

SMOKING AND MOLECULAR PROFILES OF LUNG CANCER

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HISTOLOGY AND SMOKING

TABLE 1. Baseline Characteristics of Participants in the Non-small Cell Lung Cancer Database Project According to Smoking Status

Characteristic	No. of Patients (%)				Total Sample, n = 4230
	Never Smokers, n = 618	Current Smokers, n = 1480*	Former Smokers**		
			1-12 Months, n = 380	≥ 12 Months, n = 1719	
Men	212 (34)	781 (53)	189 (50)	918 (53)	2100 (50)
Caucasians	472 (76)	1248 (84)	312 (82)	1534 (89)	3566 (85)
Age at Diagnosis: Mean (SD), y	61.3 (9.1)	61.0 (9.1)	62.1 (9.4)	68.0 (9.4)	64.0 (9.5)
Disease stage					
I and II	123 (20)	436 (29)	101 (27)	565 (33)	1195 (28)
III	149 (24)	401 (27)	99 (26)	468 (27)	1117 (27)
IV	346 (56)	676 (46)	180 (47)	686 (40)	1888 (45)
Histology					
Squamous cell	40 (6)	431 (29)	105 (28)	471 (27)	1047 (25)
Adenocarcinoma	504 (82)	756 (51)	180 (47)	907 (52)	2447 (58)
NOS and IHC	14 (2)	296 (20)	82 (22)	381 (22)	773 (18)
Other	—	—	—	—	—

Smoking Status and Survival in the National Comprehensive Cancer Network Non-Small Cell Lung Cancer Cohort

Amy K. Ferris, PhD¹, Joyce C. Hwang, PhD¹, Robert Mermel, MD¹, Carlo Cuzzocrea, MD¹, Thomas A. D'Amico, MD¹, David S. Ellinger, MD¹, Gregory P. Kalemkerian, MD¹, Katherine H. Pritchard, MD¹, Mary P. Stack, PhD¹, and Gregory A. Otterson, MD¹

In both of the ACS studies, adenocarcinoma was the most commonly documented lung cancer histology among women, both among current smokers and among never smokers, as well as among men who had never smoked (Table 3). In CPS-II, the

Conclusions: The increase in lung adenocarcinoma since the 1950s is more consistent with changes in smoking behavior and cigarette design than with diagnostic advances. [J Natl Cancer Inst 1997;89:1580-6]

Cigarette Smoking and Changes in the Histopathology of Lung Cancer

Michael J. Thun, Cathy A. Lally, John T. Flannery, Eugenia E. Calle, W. Dana Flanders, Clark W. Heath, Jr.*

Table 1. Distribution of Histologic Types of LCNS

Reference	Region	No. of Patients	Histologic Type (% of patients)				
			Adenocarcinoma	Bronchioalveolar	Squamous	Large Cell	Small Cell
Fordham et al ¹³	United States	653	76	—	10*	11	—
Toh et al ¹⁶	Singapore	286	70	—	6	—	—
Yip et al ¹⁷	Hong Kong	200	89	—	4	4	—
Brownson et al ¹⁴	United States	328	67	5	3	—	0.9
Kreuzer et al ¹⁸	Germany	118	64	—	12	—	11
Ko et al ¹⁹	Taiwan	106	65	—	17	3	15
Kabat and Wynder ¹¹	United States	134	82	12	16	4	5
Stockwell et al ²⁰	United States	210	61	—	17	—	7
Boffetta et al ²¹	Europe	650	51	—	27*	—	—
Kubik et al ²²	Czech Republic	51	48	2.1	21	2	4
Dibble et al ¹⁵	United States	180	47	—	11	—	—
Gürsel et al ⁹	Turkey	114	40	—	13	3	21

Abbreviation: LCNS, lung cancer in never smokers.
*Includes small-cell carcinoma.
†Hoyberg classification.

Lung Cancer in Never Smokers: A Review
Jemaliramus Subramanian and Ramaswamy Govindan

What is the point?

- Never smokers - profiles of adenocarcinoma
 - Clear majority, some exceptions
- Current and former smokers
 - Still AdCa with highest frequency
 - Most of the Squamous and small cell

There is a time and a place
for decaf coffee.

Never and in the trash.



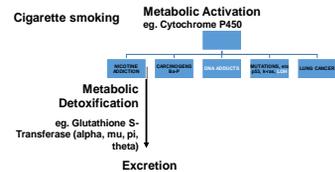
MOLECULAR CONSEQUENCES OF TISSUE INJURY FROM SMOKING

Box 1 | How tobacco causes cancer

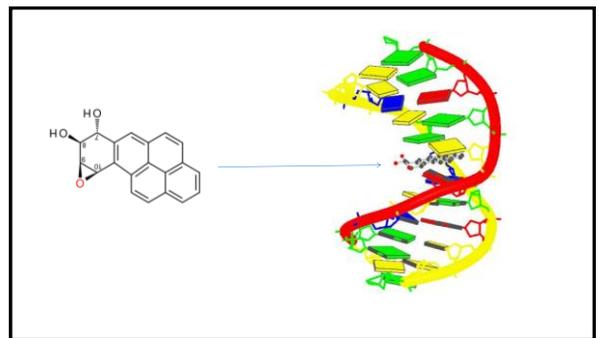
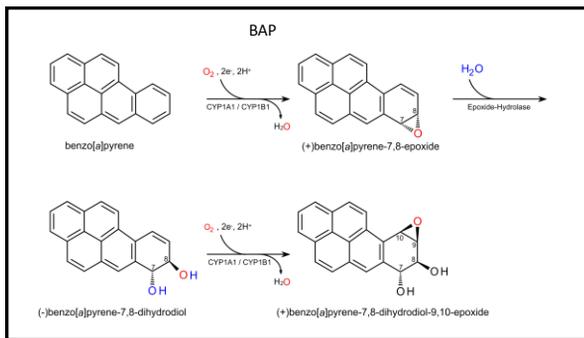
Cigarette smoke contains several thousand chemicals including over 60 identified as carcinogens by the International Agency for Research in Cancer (IARC). The most potent carcinogens are the polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene (BAP) and the tobacco-specific nitrosamine known as nicotine-derived nitrosoaminoketone (NNK). Phase I enzymes (cytochrome P450 enzymes; CYPs) catalyze addition of an oxygen atom to the carcinogen, increasing its water solubility and rendering it more excretable. This solubility is further assisted by the action of phase II enzymes (such as glutathione S-transferases; GSTs). However, some of the intermediates formed by the P450 enzymes are electrophilic and are reactive. Such intermediate metabolites might bind covalently to DNA at certain specific sites, forming bulky adducts. Adduct formation can lead to apoptosis, or they can be removed by the nucleotide excision repair system¹⁴¹. If they persist, they can lead to mutations in the *KRAS* or *TP53* genes, which are key events in lung cancer pathogenesis. These mutations might also result in genomic instability, initiating the plethora of other genetic and epigenetic changes found in most epithelial cancers. Because adduct formation and persistence is so crucial to carcinogenicity, the balance between activation, detoxification and DNA repair has an important role in determining susceptibility to cancer.

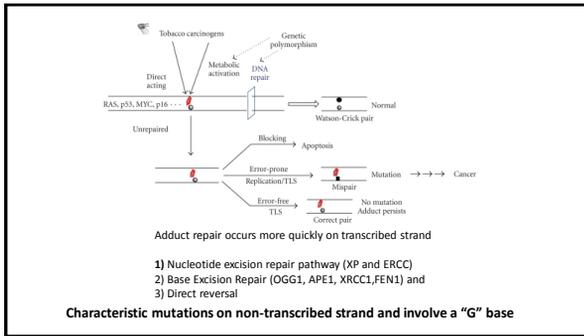
The Scheme:

From Nicotine Addiction to Lung Cancer

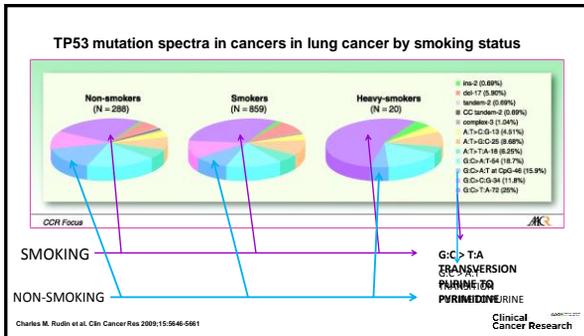


Modified from Hecht JNCI,
1999





P53 MUTATION AND SMOKING

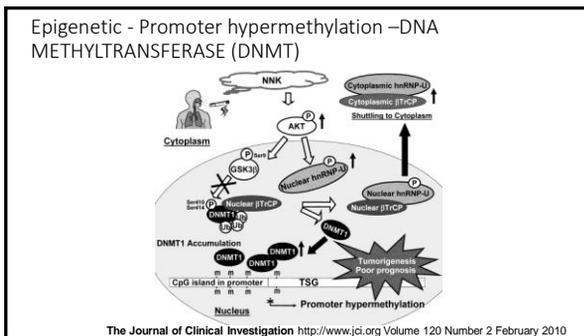


NNK, 4-methylnitrosamino-1-(3-pyridyl)-1-butanone

Promoter hypermethylation

Belinsky
 Proc. Natl. Acad. Sci. USA
 Vol. 95, pp. 11891-11896, September 1998

Aberrant methylation of p16 INK4a is an early event in lung cancer and a potential biomarker for early diagnosis

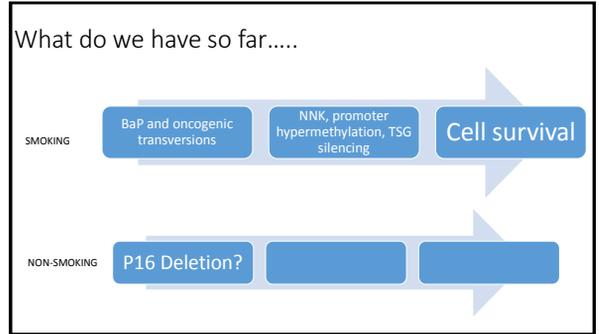


Gene	Studies (n)	Overall OR (95% CI)	χ^2	P value	smoking/non-smoking NSCLC patients (n)
CDKN2A	36	2.33 (1.96, 2.77)	38%	<0.0001	2957/1192
RASSF1	14	1.75 (1.15, 2.65)	57%	0.008	1046/441
MGMT	8	2.51 (1.81, 3.46)	19%	<0.0001	478/339
RARB	7	1.77 (1.29, 2.42)	0%	0.0004	507/279
DAPK	7	2.04 (1.40, 2.99)	27%	0.0002	427/192
FHIT	5	2.81 (1.33, 5.95)	52%	0.007	406/112

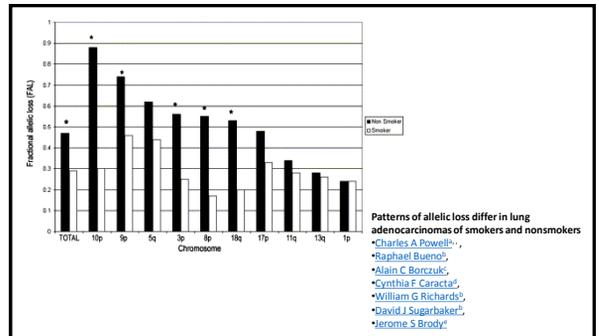
Sci Rep. 2015 Mar 10;5:8897. doi: 10.1038/srep08897.
 Meta-analyses of gene methylation and smoking behavior in non-small cell lung cancer patients.
 Huang T¹, Chen X², Hong Q³, Deng Z⁴, Ma H⁴, Xin Y⁴, Fang Y⁵, Yu H², Wang R⁶, Zhang C⁷, Ye M⁸, Duan S⁹.

In conclusion, our results demonstrate that *p16* inactivation occurs at similar frequencies regardless of the mutation status of *EGFR*, *KRAS*, and *STK11* in lung adenocarcinoma. However, the patterns of inactivation mechanism differ significantly depending upon the genetic mutation present. We also confirm that *p16* methylation is linked to *KRAS* mutation and is mutually exclusive with *EGFR* mutation. Our results indicate that these genes are involved in different pathways and play different roles in development of lung adenocarcinoma. Furthermore, our meta-analyses confirm the modest correlation between *p16* methylation and smoking, and the trend of higher frequencies of *p16* HD among never smokers. These findings support the concept that tumors arising in never smokers are driven by distinct molecular mechanisms in lung tumorigenesis

[Tam and Gazdar, J Thorac Oncol. 2013 Nov; 8\(11\): 1378-1388.](#)



Allelic imbalance and CNA



Explanation – more LOH in the field of smokers, but more denovo CNA in non-smokers

Gene expression

Unique to Tns versus Nns		Gene Expression in Lung Adenocarcinomas of Smokers and Nonsmokers	
TGFR2	D50683	0.23	Charles A. Powell,* Avrum Spira,* Adnan Deri, Charles DeLisi, Gang Liu, Alain Borczuk, Steve Busch, Sudhir Sahasrabudhe, Yangle Chen, David Sugarbaker, Raphael Bueno, William G. Richards, and Jerome S. Brody
TGFR3	L07594	0.35	
DPT	Z22865	0.32	
Endoglin	X72012	0.27	
CTGF	M92934	0.32	
Muc1	HG371	2.74	
CSNK1	U29174	1.44	
Pik	U01038	1.41	
BCL3	U05681	0.69	
Axl	HG162	0.62	
Fez1	U60600	0.31	
BTG1	X61123	0.57	
ICAM	M24283	0.28	
PCAM	L34657	0.21	
TNA	X64559	0.02	
MDK	M92450	3.91	

Gene	Expression in tumors of never-smokers and smokers Fold change P value	Expression in tumors and normal lung of never-smokers Fold change P value	Expression in tumors and normal lung of smokers Fold change P value
AHR	1.16 (0.89-1.72), 0.0078	1.09 (0.89-1.32), 0.5	0.86 (0.71-1.07), <0.0001
ACE2	0.33 (0.19-0.59), 0.0001	0.38 (0.23-0.62), <0.0001	0.88 (0.71-1.07), <0.0001
ACE	1.12 (0.82-1.54), 0.294	2.29 (2.03-2.57), 0.0001	2.2 (2.03-2.38), 0.0001
AIR	1.57 (0.74-3.32), 0.0078	0.83 (0.74-1.35), <0.0001	0.86 (0.71-1.07), <0.0001
AHRCT	0.45 (0.1-2.0), 0.0001	0.88 (0.81-1.17), <0.0001	0.88 (0.81-1.17), <0.0001
CDKN2A	1.17 (2.002-2.2), 0.0404	0.87 (0.80-1.0), 0.0001	0.84 (2.20-1.0), <0.0001
CDKN2B	1.22 (2.01-2.35), 0.0046	0.89 (2.01-2.46), <0.0001	0.84 (2.20-1.0), <0.0001
CDKN2C	2.15 (2.13-3.0), 0.0001	1.29 (2.10-2.6), 0.0001	0.45 (0.31-0.6), 0.0001
CDKN3	1.89 (2.12-3.0), <0.0001	1.29 (2.10-2.6), 0.0001	0.43 (0.30-0.6), <0.0001
DGKB	1.04 (0.76-1.7), 0.3080	0.86 (0.76-1.0), 0.0001	0.81 (0.70-0.9), 0.0001
EPOR	2.66 (0.90-8.0), 0.0001	0.83 (0.91-1.0), <0.0001	0.81 (0.91-1.0), <0.0001
EGFR	0.95 (2.20-2.7), 0.709	1.48 (2.30-3.0), 0.0001	1.47 (2.30-3.0), 0.0001
ERCC1	1.07 (0.61-1.5), 0.0001	1.09 (1.02-0.96), 0.0001	1.4 (1.24-1.5), 0.0001
JGFB1	1.42 (3.00-0.7), 0.0001	1.77 (3.00-0.7), 0.0001	1.11 (0.97-1.3), 0.0001
JGFB2	0.80 (0.6-1.1), 0.1151	0.82 (0.61-1.1), 0.0001	1.04 (0.76-1.5), 0.0001
JGFB3	0.79 (2.10-3.0), 0.7321	1.8 (2.10-3.0), 0.0001	1.19 (2.10-3.0), 0.0001
PPP1R1B	2.11 (0.40-1.0), 0.0001	0.89 (0.81-1.0), <0.0001	0.88 (0.81-1.0), <0.0001
SLC22A1	1.76 (0.10-3.0), <0.0001	0.85 (0.81-1.0), <0.0001	0.84 (0.76-1.0), <0.0001
SOX2	1.06 (2.01-1.0), 0.0001	0.86 (2.01-1.0), <0.0001	0.82 (1.38-1.4), 0.0001
TGFB2	1.82 (0.44-2.7), 0.0001	0.82 (0.71-0.97), <0.0001	0.82 (0.71-0.97), <0.0001
TGFB3	1.83 (0.21-1.2), 0.0001	0.89 (0.21-1.2), <0.0001	0.83 (0.21-1.2), <0.0001

TGFR2 higher in non-smoker than smoker's tumors
Loss of TGFR2 occurs in both smoker's and non-smoker's tumors relative to normal tissue.

Molecular profiles of non-small cell lung cancers in cigarette smoking and never-smoking patients

Szymanska-Nabedka A, Jozwiak T, Skrzypski M, Mlynar T, Mieses M, Domanska H, Tarnowski K, Kuzniak P, Szymanski M, Marczak T, Pawlowski M, Kozminski W, Jozwiak P

Table 2. Cell cycle genes differentiating current from never smokers (C/N) in the early stage tumor (T) tissue sample, and corresponding values in the former/never smoker (F/N) and in the smokers' paired tumor/non-tumor tissue (T/NT) comparisons.

Probe ID	Gene	Chromosomal Location	Current/Former	F/N	T/NT	P-value
204441_at	NEK2	14q22.2-q41	3.45	0.001		
204322_at	TRO	8q23-q21	3.27	<0.0001		
191808_at	PRK1	15q24.1	3.09	0.0007		
207504_at	CEMP1	14q22-q41	2.88	<0.0001		
203993_at	BRCC1	17q25	2.72	0.0002		
205923_at	WDR32	8q27	2.67	0.0001		
191994_at	ASPM	1q31	2.59	0.0009		
191853_at	CK2D	16q13.1	2.54	0.0006		
201991_at	CCNB1	14q24	2.36	0.0002		
205176_at	CK2D	16q22	2.36	0.0006		
122071_s_at	MDCGAP1	12q13.13	2.25	0.0003		
205214_at	CK2C	12q13.13	2.23	0.0004		
191936_at	KIF11	3q13.1	2.22	0.0002		
206642_at	BRCC1	17q25	2.17	0.0001		
191922_s_at	TREX2	20q11.2	2.06	0.0006		
205916_at	CK2D	16q22-q11	1.96	<0.0001		
212108_at	MPK2	10q24-q24	1.95	<0.0001		
207106_at	KIF20A	12q13.1-q13.3	1.92	<0.0001		
211174_at	KIF20C	16q14	1.78	0.0004		
212322_at	CKAP2	16q14	1.74	0.0004		
211484_at	PLA2	4q27-q28	1.74	0.0001		
191982_s_at	NEK2	14q22-q41	1.57	0.0007		
214884_at	IRAK1	10q10-q11	0.85	0.0003		
206625_s_at	MDC21	16q25-q25	0.86	0.0001		
202124_at	CDKN2A	12q13.2	0.84	0.0003		
206661_s_at	CDKN2A	12q13.2-q23	0.84	0.0003		

Cell cycle/mitotic spindle
Current smokers
Lavioli MT, Draehwa T, Ruzsanna M, Figueira DL, Liu PC et al. (2008) Gene Expression Signature of Cigarette Smoking and Its Effect on Lung Adenocarcinoma Development and Survival. *PLoS ONE* 3(2): e1881. doi:10.1371/journal.pone.0022851

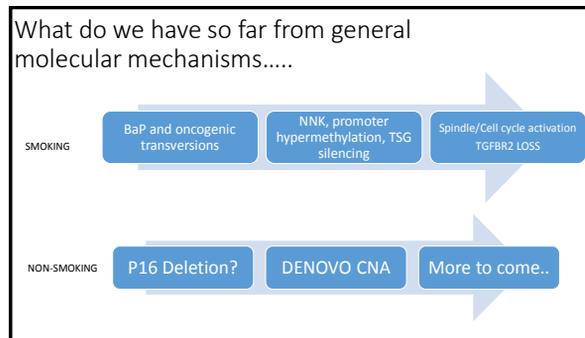
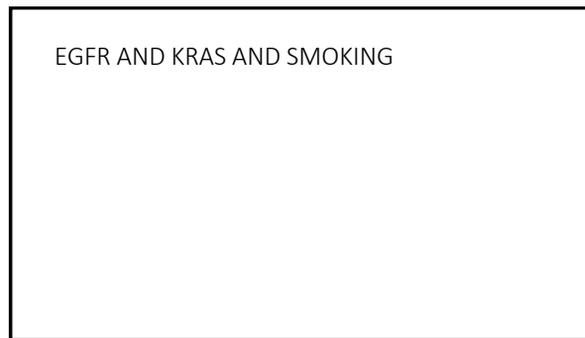


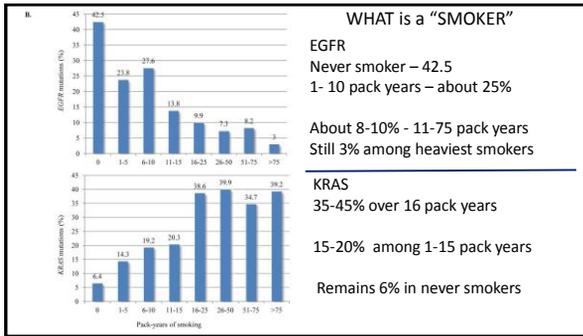
Table 3. Molecular Characteristics of LCINS and Tobacco-Related Lung Cancer Patients

Molecular Markers	LCINS	Tobacco-Associated Lung Cancer
Chromosomal aberrations		
16p DNA gain	Common, 59%	Very rare, < 5%
Gene mutations		
p53 G→T to G→A transversions*	Low, ratio = 0.23	High, ratio = 1.5
p53 transition mutations*	Very common, 83%	Rare, 20%
K-Ras	Very rare, 0%-7%	Common, 30%-43%
EGFR-TK	Common	Rare
Epigenetic changes		
p16 and APC methylation ratio	Low	High
Hypermethylation of MMLH1	Common	Rare
Hypermethylation of MMSH2	Common	Rare

Abbreviations: LCINS, lung cancer in never smokers; EGFR-TK, epidermal growth factor receptor tyrosine kinase.
*Data from women with LCINS
†Loss of protein expression in mismatch repair genes.

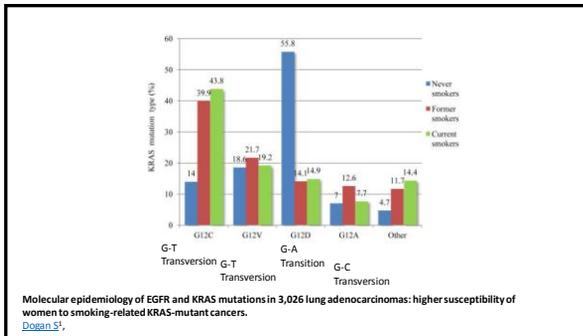
What is the definitions of rare and very rare?
Lung Cancer in Never Smokers: A Review
Indira Senanayake and Ramaswamy Govindan





LUNG CA KRAS mutations

CODON 12,13	COSMIC	Amino acid	% of mutants	DNA sequence
G12A	Gly-Ala	7%	G-C Transversion	
G12C	Gly-Cys	41%	G-T Transversion	
G12D	Gly-Asp	15%	G-A Transition	
G12R	Gly-Arg	3%	G-C Transversion	
G12S	Gly-Ser	5%	G-A Transition	
G12V	Gly-Val	20%	G-T (Transversion)	
G13A	Gly-Ala	<<1%	G-C Transversion	
G13C	Gly-Cys	3%	G-T (Transversion)	
G13D	Gly-Asp	2%	G-A (Transition)	
G13V	Gly-Val	<<1%	G-T (Transversion)	



ALK AND SMOKING

Table 1. Clinicopathologic characteristics of ALK-rearranged and ALK germ-line NSCLC

Characteristics	ALK rearrangement	ALK germ-line	P
No. cases	20 (4)	238 (94)	
Sex, n (%)			
Male	11 (55)	127 (53)	0.16
Female	9 (45)	211 (87)	
Age (yr), median (range)	51 (29-76)	66 (29-90)	0.0002
Smoking status, n (%)			
Never smoker	14 (70)	71 (23)	<0.0001
Smoker	6 (30)	237 (97)	
Unknown	0 (0)	30 (19)	
Tumor status, n (%)			
pT1	4 (20)	103 (30)	0.15
pT2	2 (10)	119 (35)	
pT3	6 (30)	10 (3)	
pT4	6 (30)	37 (11)	
Not evaluated	14 (70)	69 (20)	
Lymph node status, n (%)			
Negative	4 (20)	176 (52)	0.13
Positive	4 (20)	81 (24)	
Not evaluated	10 (50)	81 (24)	
Stage, n (%)			
I	4 (15)	165 (49)	0.0001
II	6 (30)	26 (9)	
III	6 (30)	67 (20)	
IV	16 (80)	77 (23)	

NOTE: Due to rounding not all percentages total 100.
 *Tumor and node status were based on pathology evaluation (pStage). Stage was based on both radiology and pathology evaluation (cStage).

Characteristics	ALK-Negative	ALK-Positive	P
N	1057	35	
Age	62.88	61	0.581
Smoker			
Male	404	13	<0.001
Female	260	19	
Unknown	3	3	
Smoking habit			
Never	140	16	<0.001
Smoker	451	10	
Unknown	9	9	
Biopsy			
ADC	750	26	0.389
SQC	55	0	
LCC	47	2	
NSC	58	1	
Others	12	1	
Unknown	3	3	
Stage			
I-II	308	5	0.004
III	282	21	
Unknown	9	9	
EGFR			
Wild type	308	6	1
Mutated	29	0	
Unknown	29	29	

NOTE: ADC, adenocarcinoma; NSC, non-small cell carcinoma; LCC, large cell carcinoma; SQC, squamous cell carcinoma; EGFR, epidermal growth factor receptor.

**OVERALL RATE 3.2%
 Smoker 2.1%
 NON-SMOKER – 10%**

Assessment of ALK Status by FISH on 1000 Spanish Non-Small Cell Lung Cancer Patients.
 Vidal, Joana; Clavé, Sergi; de Muga, Silvia; Gonzalez, Iria; Pijuan, Lara; MD, PhD; Gimeno, Javier; Remon, Jordi; Reguart, Noemi; MD, PhD; Vinolas, Nuria; Girones, Regina; MD, PhD; Berret, Lilia; Majem, Margarita; Bosch-Barrera, Joaquin; MD, PhD; Porta, Rut; MD, PhD; Alonso, Nieves; Palmero, Ramon; Tass, Alvaro; Alonsell, Joan; MD, PhD; Espinet, Blanca; Salido, Maria; Arriola, Eulene; MD, PhD
 Journal of Thoracic Oncology 9(12):1816-1820, December 2014.
 DOI: 10.1097/JTO.0000000000000361

Helders Klauer | OvidSP

ROS1 TRANSLOCATION AND SMOKING

ROS1 TRANSLOCATION AND SMOKING

Table 1. Demographics and Clinical Characteristics of Patients With ROS1-Positive NSCLC

Demographic or Clinical Characteristic	All Patients (n = 1,072)		ROS1 Positive (n = 118)		ALK Positive (n = 31)		ROS1 Negative (n = 1,058)		P (ROS1 positive v ROS1 negative)
	No.	%	No.	%	No.	%	No.	%	
Age, years									
Median	62.0		49.8		51.6		62.3		< .001
Range	32-87		32-79		29-73		32-87		
Sex									
Male	523	49	7	39	17	55	516	49	480
Female	550	51	11	61	14	45	539	51	
Smoking history									
Never-smoker	239	22	14	78	13	42	225	21	< .001
Light smoker	62	6	1	6	1	3	61	6	
Smoker	826	77	2	11	3	10	823	77	
NA	77	7	1	6	14	45	76	7	

ROS1 Rearrangements Define a Unique Molecular Class of Lung Cancers

Erwin Dreyhan, Hua F. Shen, Kai Hong Spangola, Yu. Borkov, Ekaterina Chelvan, M. Lodi, Noreen T. McKeown, Peter P. Awram, Shoshana David, Tanya Abraham-Coleman, Bing Gao, Jeremy J. Park, Ashu M. Sarm, Shouqun Chen, Ernie C. Wilton, Steven J. Kazis, Jeffrey W. Park, Daniel F. Costine, Douglas S. Lim, J. Stephen Michienzi-Graham, William J. You, and S. Sanku Lippman

BRAF AND SMOKING

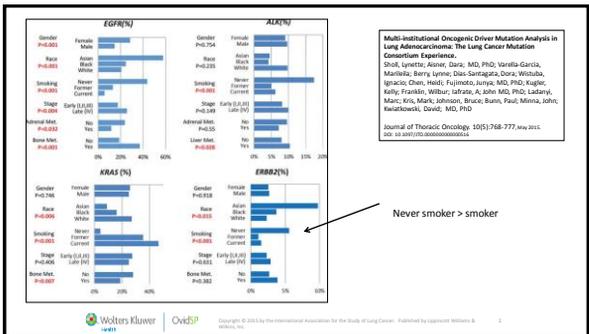
Table 2. Association between BRAF mutation and gender, smoking, histology and stage in NSCLC.

Outcome	Mutant BRAF (%)	Statistical Method	Test of association OR (95%CI)	Heterogeneity test P	Chi ²	I ²	P
Gender							
Male	832224373	M-H, Fixed, 95%CI	0.79 (0.57, 1.10)	0.16	9.23	17%	0.32
Female	761972481						
Smoking							
Former/current	1202576468	M-H, Random, 95%CI	0.65 (0.45, 1.02)	0.50	19.25	64%	0.01
Never	381248354						

Former current 4.69% VS Never 3.04 %, but
BRAF^{V600E} mutation was also significantly more frequent in never-smokers compared to current or former smokers (OR = 0.14 95%CI = 0.05-0.42)

Chen Q, Zhang JQ, Huang JF, Liu K, Chiu ZH, et al. (2014) BRAF Mutations in Patients with Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *PLoS ONE* 9(8): e101294. doi:10.1371/journal.pone.0101194

ERRB2 mutation AND SMOKING



MAP2K1 (MEK1) AND SMOKING

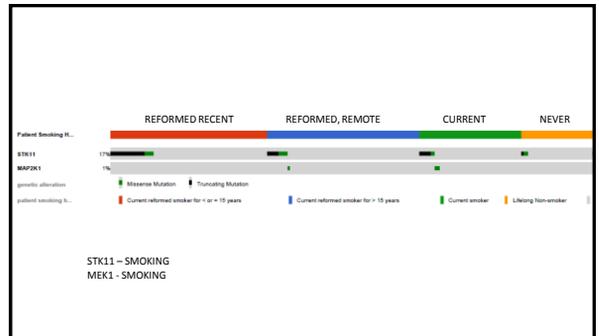
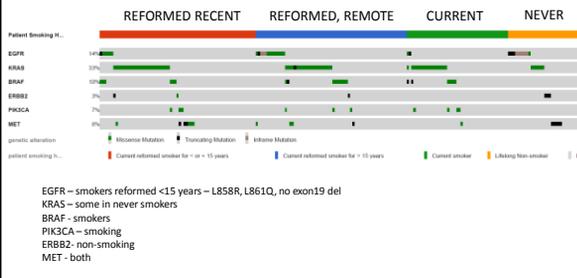
Table 2. Clinical characteristics of patients with MAP2K1 (MEK1) mutations

Smoking history	
Never	3% (1/36)
Former <10 pack years	3% (1/36)
Former >10 pack years	94% (34/36)
Pack years	Median 48 pack years (range, 0-160)
Age at diagnosis	Median 68 (range, 48-89)
Sex	
M	50% (18/36)
F	50% (18/36)
Stage at presentation	
IA	19% (7/36)
IB	11% (4/36)
IIA	11% (4/36)
IIB	11% (4/36)
IIIA	3% (1/36)
IIIB	6% (2/36)
IV	39% (14/36)
Race	
Caucasian	91% (33/36)
Asian	3% (1/36)
Unknown	6% (2/36)

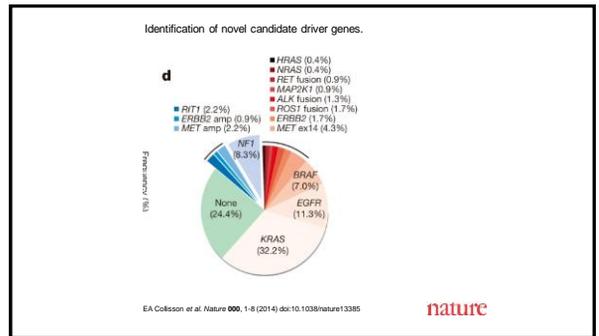
MAP2K1 (MEK1) Mutations Define a Distinct Subset of Lung Adenocarcinoma Associated with Smoking

Marie E. Arcila¹, Alexander D'Adamo¹, Brooke E. Sivolter¹, Christine M. Louf¹, Laetitia Bonin¹, Boris Hainaut¹, Mark G. Krutzik¹, David B. Solit¹, and Marc Ladanyi^{1,2}

CBIOPORTAL AND TCGA



MET MUTATION AND SMOKING



Response to MET inhibitors in patients with stage IV lung adenocarcinoma harboring *MET* mutations causing exon 14 skipping

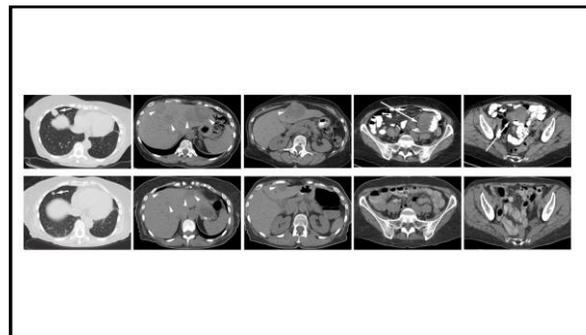
Authors: Paul K. Paik^{1,2}, Alexander Dulim^{1,3}, Helou Yu⁴, Niranda Balkman⁵, Michelle S. Gimsing⁶, Laura Bressi⁷, Miklos Schatzl⁸, Michael F. Berger^{9,10}, Charles M. Rudin¹¹, Marc Ladanyi¹²

Liu...Stoopler... Halmos, Borczuk JCO 2015
Sarcomatoid CA (Pleomorphic giant or spindle) – 8 of 36 cases tested
Stage 4 patient with response to crizotinib

Sample	2	5	6	16	31	32	38
MET exon 14							
ERAS/EGFR/UBAF/ALK							
ANY Squamous							
ANY Adenocarcinoma							
ASGG							
ANY Giant cell							
Giant cell only							
ANY SOLID							
ANY Actin ⁺							
ANY MF							
ANY LEP							
ANY PAT							
CD133 ⁺ only							
Non-smoker							

black - no data available

Four of 8 patients were non-smokers.
One patient had a pleomorphic carcinoma, reported as non-smoker
Four responded to crizotinib or cabozantinib



SECOND HAND SMOKE

Molecular and Cellular Pathobiology

Cancer Research

Whole-Genome Sequencing of Asian Lung Cancers: Second-Hand Smoke Unlikely to Be Responsible for Higher Incidence of Lung Cancer among Asian Never-Smokers

Vidhya G. Krishnan¹, Philip J. Ebert², Jason C. Ting³, Elaine Lim^{4,5}, Swee-Seong Wong³, Audrey S.M. Teo¹, Yong G. Yue⁶, Hui-Hoon Chua⁷, Xiwen Ma⁸, Gary S.L. Loh¹, Yuhua Lin⁹, Joanna H.J. Tan¹, Kun Yu¹⁰, Shewli Zhang¹¹, Christoph Reinhard¹², Daniel S.W. Tan¹³, Brock A. Peters¹⁴, Stephen E. Lincoln¹⁵, Dennis G. Ballinger¹⁶, Jason M. Laramie¹⁷, Geoffrey B. Nilsen¹⁸, Thomas D. Barber¹⁹, Patrick Tan^{1,6,8,10}, Axel M. Hillmer¹, and Pauline C. Ng¹

Cancer Res. 74(21):6071-81. ©2014 AACR.

Eur Respir J. 2015 May;45(5):1415-25. doi: 10.1183/09031936.00097314. Epub 2015 Mar 5.

No impact of passive smoke on the somatic profile of lung cancers in never-smokers.
Couraud S¹, Debieuvre D¹, Moreau L¹, Dumont P¹, Margery J¹, Quoix F¹, Duvert B¹, Cellerin L¹, Baize N¹, Tavio T¹, Coudurier M¹, Cadranet J¹, Missy P¹, Morin F¹, Mornex JF¹, Zaïrman G¹, Souquet P; on behalf of the BioCAST/FACT-1002 study investigators.

Table 1
Genetic and epigenetic features of lung cancer in never smokers and ever smokers.

Molecular characteristic	Never smokers	Ever smokers	Clinical significance	Reference
Genetic mutations				
EGFR tyrosine kinase mutation	45%	7%	Sensitivity to EGFR-TKI	Shigematsu et al. [27]
KRAS codon 12, 13 mutations ^a	15%	22%	Resistance to EGFR-TKI	Riely et al. [41]
Total	15%	18%		
G → T or G → C transversions	1%	14%		
G → A transitions	14%			
PS1 mutations	15%	38%		Toyooka et al. [40,50]
G → T transversions	0.23	1.5	Unknown	
C → T/C → A/TGG ^b	8.5%	0.8%	Sensitivity to ALK inhibitors	Wong et al. [50]
EMIL4-ALK fusion gene	Low	High	Unknown	Toyooka et al. [40,50]
Epigenetic alterations				
Methylation index ^c	Low	High	Unknown	Toyooka et al. [40,50]
CDKN2A and APC methylation ^d	Low	High	Unknown	Pullang et al. [61]
MCM1 methylation ^e	66%	47%	Unknown	

Abbreviations: EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.
^a In the analysis limited to adenocarcinoma.
^b In the analysis limited to female.

Lung cancer in never smokers: Change of a mindset in the molecular era
Young Joo Lee¹, Joo-Hang Kim^{1,c}, Se Kyu Kim⁵, Sang-Jun Ha⁴, Tony S. Mok⁶, Tetsuya Mitsudomi¹, Byoung Chul Cho^{1,b,c}

Table 3. Key biomarkers of differences in lung cancer between ever smokers and never smokers

Biomarker	Never smokers	Reference
TP53 mutation spectrum	Lower frequency of G:C to T:A mutations	Hainaut et al. (102)
	Lower frequency of mutations at hotspots	Vahakangas et al. (43)
KRAS mutations	Lower frequency of mutations at hotspots	Toyooka et al. (50)
	Lower frequency	Koshiba et al. (36); Tam et al. (39)
STK11 (LKB1) mutations	Lower frequency of transversions	Riely et al. (44)
	Higher frequency	Kosunen et al. (49)
EGFR mutations	Higher frequency	Mitsudomi et al. (148); Shigematsu et al. (23, 41)
HR23 mutations	Higher frequency	Shigematsu et al. (38)
EMIL4-ALK translocations	Higher frequency	Wong et al. (50)
N-tyr expression	Higher level	Le Calvez et al. (111)

Clin Cancer Res 2009;15(18) September 15, 2009 5654 www.aacrjournals.org

MOLECULAR EVENT	NEVER SMOKER	SMOKER	HEAVY SMOKER
ADGUCT INDUCED TRANSVERSION/PSI	LOW	HIGH	HIGHEST
PROMOTER HYPERMETHYLATION	LOW	HIGH	
P53	LOW	HIGH	
MLH1/MSH2	HIGH	LOW	
GENE EXPRESSION			
CELL CYCLE/MITOTIC SPINDLE	LOW	HIGH	
TOP2B2	LOSS	LOSS (more profound loss)	
COPY NUMBER ALTERATION	LOSS	ON BACKGROUND OF LOH	
P16 DELETION	HIGHER FREQ	LOWER FREQ	
1p GAIN	HIGHER FREQ	LOWER FREQ	
GENE MUTATION/TRANSLOCATION			
EGFR	HIGHER FREQ	LOWER FREQ	LOWEST (P)
KRAS	HIGHER FREQ	LOWER FREQ	HIGHEST (APQ)
KRAS G-A	HIGHER FREQ	LOWER FREQ	
ERBB2	HIGHER FREQ	VERY LOW FREQ	
ALK	HIGHER FREQ	LOWER FREQ	
BOS	HIGHER FREQ	LOWER FREQ	
BET	HIGHER FREQ	LOWER FREQ	
BRN3-G	LOWER FREQ	HIGHER FREQ	
BRAT	LOWER FREQ	HIGHER FREQ	
PIK3CA	LOWER FREQ	HIGHER FREQ	
MET	LOWER FREQ	HIGHER FREQ	
MAPK3(MEK3)	VERY LOW FREQ	HIGHER FREQ	
STK11	LOWER FREQ	HIGHER FREQ	

So, what next

- Selection of testing by smoking status not simple
- Mechanisms of smoking related cancer better understood
- Mechanisms of non-smoking cancer poorly understood
- Second hand smoke related carcinoma poorly understood

