Review

Genes Associated with Succeptibility to Lung Adenocarcinoma Among Never Smokers Suggest the Mechanism of Disease

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Abstract. *Global statistics estimate that 15% of all cases of lung cancer in men and 53% in women are not attributable to smoking, and these data indicate that worldwide, approximately 25% of patients with lung cancer are never smokers. The etiology of lung cancer is disputed. The present study reviews the genes associated with susceptibility to lung cancer among never smokers and suggests possibilities for the involvement of metabolic syndrome. The environment appears to have changed the genes susceptible to lung cancer. Classical genes associated with lung cancer are decreasing and novel emerging genes may reflect changes in lifestyle. We provide evidence that the genes associated with susceptibility to lung cancer in never smokers are very similar to those reported in patients with metabolic syndrome, and that simply quitting smoking is not sufficient as the primary means of preventing lung cancer.*

The purpose of this article is to review the genes associated with susceptibility to lung adenocarcinoma among never smokers, including a description of the mechanism of disease. Lung cancer is a leading cause of death in both developed and developing countries. It comprises of 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) (1, 2). The increasing 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 (1, 2). Among never smokers with lung cancer, over 65% of patients had AC (3). The absolute numbers of female patients with lung AC were not high compared to the numbers of male patients with lung AC, but a high percentage of AC in females was observed (1-8).

Global statistics estimate that 15% of all lung cancer cases in men and 53% in women are not attributable to smoking, and these data indicate that worldwide, approximately 25% of patients with lung cancer are never smokers (4). More never-smoker patients with lung AC were female, younger and showed better prognosis (5-8). NSCLC in never smokers is currently on the rise (7), and there is a question as to whether it might be a whole different disease altogether (3, 5).

The reason why AC is increasing remains unknown. The use of cigarette filters, and air pollution have been pointed-out as possible reasons (9). Santoro *et al*. explained that the proportion of never smokers with lung cancer is expected to increase in parallel with successful cessation programs (10). If patients were never smokers, the following exposures have been considered: second-hand smoke, radon, outdoor air pollution, cooking oil fumes, coal fumes and asbestos (7, 9, 10). Cessation of smoking is absolutely necessary but by itself is not sufficient for total prevention of lung cancer, because obesity, lack of physical activity, heavy alcohol consumption and consuming food with a high fat content all lead to metabolic syndrome, which causes a high percentage of cancer (9, 11). Very recently Mazieres *et al*. examined 140 women with AC (63 never-smokers and 77 former/current smokers) and found that the never smokers were characterized by a higher frequency of lipidic features (60.3% *vs*. 37.7%) compared with smokers (12).

The present review analyzes recent work on genes associated with susceptiblity to lung AC among never

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smokers, and demonstrates that this information on susceptibility genes suggests the etiology of recent emerging lung cancer in never smokers.

Classical Genes Associated with Susceptibility to Lung Cancer

Xenobiotic genes. Our previous article (9) showed that genes related to lung cancer susceptibility had changed over the last 20 years in Japan (all referenced articles are in English with peer review). The odds ratios (ORs) of the rare alleles of cytochrome P450 1A1 *(CYP1A1)*2A*, *CYP1A1*2B*, and glutathione S-trannsferase M1 (*GSTM1*) null-type genes were investigated by a meta-analysis method. The incidence of lung cancer comparing "before 2000" with that "after 2001" for the population with *CYP1A1*2A (m2/m2)* was much greater than that with *CYP1A1*2A (m1/m1)* (averaged OR of 2.493 *vs.* 0.899, respectively). There were no statistical differences in ORs between *CYP1A1*2B (Val/Val)* and *CYP1A1*2B (Ile/Ile)*, or between *GSTM1* null and positive types (9).

A recent report by Lopez-Cima *et al.* (13) showed that negative data in the *CYP1A1, GSTM1*, glutathione S-trannsferase T1 (*GSTT1*), glutathione S-trannsferase P1 (*GSTP1*) metabolic genes with no gene-gene association between them in 789 cases (SC=313; AC=246) and 789 controls in northern Spain. However, ethnic differences were not taken into consideration in this study. The distribution of gene polymorphism for both *CYP1A1*2A* and *CYP1A1*2B* is not the same in all races. An ethnic difference may be considered due to the fact that the allelic frequency of *CYP1A1*2A (m2/m2)* and *CYP1A1*2B (Val/Val)* among Caucasians was about 10-fold less than among Japanese (9). Chen *et al.* conducted a meta-analysis of 71 studies (12,815 patients and 17,553 controls; East Asians=32%, Caucasians=24%, other ethnic origins=24%), and revealed ORs for lung SC in those with *CYP1A1*2A* and *CYP1A1*2B* of 1.19 and 1.20, respectively, but showed no association with other histological types of lung cancer (14). The above data suggest that exposure to higher-than-present concentrations of chemical agents, including tobacco smoke, air pollution, occupational chemicals and others, induced *CYP1A1* and *CYP1A2* genes in the past.

Numerous studies on the association between *GSTM1, GSTT1* and *GSTP1* genes and the risk of lung cancer have been reported and demonstrated higher ORs for lung cancer among smokers (15-17). Wenzlaff *et al.* reported no significant association in never-smoker patients with lung cancer between single or combinations of genotypes of *GSTM1, GSTT1* or *GSTP1* and lung cancer risk (18).

Among xenobiotic genes, new candidate genes have emerged in parallel with the increase in cases of lung AC. The combination of *CYP1A1*2B (Ile462Val)* genotype and myeloperoxidase G/G (*MPO G/G*) genotype also showed a significantly increased risk of lung AC (19). Osawa *et al.* showed increased ORs in those with the combinations *CYP1A2*1FA/A* or *CYP1A2*1CG/G*, and N-acetyltransferase 2 (*NAT2*) slow genotype to be 4.95 and 3.31, respectively, as shown in Table I (20). The slow genotype and the fast genotype among the polymorphisms of *NAT2* were shown to be related to risk of lung cancer among never-smoker women (21). Increased meat consumption may cause induction of NAT2 (20, 21). Changes in lifestyle may result in the increased activity of these xenobiotic genes.

Tumor-suppressor genes, TP53 and TP63. TP53 mutations have been reported more frequently in lung carcinomas of smokers than among never smokers (22, 23). Lee *et al.* showed that *TP53* mutation and methylation of the RAS association domain family 1A (RASSF1A) promoter were more frequently seen in smokers with SC than in never smokers with AC (24).

TP63 encodes p63, a component of the p53 protein, and the *TP63* locus on chromosome 3q28 has two single nucleotide polymorphisms (SNPs) (rs4488809 and rs9816619), which were shown to be associated with lung AC among never-smoker females in Asia in a genome-wide association study (GWAS) (25). Moreover, besides *TP63*, rs952481 in chromosome 3 open reading frame 21 (*C3orf21*) (described later in detail) was also found in the same GWAS (26). *C3orf21* encodes a UDP-xylose:α-xyloside α1, 3-xylosyl-transferase, which plays an important role in the formation of notch epidermal growth factor (NOTCH EGF) repeats (described in detail below).

DNA damage-repair genes. Several DNA damage repair-genes have been reported in association with lung cancer, *e.g.*, human 8-oxoguanine DNA glycosylase (*hOGG1*), nucleotide excision repair (NER) genes [*ERCC1, XPB/ERCC3, XPG/ERCC5, CSB/ERCC6* and *XPC*], NAD(P)H: quinoneoxidoreductase (*NQO1*), cytosine DNA-methyltransferase-3B (*DNMT3B*), O^6-alkylguanine DNA alkyltransferase (*AGT*), X-ray repair cross complementing group 1 (*XRCC1*), O^6-methylguanine-DNA methyltransferase (*MGMT*) (9). Among heavy smokers with SC, these gene polymorphisms had significantly high ORs for their association with lung cancer (9). This is reasonable because tobacco smoke contains carcinogenic chemicals which damage DNA, and if these gene polymorphisms negative affect repair of damaged DNA or prevent the formation of DNA-adducts, the resultant reduced DNA-repair capacity would play a role in the carcinogenesis of tobacco-related cancer (9).

Susceptibility Genes Found by GWAS

15q25, Nicotine acetylcholineesterase genes. GWAS for lung cancer reported by Amos *et al.* (27), Hung *et al.* (28) and Thorgeirsson *et al.* (29) indicated an association between chromosome 15q variants (in particular rs16969968 and

Table I. *Genes associated with susceptibility to lung cancer in never smokers (2005-2013).*

Author(s)	(Year) Gene Cases/controls	Comments	Ref. no.
1. Classical Genes, never smokers			
Xenobiotic genes			
Lopez-Cima *et al*.	(2012) *CYP1A1/GSTM1/GSTP1/GSTT1* (789/789)	No association	13
Chen *et al*.	(2011) *CYP1A1* (meta-analysis of 71 case-control studies)	No association	14
Osawa *et al*.	(2007) *CYP1A2*1F A/A, CYP1A2*1C G/G* and *NAT2* slow	OR 4.95, 3.31	20
Larsen *et al*.	(2006) *CYP1A1* Ile462Val and MPO G-463A (1,103/627)	OR 3.72 (AC)	19
Chiou *et al*.	(2005) *NAT2* fast acetylator (162/208)	OR 2.56 (female), no effect (male)	21
Tumor-suppressor genes: TP53, TP63			
Hosgood *et al*.	(2012) *TP63* (3,467/3,787, Taiwan, China, South Korea, Singapore)	OR 0.80	25
Le Calvez *et al*.	(2005) *TP53* mutation (40 never smokers/27 former/64 current)	47.5%, 55.6%, 77.4	77
DNA damage and repeair genes			
Bock *et al*.	(2005) *NQO1* T allele (161/173)	OR 0.57 (ETS exposure), 0.98 (without exposure)	78
2. Genes found by GWAS			
Cholinergic nicotine receptor genes			
Lan *et al*.	(2012) *15q25* (5,510 never-smoking female cases/4,510)	No association	38
Ito *et al*.	(2012) *15q25* (716/716, Japanese)	No association	31
Wang *et al*.	(2011) *15q25* (rs12914385) (2,405/7,622, UK)	No association	37
Timofeeva *et al*.	(2011) *15q25* (rs16969968) (894/1,805, Sweden)	OR 1.18	45
Wang *et al*.	(2010) *15q25* (rs12914385) (239/553, UK)	No association	36
Lips *et al*.	(2010) *15q25* (rs16969968) (342/3,273)	OR 1.18	34
Shiraishi *et al*.	(2009) CHRNA (264/575) (rs8034190, rs16969968, rs1051730)	OR 2.3, 2.4, 2.7	35
Wu *et al*.	(2009) *15q25* (576/576, 2,989/2,880 Chinese)	OR 1.39 (rs2036534), 1.49 (rs667282), 1.42 (rs12910984), 1.40 (rs6495309)	33
TERT and CLPTM1L			
Ito *et al*.	(2012) *5p15* (716/716, Japanese)	OR 1.17 (rs2736100), 2.48 (rs402710)	31
Pande *et al*.	(2011) *5p15.33* (rs451360) (1,681/1,235, USA)	OR 0.62	49
Hsiung *et al*.	(2010) *5p15.33* (rs2736100) (2,768/3,100, Chinese and Taiwanese)	OR 1.54	39
Jin *et al*.	(2009) *5p15.33* (1,221/1,344 Chinese)	OR 1.59 (rs2736100), 1.09 (rs402710)	47
McKay *et al*.	(2008) *5p15.33* (3,259/4,159)	OR 1.25 (402710), 1.15 (rs2736100)	79
Landi *et al*.	(2009) *5p15.33* (362/1,402)	OR 1.34 (rs2736100, TERT)	80
Other genes found by GWAS			
Lan *et al*.	(2012) *10q25.2* (rs7086803) (5,510/4,544)	OR 1.32	38
Zhang *et al*.	(2012) *C3orf21* (200/200, Chinese)	OR 0.6219 (rs2131877),	
Ahn *et al*.	(2012) *18p11.22* (434/1,000, Koreans)	OR 0.785 (rs952481)	26
Li *et al*.	(2010) *13q31.3* (rs 2352028) (377/377, 328/407, 92/161, 91/439)	OR 0.68 (rs11080466), 0.69 (rs11663246) OR 1.69	56 54
3. Driver genes			
EGFR mutation			
Li *et al*.	(2013) *EGFR* mutation in female (47.5% *vs*. 15.0% in males), never-smokers (42.3% *vs*. 13.9% in smokers), AC (44.2% *vs*. 8.0% in AC)		62
HER2			
Jo *et al*.	(2008) *HER-2* (104/105).	-3444 C>T: OR 2.65 (female), 2.26 (non-smokers), 2.19 (non-drinkers); 11985 C>T: OR 2.38 (females), 2.15 (non-smokers), 2.85 (non-drinkers)	
71			
EML4 - ALK fusion gene			
Li *et al*.	(2013) EML4-ALK fusion gene cases (3.37%, 7/208 cases with lung cancer) Five were female, non-smoking adenocarcinoma		62
4. Genes related to inflammation and natural Immunity			
Kiyohara *et al*.	(2010) *IL1B* rs1143634 (462/379, Japanese)	OR 1.51	75

GWAS: Genome-wide association studies; TERT: Telomerase reverse transpeptidase; CLPTMIL: cleft lip and palate transmembrane 1-like protein; C3orf21: chromosome 3 open reading frame 21; HER2: Human EGFR2; NAT2: N-acetyltransferase 2; NQO1: quinone oxidoreductase 1.

rs8034191) and risk of lung cancer with ORs between 1.30 and 1.32 ($p<9\times10^{-10}$ ~1×10^{-17}). The susceptibility region contains three cholinergic nicotine receptor genes, *CHRNA3, CHRNA5* and *CHRNB4*. Amos *et al*. (27) and Hung *et al*. (28) showed a direct association between the variants and the risk of lung cancer, irrespective of smoking habit. Thorgeirsson *et al*. demonstrated an association between the same genetic region and smoking habits, as well as an association with risk of lung cancer (29). Therefore, it has been argued whether the association is direct or indirect, that is, whether the risk of lung cancer is in fact associated with any smoking habit. Studies noting an association between 15q variants and nicotine dependence or smoking quantity have so far focused mainly on smokers with lung cancer and chronic obstructive pulmonary disease (29-31). Liu *et al*. demonstrated that the risk of lung cancer was more than five-fold higher among 194 patients with familial lung cancer with either copy of high-risk alleles rs8034191 (OR=7.20) or rs1051730 (OR=5.67), both of which were located in the 15q24-25.1 locus, than among 219 cancer-free controls (32). The HapMap project revealed that the risky alleles of the SNPs at chromosome 15q25, rs8034191 and rs16969968 in Caucasians were found at extremely low frequencies in Asians, suggesting that chromosome 15q25 may have less influence on the risk of lung cancer and smoking behavior in Asians than in Caucasians (31). Ito *et al*. observed no significant association between the variants of rs12914385 and rs931794 on 15q25 and risk of lung cancer in a Japanese population (31).

As noted above, the risky SNPs reported in Caucasians are extremely rare in Asians. Wu *et al*. searched novel SNPs in the *CHRNA3-CHRNB4-CHRNA5* gene cluster on chromosome 15q25 in Chinese and identified four novel SNPs, as shown in Table I (33). Moreover, they found that rs6495309T>C SNP located in the *CHRNA3* promoter region alters the ability to bind transcriptional factor organic cation transporter 1, resulting in increased CHRNA3 expression.

An association between nicotine dependence with increased serum levels of nicotine and both *CYP2A6* and *CYP2B6* genes encoding nicotine-metabolizing enzymes as well as both *CHRNB3* and *CHRNA6* genes encoding nicotinic acetylcholine receptor subunits, has been reported (9). Lips *et al*. showed a strong association between 15q gene variants and lung cancer and concluded the existence of an independent association with smoking quantity in a total of 17,300 subjects from five studies (34). The same study showed there to be no association between 15q variant and smoking initiation, cessation, and quitting smoking because the authors observed association between 15q variants and the number of cigarettes smoked per day in former and current smokers, and an association was seen in women, not in men. Although current heavy smoking controls with AA genotype showed there to be a 60% increased OR for heavy smokers, the lung cancer cases did not show such an association (34). Shiraishi *et al*. recorded an association in both smokers and non-smokers and in all histological types of lung cancers among Japanese (35).

Wang *et al*. examined the association of 15q25 and smoking, and showed an indirect link between genotype and lung cancer (36, 37). They showed no association between 15q25.1 variation and risk of AC in never smokers (36). They conducted a meta-analysis, pooling their cases and previously published studies on 2,405 never-smoker lung cancer cases and 7,622 controls, and revealed no association between 15q25 variation and lung cancer risk (37). No association between 15q25 and lung cancer in never-smoker women in Asia was noted (38, 39). This finding of no association was widely accepted in an article written by authors from 69 Institutions (40). The article also suggested that the 15q25 variant region may influence the risk of airflow obstruction, that is, lung cancer risk is not mediated solely by the effects of nicotine dependence. This derives from the authors' observations based on the correlation between 15q25 SNP genotype and *CHRNA5* expression levels in lung and sputum, combined with a finding of increased risk of airflow obstruction in never smokers (40). Moreover, they observed the 15q25.1 region meeting with the iron-responsive element binding protein 2 (*IREB2*) gene by genome-wide association. Fehringer *et al*. reported separately that the minor allele of a variant representing one of the two loci at 15q25 (rs2036534) was associated with increased IREB2 expression (41). The significance of IREB2 is that it may play an important role in the repair and remodeling processes that lead to chronic obstructive pulmonary disease in never-smoker patients. *CHRNA3/5* variant was also found to be associated with bronchial hyper-responsiveness in children not exposed to cigarette smoke (42). Thus, a number of articles note that the disease mechanism causing lung cancer is unlikely to involve tobacco addiction. Nicotine acetylcholine receptors could be involved in lung cancer through other mechanisms. It has been suggested that *N*'-nitrosonornicotine and nitrosamines may facilitate neoplastic transformation by stimulating angiogenesis and tumor growth (43), and cancer cell motility, migration and p63 expression mediated through their interaction with nicotinic acetylcholine receptors (44).

5p15, Telomerase reverse transcriptase (TERT) and cleft lip and palate transmembrane 1-like protein (CLPTM1L). GWAS have identified chromosome 5p15.33 as one of the regions that is reproducibly associated with lung cancer risk (27-29). Subsequently, an association of SNPs in the 5p15.33 region with lung cancer risk has been reported (35, 43, 45, 46). Chromosome 5p15.33 comprises of two candidate susceptibility genes, *TERT* and *CLPTM1L*. *TERT* encodes a catalytic subunit of telomerase that maintains telomere ends.

Its overexpression leads to prolongation of the lifespan of the cell and is seen in cancer cells. *CLPTM1L* is also known as cisplatin resistance-related protein 9 (CRR9p). CLTM1L confers resistance to apoptosis caused by genotoxic agents in association with up-regulation of the anti-apoptotic protein, B-cell lymphoma-extra large (BCL-XL) (35).

Although the association of rs2361000 SNP in *TERT* gene with lung cancer risk has been reported in smokers, a strong association was also demonstrated in never smokers (36, 45, 47). Broderick *et al*. observed a significant increased frequency of rs2736100 (*TERT*) as the risky allele in cases of AC, but reported no data on never smokers (48). Hsiung *et al*. observed that the most significant association was rs2736100 at 5p15.33 in lung AC among never smokers (39). Fine mapping analysis of genetic variants in the 5p15.33 region conducted by Pande *et al*. revealed four SNPs associated with lung cancer risk; rs4975538 is an intronic SNP in *TERT*, rs451360 and rs370348 are intronic SNPs in *CLPTM1L* and rs4975615 is in the intergenic region between two genes (49). The rs451360 was significant among never smokers (49).

6q21, BAT3. Recent papers focusing on never-smoker women in Asia (38, 39) showed no evidence of association with lung cancer at 15q25 but found three new susceptible loci at 10q25.2, 6q22.2 and 6q21.32 besides 5q15.33 (*CLPTM1L* and *TERT*) and 3q28. The association of 6q21.33 and risk of lung cancer shown by Wang *et al*. (36, 43) and Broderick *et al*. (48) could be considered to mediate through a number of transcripts mapping the region of linkage disequilibrium (LD). They wrote that *BAT3* represents a strong candidate for lung cancer susceptibility because it is implicated in apoptosis and the protein complexes with EIA-binding protein p300, required for acetylation of p53 in response to DNA damage (48).

The associated risk loci mapping 6p21.33 in which rs3117582 localizes to intron 1 of *BAT3* and rs3131379 localizes to intron 10 of *MSH5* were revealed by GWAS (43). *MSH5* is involved in DNA mismatch repair (MMR) and meiotic recombination. The deficiency of MMR leads to lung cancer. The C allele of rs3117582 is associated with increased risk (OR 1.16), but there is no report of lung cancer in never smokers.

10q25, Vesicle transport through interaction with t-SNAREs homologue 1A (VTI1A). The strongest new association signal, rs7086803 at 10q25.2, located at intron 7 of the *VTI1A* gene, has been implicated in lung carcinogenesis (38). VTI1A is involved in ACRP30-containing vesicles in adipocytes, and lower amounts of VTI1A in cultured adipocytes can inhibit adiponectin secretion (50). A low level of adiponectin leads to cardiovascular diseases in metabolic syndrome (51). An association between lower adiponectin levels and lung cancer has been reported (52). Petridou *et al*. showed a relation between adiponectin receptors and the risk of lung cancer but no significant relation with circulating adiponectin levels in smoking patients with lung cancer (53). These alterations may be based on differences in lifestyles, including factors such as obesity and lack of physical activity among others.

Other genes found by GWAS. A GWAS on never smokers conducted by Li *et al*. revealed 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 tissue (54). Down-regulation of *GPC5* may contribute to the development of lung cancer in never smokers. *GPC5* is a member of the glypican gene family. Glypicans are a family of heparin sulphate proteoglycans, and the main function of the membrane-attached glypicans is to regulate the signaling pathway of wingless transformation (WNT), hedgehog, fibroblast growth factors, and bone morphogenetic proteins (54).

Tessema *et al*. reported that never smokers with primary lung AC had a significantly higher prevalence of methylation of *TNFRSF10C* (a TNF receptor family member that modulates apoptosis), 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 (55).

Genotypes of C3orf21, which plays an important role in the formation of NOTCH EGF repeats, as described above in *TP63*, were nominally-associated with a reduced risk of lung AC among never smokers. C3orf21 is located in 3q29 (26). Chromosomal imbalance in 3q29 has been reported in various types of cancer: NSCLC, prostate cancer, and head and neck squamous cell carcinoma (26). Another novel susceptible locus, 18q11.22 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 also reported in Korean never smokers with NSCLC (56).

Driver Genes: *EGFR, KRAS, BRAF, PIK3CA*, and *EML4-ALK*

Epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma viral oncogene (*KRAS*), protooncogene B-Raf (*BRAF*), phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) and *EML4-ALK* are known as driver genes, and mutations of these genes are seen in patients with AC. Among these the frequency of *EGFR* mutation was about 50% in non-smoking patients with AC (57).

EGFR mutation. EGFR tyrosine kinase inhibitors (EGFR-TKIs) are dramatic anticancer agents, *e.g.* gefitinib and erlotinib, for lung cancer, especially for AC (58). It was noted that the *EGFR* mutation in lung cancer associated with sensitivity to EGFR-TKI occurs more frequently in Asian women non-smokers with AC (59-60). *EGFR* mutation is also considered to be an early event in the pathogenesis of lung AC (60). Wilkerson *et al*. clearly demonstrated a relation between the subtypes of AC (bronchioid, magnoid, and squamoid) and sequence mutation, copy number, chromosomal instability and methylation (61). Bronchioid was found to occur in female non-smoker patients with a superior survival outcome and who present with well-differentiated, bronchioalveolar morphology, early-stage and *EGFR*-mutated cancers. On the other hand magnoid and squamoid ACs were found in male patients exposed to smoking, with poor survival outcome and late-stage cancer, and with *KRAS*, *TP53* or serine/threonine kinase 11 (*STK11*) mutations. *STK11* gene regulates cell polarity and functions as a tumor suppressor. The magnoid subtype exhibited increased hypermethylation, a phenomenon similar to the CpG-island-methylator-phenotype observed in other types of cancers (62). EGFR-TKI was used as a potential breakthrough for the treatment of metastatic AC of lung in never smokers (63).

As noted above, AC appears to have a predilection for women, and the association of AC with a smoking habit may be less than that for the other histological subtypes of lung cancer (59). Association of *EGFR* mutation and estrogen receptor (ER)-α and -β with lung carcinogenesis has been reported (59, 64). Shimizu *et al*. showed the presence of membranous ERα expression together with *EGFR* mutation to be an independent factor for survival in patients with lung AC, suggesting a crosstalk between membranous ERα and *EGFR* mutation (59). Very recently Mazieres *et al*. examined 140 women with AC (63 never smokers and 77 former/current smokers) and found that the never smoker patients with AC were characterized by higher age (67 *vs*. 58.7 years) and higher frequency of lipidic features (60.3% *vs*. 37.7%) compared with smokers (12). They also observed increased frequency of *EGFR* mutation and ERα expression in never smokers with AC (12).

Li *et al*. clearly demonstrated *EGFR* mutations in 24.5% (51/208 cases) of patients with lung cancer, and these mutations were identified at high frequencies 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) (62).

As the study found patients carrying germline *EGFR* mutations in cases of familial lung AC, genotyping can be used to predict benefit for treatment with EGFR-TKI, and can also be used as a screening tool to identify patients at-risk of carrying germline *EGFR* mutations (65). Better response to TKIs was seen in non-smoker (or light smoker) female with lung AC (66). Yamauchi *et al*. identified a set of 139 gefitinib-sensitive genes which are involved in cancer phenotypes and found that EGF signaling status in cancer cells underlies an aggressive phenotype of cancer cells (67). This is useful for the selection of patients with early-stage lung AC with poor prognosis. Jou *et al*. revealed polymorphism of *EGFR* intron 1 in female never smokers with lung cancer (68). Ren *et al*. observed that 82.7% of lung ACs from non-smoker females were found to harbor oncogenic mutations in the following genes: *EGFR, HER2, EML4-ALK, KRAS, BRAF,* and *PIK3CA* (69). A higher human papillomavirus (HPV) may participate in Asian non-smoking lung AC, which responds to EGFR-TKIs (70).

HER2. A proto-oncogene of the receptor tyrosine kinase superfamily, HER2 acts as a binding partner of other members of the EGFR family in the activation of EGFR signaling. Jo *et al*. revealed that polymorphisms of the *HER2* gene are associated with an increased susceptibility to lung cancer in female, non-smoker and non-drinker subgroups in a Korean population (71).

EML4-ALK. A fusion protein between EML4 protein and the intracellular signaling portion of the ALK tyrosine kinase receptor has been identified in a small subset of NSCLC patients by Soda *et al*. (72). Li *et al*. identified seven patients (3.37% out of 208 patients with lung cancer) who harbored the *EML4-ALK* fusion gene (62). Six out of the seven positive patients were non-smokers (7.69%, 6/78). The incidence of *EML4-ALK* translocation in female non-smoking patients with AC was as high as 15.2% (5/33) (62).

KRAS. Dogan *et al*. revealed that the *KRAS* mutation occurred in 34% of smokers and in 6% of never smokers, but *KRAS* G>A transition mutations were more likely to be found in never smokers than in smokers (mostly *G12D*; 58% *vs*. 20%) while *KRAS* G12C, the most common G>T transversion mutation, was seen in smokers (73). Dogan *et al*. suggested this different *KRAS* mutation could be useful in determining the presence of second-hand smoke in never smokers with lung AC.

Genes Related to Inflammation/Innate Immunity

Interleukin-1 beta (IL1B). Several SNPs have been examined in the *IL1B* gene. T>C at position-511 (rs16944), C>T at position -31 (rs1143627) and C>T at position +3954 (rs1143634), of the *IL1B* gene have been investigated. The rs16944 SNP is known to be correlated with increased intracellular IL1B levels (74). *IL1B* (rs1143634, 3954C>T) was investigated in a case-control study comprising of 462 lung cancer cases and 379 controls in a Japanese population (75). Association of T allele carriers of the *IL1B* rs1143634

Table II. *Characteristic susceptibility genes in never smokers with AC.*

Susceptible gene	Evidence	Related signal pathways/comments
NAT2	Risk for never-smoking women (21)	Fast acetylator
TP63	Found by GWAS for never-smoker AC in Asia	p63 is one component of p53 (25)
C3orf21	Reduced risk of never smoker AC	Encodes a UDP-xylose-α-xyloside α1, 3-xylosyl-transferase which is involved in the formation of NOTCH EGF repeats (26)
BAT3	Found by GWAS for never smoker AC in Asia	It is implicated in apoptosis and protein complexes with EIA-binding protein p300, required for acetylation of p53 in response to DNA damage (48)
VTI1A	Strong new association signal	Involved in Acrp30-containing vesicles in adipocytes. Its lower levels in adipocytes can inhibit adiponectin secretion (38)
TNFRSF10C	These three genes are methylated in lung	TNF receptor family member, neuronal differentiation
BHLHB5	AC among never smokers	inhibitor RNA binding protein regulating meiotic
BOLL		G_2/M transition (55)
EGFR	This mutation is an early event in carcinogenesis of lung AC (60)	Association of EGFR mutation and estrogen-α and -β with lung carcinogenesis has been noted (59, 64)

NAT2: N-acetyltransferase 2; C3orf21: chromosome 3 open reading frame 21; BAT3: HLA-B-associated transcript 3; TNFRSF10C: a TNF receptor SF10C; BHLHB5: basic helix-loop-helix (bHLH) transcription factor 5; BOLL: boule-like RNA-binding protein; EGFR: epidermal growth factor receptor.

polymorphism with risk of lung cancer was seen in never smokers, with an OR 1.11, but higher risk was observed in smokers (OR=5.45) and in heavy alcohol drinkers (OR=2.48). SNPs in *IL2RB* and *BCL2L14* are known to be risky in current smokers and in former smokers (76). There are no reports on genes related to innate immunity in never smokers with AC.

Summary and Conclusion

Approximately 25% of patients with lung cancer worldwide (15% men, 53% women) are estimated to be never smokers. The genes associated with susceptibility to lung cancer in smokers are very different from those for susceptibility to AC in never smokers. Several characteristic genes have been found in never smokers with AC: *NAT2, TP63, C3orf21, BAT3, VTIIA, TNFRSF10C*, and *EGFR*, as shown in Table II.

Among them, the *EGFR* gene is the most notable and frequently reported, regardless of differences in ethnicity. It is seen in the early stage of AC in never smokers. Saxena *et al*. reported a bi-directional crosstalk between leptin and insulin-like growth factor-1 signaling promotes invasion and migration of breast cancer cells, *via* transactivation of EGFR, *i.e*., carcinogenesis in never-smoker women with lung AC is very similar to that in breast cancer (81). *VTI1A* is also related to the mechanism of cancer occurrence in metabolic syndrome *via* association with lower adiponectin (38). Zhang *et al*. reported strong evidence of linkage of 5p14 with metabolic syndrome and risk of cancer (11). Obesity, metabolic syndrome and type II diabetes mellitus should be considered as pre-cancerous states and prevented. Imielinski *et al*. revealed a mean exonic somatic mutation rate of 12.0 events/megabase and identified the majority of genes previously reported as being significantly mutated in lung AC (82). A recent report revealed methylation variability in the etiology and pathogenesis of obesity (83). The environment appears to have changed the genes invoved in susceptibilility to lung cancer. An epidemiological survey on lung cancer among never smokers with/without susceptible genes should be conducted from the viewpoint of lifestyles because obesity, metabolic syndrome and diabetes mellitus indicate a higher risk for lung cancer (52, 53).

In conclusion, prevention is the most important and most valuable factor. Cessation of smoking is, of course, necessary, but in and of itself is not sufficient to prevent lung cancer altogether because a quarter of patients with lung cancer are never smokers. It is more important to provide effective education to improve lifestyle with emphasis on prevention of obesity, metabolic syndrome, diabetes mellitus, and heavy drinking, and promoting daily physical activity, especially in the so-called developed countries.

Conflicts of Interest

The Authors confirm that there are no conflicts of interest regarding the contents of this article.

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