutation has been reported in lung carcinogenesis.	Female

BHLHB5, Basic helix-loop-helix transcription factor 5; BOLL, boule-like RNA-binding protein; C3ORF21, Chromosome 3 open reading frame 21; EGFR, epidermal growth factor receptor; EGFR-TKI, EGFR-tyrosine kinase inhibitor; OR, odds ratio; NSCLC non-small cell lung cancer; TNFRSF10C, tumor necrosis factor receptor superfamily member 10C; VTL1A, vesicle transport like protein 1A.

female patients, 55% had AC, 25% SC, while among 6,796 male patients, 30% had AC and 57% SC (1990~2000) (87).

Yang *et al*. showed a strong association between cigarette smoking history and lung AC in a prospective cohort of 41,836 Iowa women aged 55-69 years with 13 years of follow-up (84). Two-thirds of the enrolled population were never smokers; lung AC was seen in 25%, SC in 8% and SCLC in 4% of all lung cancer. Moreover, they found that women who developed SC consumed more alcohol but less fruit than women with other cancer types, and women who developed SCLC had higher waist circumferences than women with other types of cancer. Women who developed lung cancer were compared with smoker cancer cases, and the differential factors seen in never-smoker cases were higher education, consumption of more fruit, less alcohol and less physical activity.

Seki *et al*. reported the effects of ETS of spouses on lung cancer in 1,670 cases and 5,855 controls and noted a marginal association of ETS with female lung cancer risk (OR=1.31), whereas no significant association was observed for lung cancer in men (23). Moreover, a recent report by ILCCO noted that ETS exposure in never smokers or former and current smokers showed a strong association with SCLC (24).

Possibility of Metabolic Syndrome Participating in Lung AC in Never Smokers

Yang *et al*. surveyed body mass index (BMI) and waist circumferences in a prospective cohort of 41,836 Iowa women aged 55-69 years with 13 years of follow-up as described above (84). They showed patients with lung cancer had significantly higher waist circumference ($p<0.15$). Zhang *et al*. reported that a comprehensive analysis of adiponectin quantitative trait loci (QTLs) associated with gene expression correlation identified genes related to metabolic syndrome with a potential role in carcinogenesis (88). As discussed above, genes related to susceptibility to lung AC in never smokers include classical genes (participating in detoxifying or metabolizing carcinogenic agents derived mainly from tobacco smoke, tumor-suppressor genes such as *TP53* and *TP63*, and DNA damage-repair genes), genes found by GWAS (nicotine acetylcholine esterase genes, *TERT* and *CLPTM1L, VTL1A, GPC5, TNFRSF10C, C3ORF21*, hypermethylation of *TNFSF10C*, *BHLHB5*, and *BOLL*), and driver genes (EGFR, KRAS, BRAF, PIK3CA, EML4-ALK) have been reported (17). Although these genes are not related to metabolic syndrome, *EGFR, VTL1A, TNFRSF10C, C3ORF21* and hyper-methylation of TNFSF10C, BHLHB5, and BOLL are involved in the metabolic pathways of metabolic syndrome (Table II). Mazieres *et al*. reported a close relationship between lung AC in never smokers and metabolic syndrome (89). They examined 140 women with AC (63 never smokers and 77 former/current smokers) and found that never smokers were characterized by a higher frequency of lipidic features (60.3% *vs*. 37.7%) compared with smokers (89). Obesity, lack of physical activity, heavy alcohol consumption and a diet of food with high fat content all lead to metabolic syndrome and a high percentage of cancer (90, 91). Metabolic syndrome is frequently complicated with type-2 diabetes mellitus, which is associated with increased risk of lung cancer, especially among female diabetic patients with RR=1.14 (92).

Predominance of Women Among Never Smokers

Among the never-smoker patients with lung AC, there were fewer female patients than male patients. However, the percentage of never smokers among total females with lung AC was over 50%. It has been reported that these female patients were younger and had better prognoses, as mentioned above (6-12).

It remains unknown why lung AC is seen in Asian women never smokers (4, 16). Association of *EGFR* mutation and estrogen receptor (ER)-α and –β with lung carcinogenesis has been reported (93, 94). Mazieres *et al*. observed increased frequency of *EGFR* mutation and ERα expression in never smokers with AC with higher frequency of lipidic features (89). Li *et al*. also revealed that *EGFR* mutations were seen in 24.5% (51/208 cases) of patients with lung cancer. These mutations were identified with higher frequency in females (47.5% *vs*. 15.0% in males), never smokers (42.3% *vs*. 13.9% in smokers), and patients with AC (44.2% *vs*. 8.0% in patients with non-AC) (58). Moreover, human papillomavirus (HPV) infection may be involved in Asian non-smoking lung AC, which responds to EGFR-TKIs (95). Women with early menarche or late menopause showed significantly increased risk of lung cancer (96). Further epidemiological research should be conducted to clarify these points.

Interaction of Susceptibility Genes and Suspected Carcinogens

There is much information on genes related to susceptibility to lung AC in never smokers as detailed above. Comparing original articles of the 1990s with those published after 2000 by meta-analysis, Okazaki *et al*. reported that the role of classical genes associated with lung cancer is decreasing and novel genes are emerging (2010), a fact that may reflect changes in lifestyle in Japan (3). Although the carcinogenesis of lung AC in smokers is simple, that in never smokers is complicated. However, clarification is necessary for primary prevention of lung AC. Moreover, the numbers of patients with lung AC in never smokers is increasing for both sexes. Generally the frequency among female never smokers was predominant in lung AC. In developed countries, even though the frequency in men is less than in women, that in never smoker male patients increases after quitting smoking (4).

Different genes associated with susceptibility to cancer of course relate to different metabolic pathways to lung AC. For example, never smokers exposed to ETS exhibited the changes related to classical genes as Bennett *et al*. suggested (34). Members of the same group, Olivo-Marston *et al*. showed that ETS exposure during childhood might result in more susceptibility to ETS in never smokers with a haplotype of *MBL2*, suggesting alteration in inherited genetic variants of innate immunity genes (67). Li *et al*. found glypican-5 to be a novel gene related to susceptibility to lung AC in never smokers, and showed the possibility of a role for ETS in carcinogenesis in never smokers (54). Although the role of carcinogens in never smokers with most defined genes related to susceptibility remains unknown, the reported interrelations are shown in Table III.

Table III. *Suspected carcinogens and genes involved in susceptibility to lung AC reported among never smokers.*

Suspected carcinogen	Gene
Environmental tobacco smoke	1. Classical genes *CYP1B1 Leu432Val/CYP!A1 Ile462Val* (33, 36), *GSTM1* null (34, 35, 36), *NQO1* T allele (41), AGT gene (42) 2. GWAS *GPC5* (54) 3. Driver genes *EGFR* mutation (60) 4. Immunity-related *MBL2* haplotype (67)
Radon	1. Classical genes *GSTM1* and *GSTT1* gene deletion (29)* *TP53* (29)* DNA-repair gene polymorphisms (29)*
Indoor cooking oil fumes	1. Classical genes NAT2 (37), *ATMrs189037 AA* genotype (40),
Indoor wood combustion	1. Classical genes *GSTM1* and *GSTT1* gene deletion (36)
Hormone replacement therapy	?
Infection	Oncogenic virus?

GWAS, Genome-wide association study. *Choi *et al*. (29) reviewed genes susceptible to radon (includes 28 genes).

Lee *et al*. clearly demonstrated that *EGFR* mutation rate was 56.6% in lung cancer in never smokers without ETS exposure, 44.0% in lung cancer in never smokers exposed for <45 ETS smoker years and 25.7% in lung cancer in never smokers exposed for ≥45 ETS smoker years (60). The same trend was seen for childhood ETS exposure, and household *vs*. workplace ETS, *i.e*. *EGFR* mutation rate was higher in never smokers without ETS, but a high level of ETS was associated with a low *EGFR* mutation rate; the *EGFR* mutation rate was lowest in smokers with lung cancer. According to the review of Choi *et al*., radon is recognized as the second leading carcinogen of lung cancer, and they listed the genes related to susceptibility as shown in Table III (29).

Subramanian and Govindan reviewed pre-existing lung diseases, oncogenic viruses and human papillomavirus in carcinogenesis of lung cancer in never smokers (97), and

they also referred to Schabath *et al*.'s study (98), in which estrogen replacement therapy was used to exert a protective effect on women against developing lung cancer. Hormone or hormone replacement therapy should be investigated from the viewpoint of carcinogenesis between carcinogen and susceptible genes; further research is necessary.

We reported the possibility of genes associated with metabolic syndrome being related to lung AC in never smokers (17). However, while ETS and the other agents shown in Table III are suspected carcinogens, it is not yet clear whether they actually are. The references shown in Table II did not reveal the physical characteristics of metabolic syndrome such as body weight, body length, BMI, waist circumferences, hypertension, hyperlipidemia, blood sugar levels and hemoglobin A1c (HbA1c) levels (99). Even if the study subjects of these reports had the physical characteristics of metabolic syndrome, ETS or other carcinogens, drugs, infectious agents might be responsible for causing lung cancer because metabolic syndrome, obesity and type 2 diabetes mellitus are known to be complicating factors in malignant disease. The carcinogen(s) involved in never-smoker patients with lung cancer and metabolic syndrome requires further elucidation.

Future Directions

For primary prevention of lung AC in never smokers, of course, it is necessary to educate the general population that they should quit smoking and reduce ETS. We should promote the conduct of epidemiological surveys of suspected carcinogens in individual districts in order to clarify the carcinogenesis of lung AC in each case with genes related to susceptibility to cancer.

The relationship between AC and metabolic syndrome is especially important, because in general Asians are increasingly suffering from increased obesity and type-2 diabetes mellitus (92) as their life-styles change to include more Western-type foods and they engage in less physical activity. A recent report by Zanetti *et al*. showed the importance of ethnic groups with respect to susceptibility genes (100). The interaction of these genes and carcinogens, even if they are only suspected, should be investigated. The well-known review by Sun *et al*. (6) pointed out that *EGFR* mutation in never smokers *vs*. *KRAS* mutation and *TP53* mutation in never smokers are frequently seen, and these differences in never smokers support the idea that different carcinogens are involved for different groups of never smokers. Moreover, the study of different oncogenic mutation spectra of lung AC in never smokers can lead to better selection of effective treatments and improve prognosis. We could establish strategies for primary prevention of lung AC in never smokers if we start to conduct surveys in individual districts.

Conflicts of Interest

The Authors confirm that there are no conflicts of interest regarding the contents of this article. This study was approved by the Ethics Committee of the International University of Health and Welfare (13-B-130; October 10, 2015).

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