2023 대한결핵 및 호흡기학회
금연연구회 심포지엄
2023-09-02

Smoking related Lung Cancer

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Today

- Smoking as a risk factor of lung cancer
  - Smoking and oncogenic mutation of lung cancer
- Impact of smoking on treatment outcome in lung cancer patients
  - Targeted therapy
  - Immunotherapy
- E-cigarette and lung cancer
- Effect of smoking cessation on lung cancer and mortality

Today

- **Smoking as a risk factor of lung cancer**
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  - Immunotherapy
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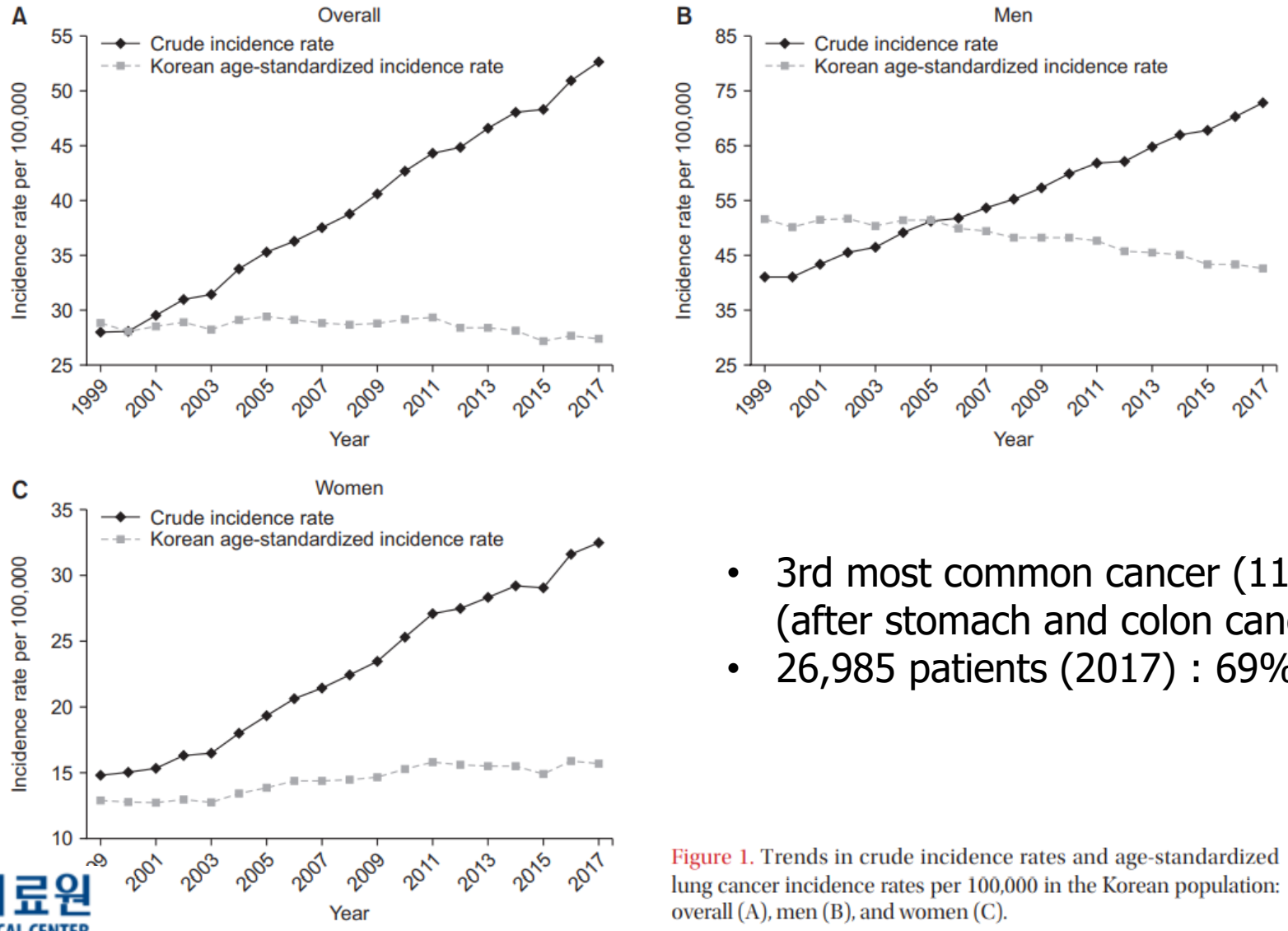
- Effect of smoking cessation on lung cancer and mortality

Recent Trends of Lung Cancer in Korea

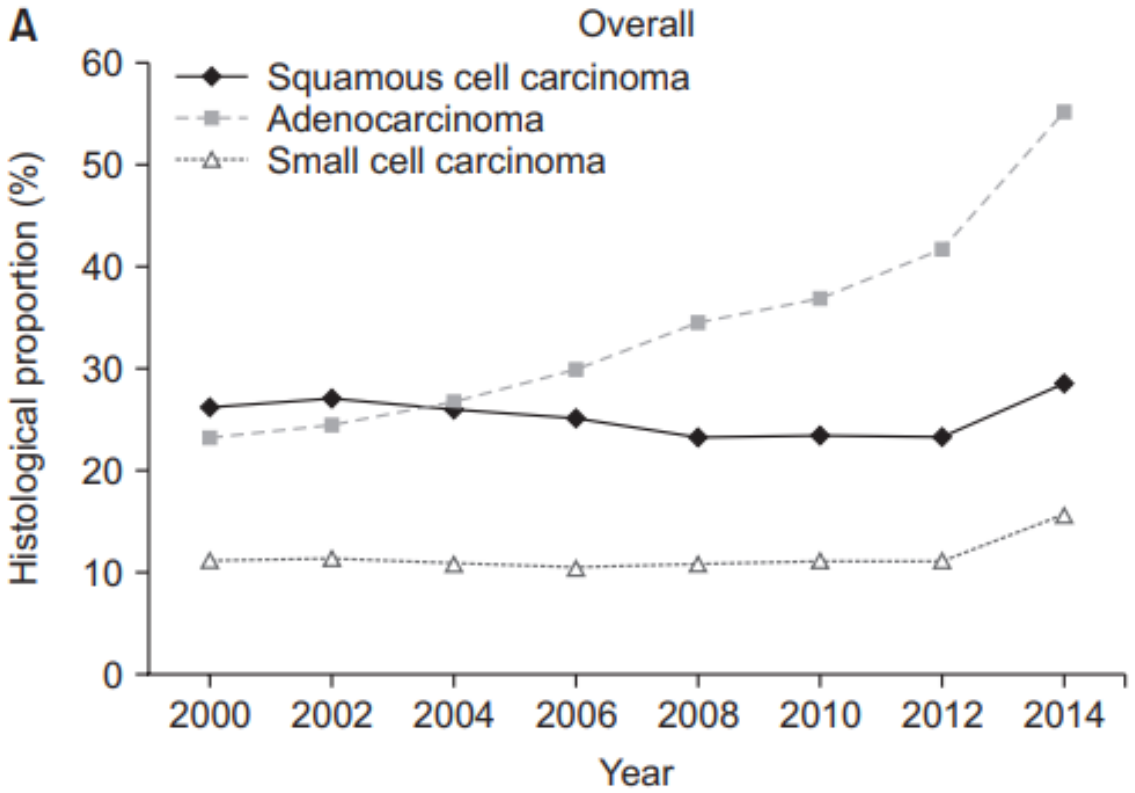


- 3rd most common cancer (11.6%)
  (after stomach and colon cancers)
- 26,985 patients (2017) : 69% male, 31% female

Figure 1. Trends in crude incidence rates and age-standardized lung cancer incidence rates per 100,000 in the Korean population: overall (A), men (B), and women (C).

Tuberc Respir Dis 2021

Recent Trends of Lung Cancer in Korea



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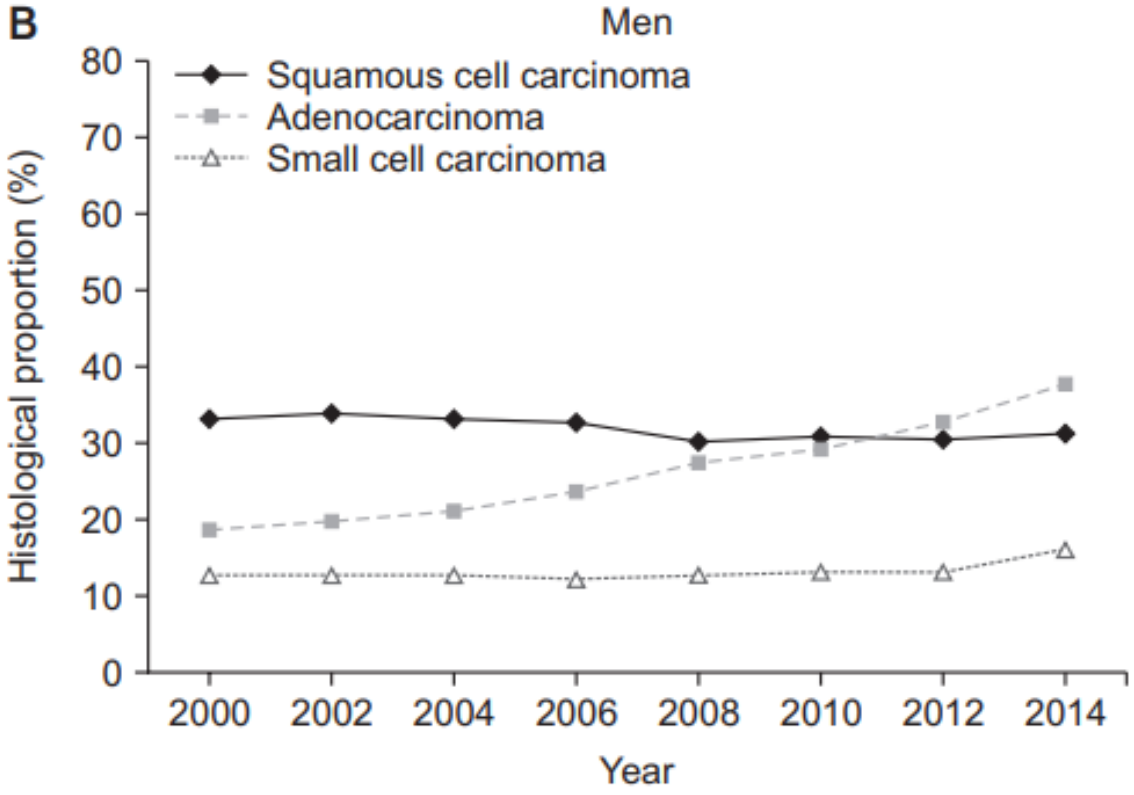

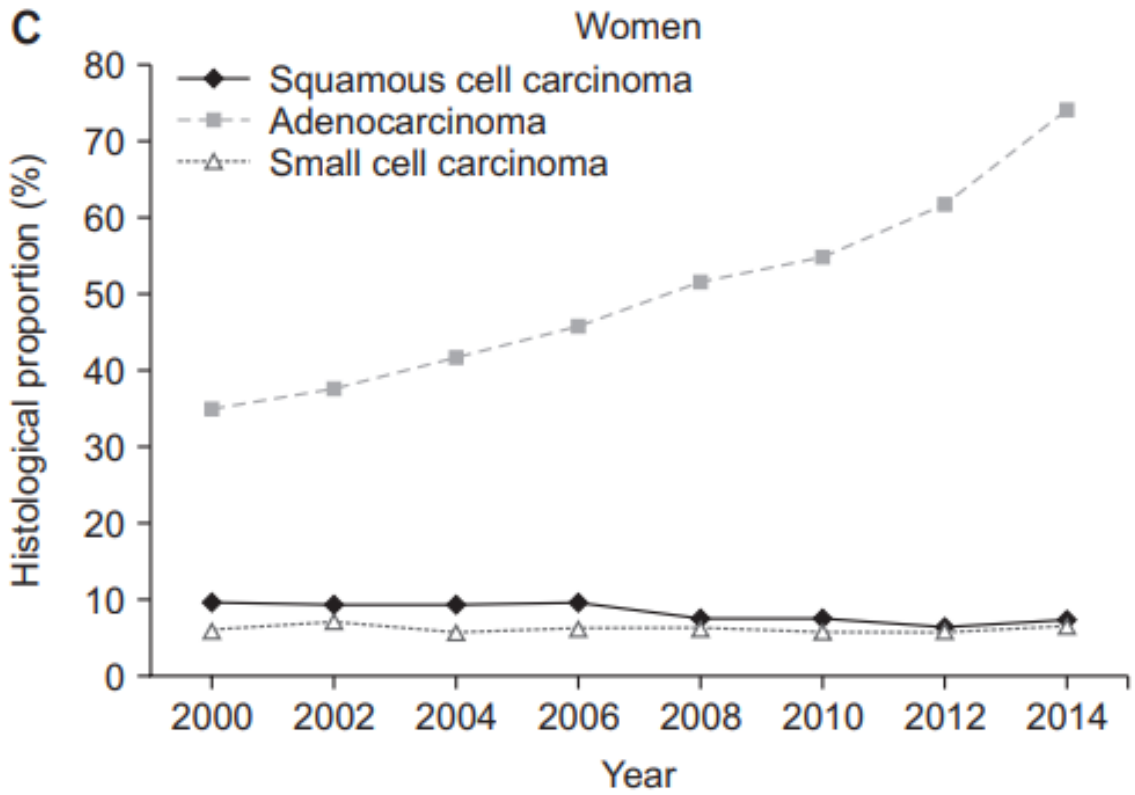

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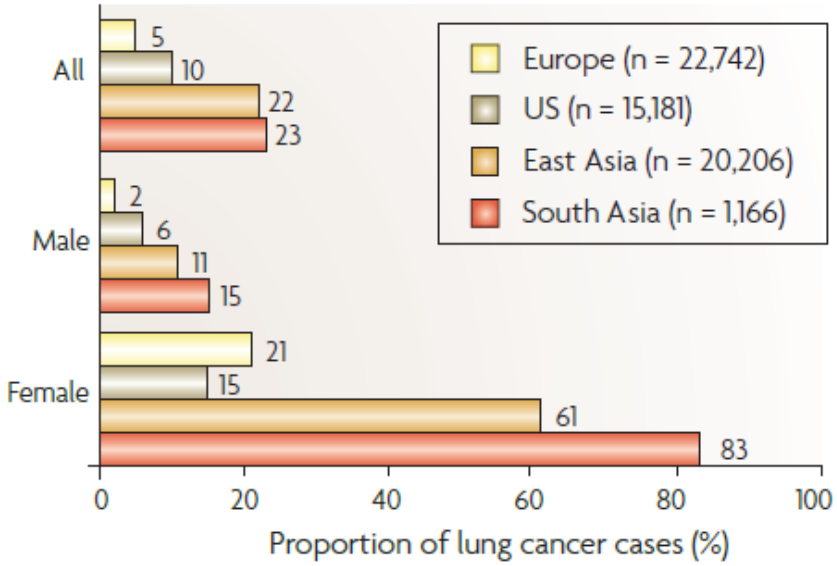
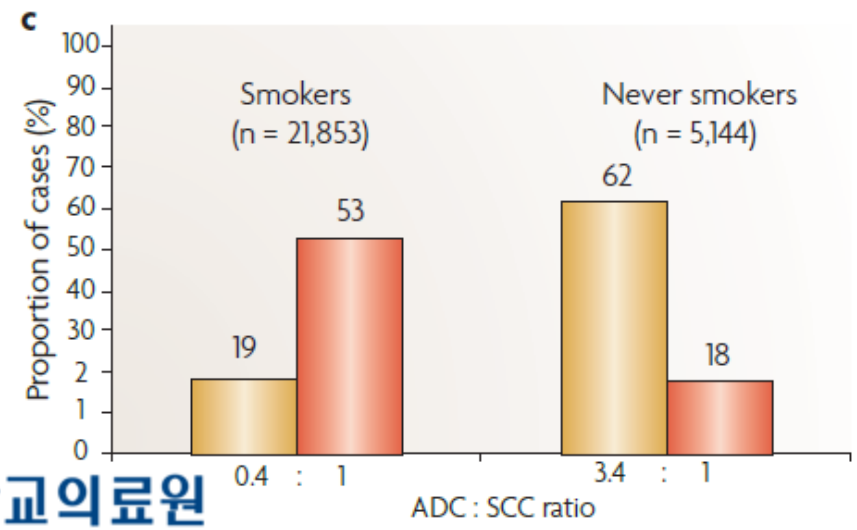
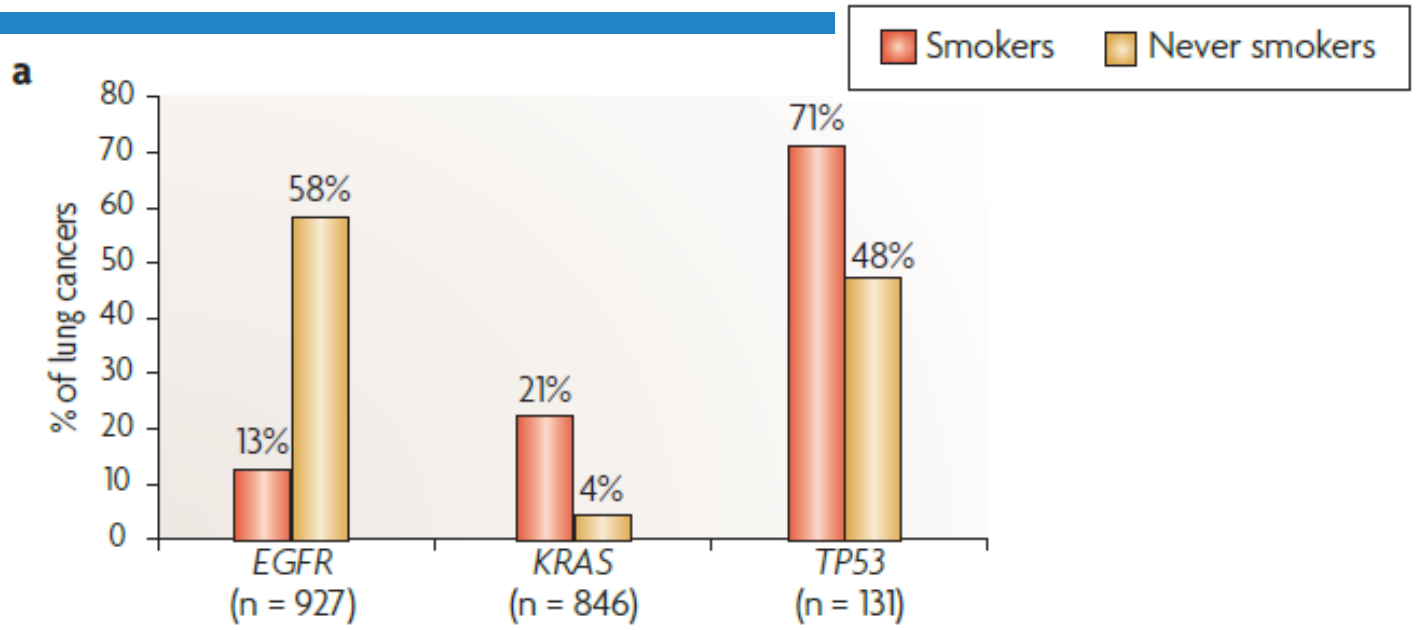
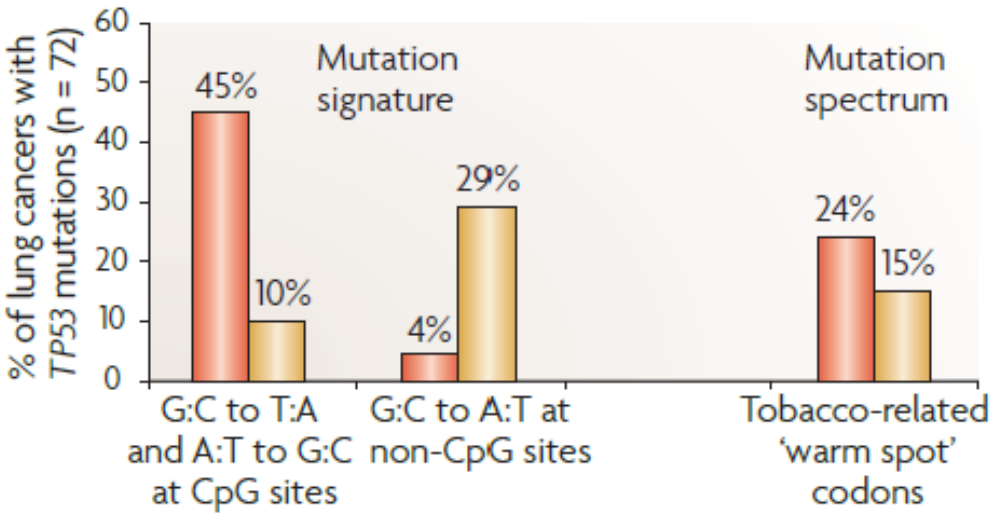
Never-smoker lung cancer









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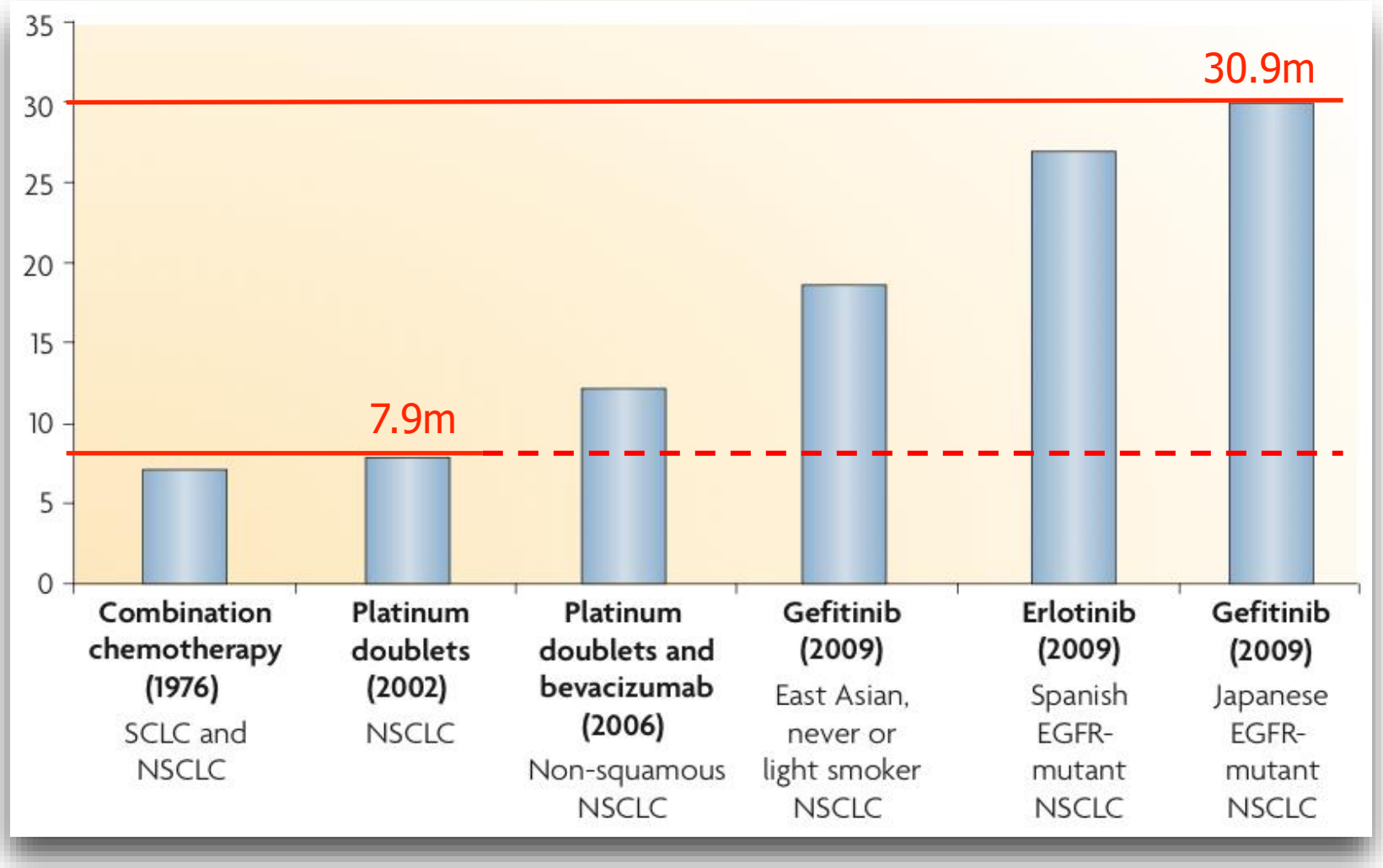
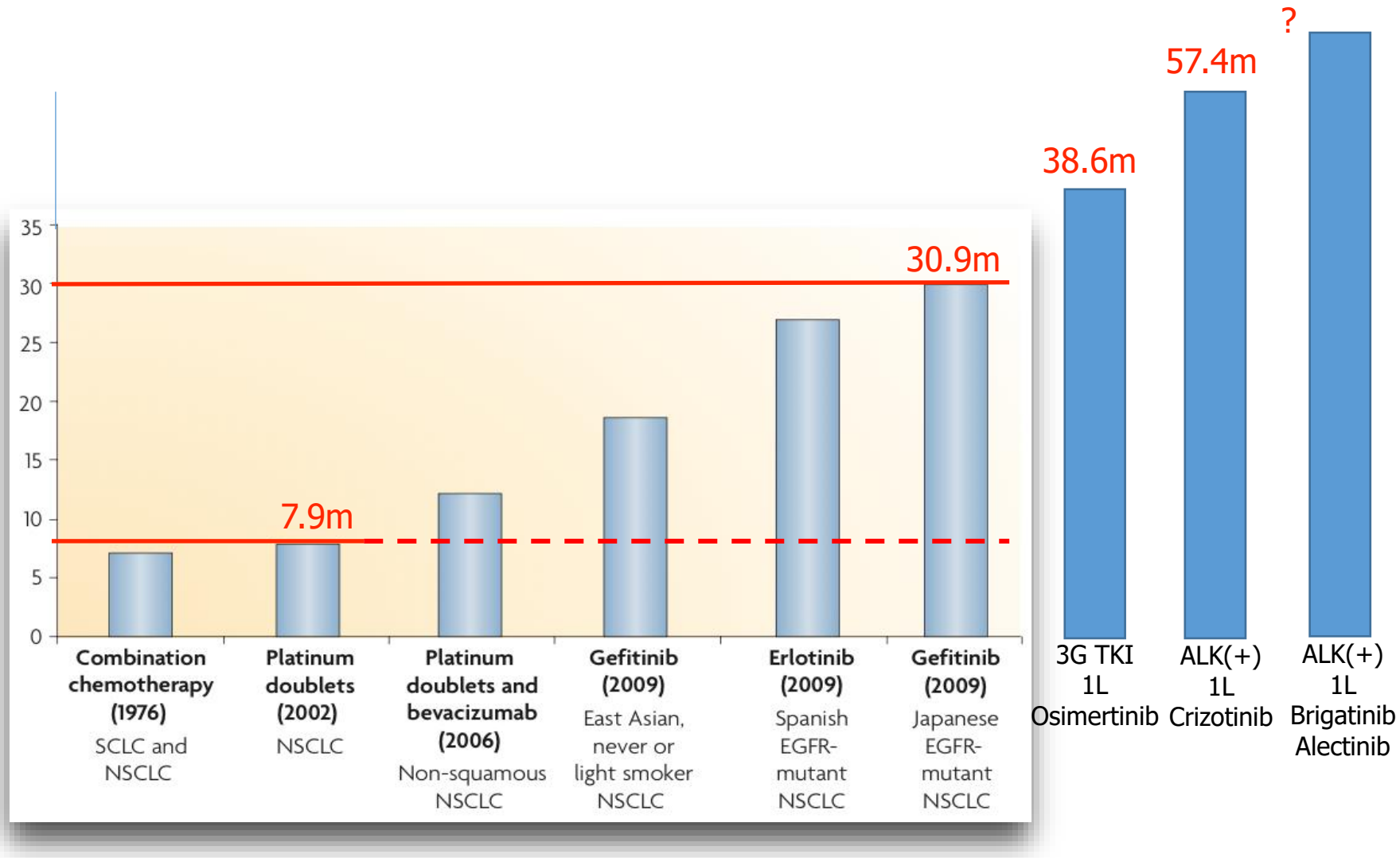
Nat Rev Cancer 2007;7(10):778-90

Progress in Overall Survival



W Pao et al. Nat Rev Cancer. 2010

Progress in Overall Survival in NSCLC



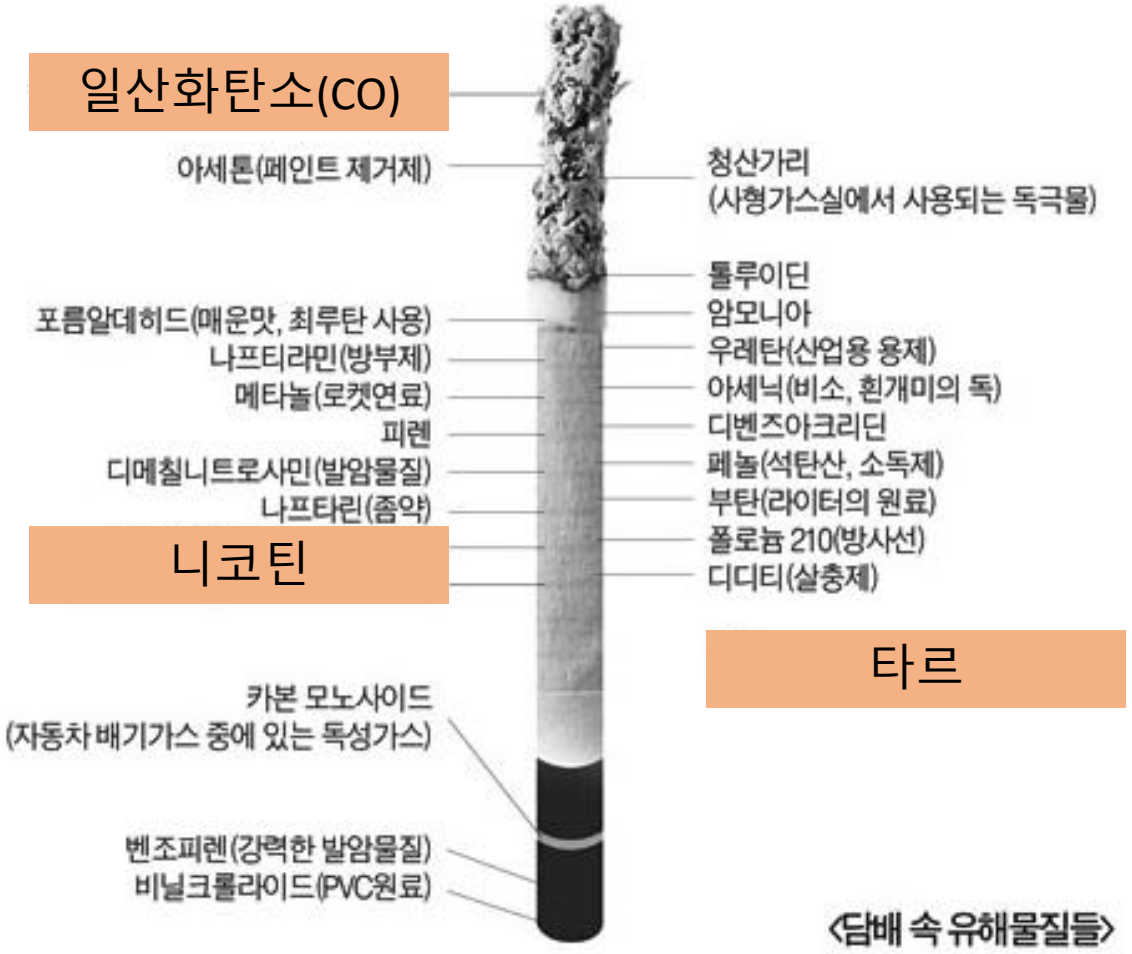
Reality: Smoking- Still, important

- EGFR mutation : 30-40% of lung adenocarcinoma
- ALK rearrangement : 2-7% of lung adenocarcinoma

- Negative population in EGFR, ALK in adeno?
- Squamous cell lung cancer, small cell lung cancer? – smoking related

- Lung cancer with smoking → Treatment response ?
- Lung cancer with COPD…

흡연 = 니코틴 중독



〈담배 속 유해물질들〉

Tobacco-associated lung carcinogenesis

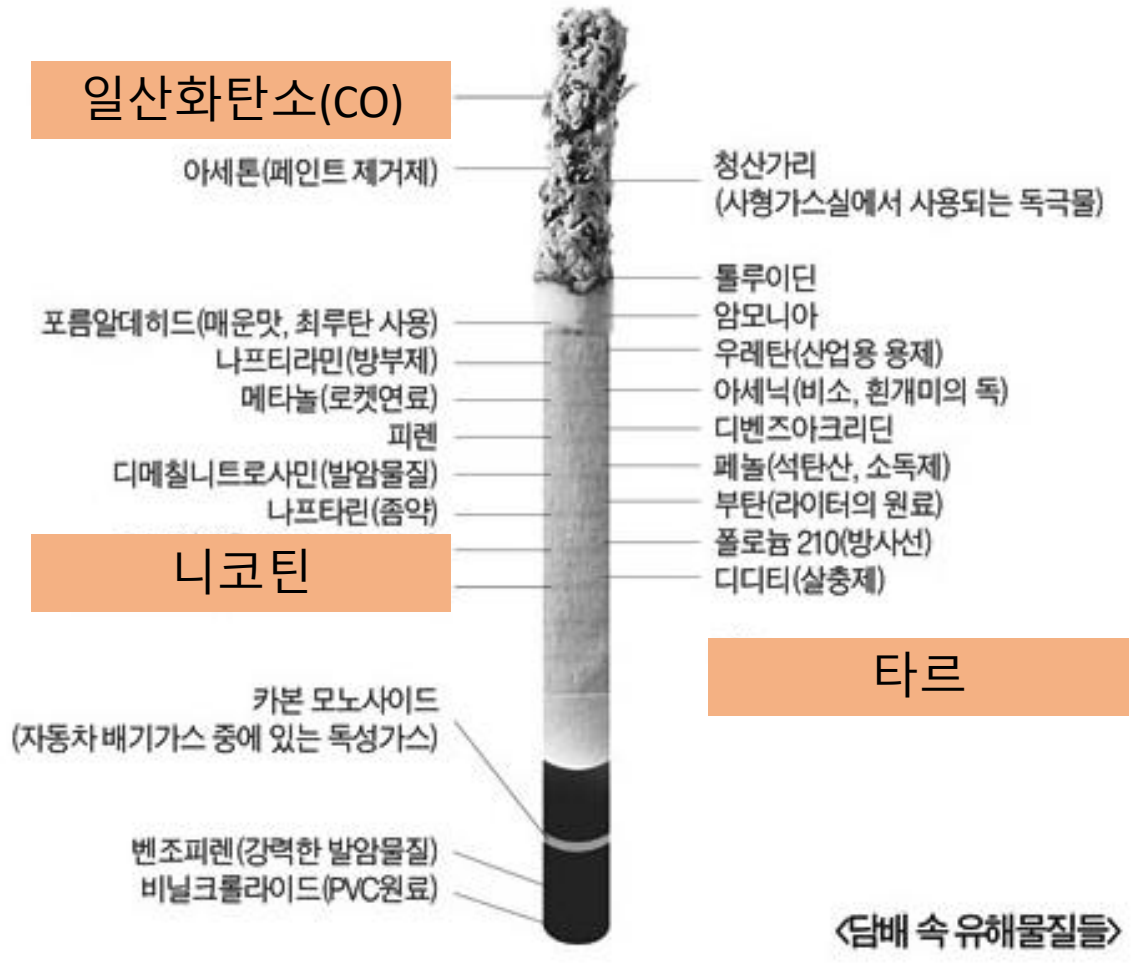


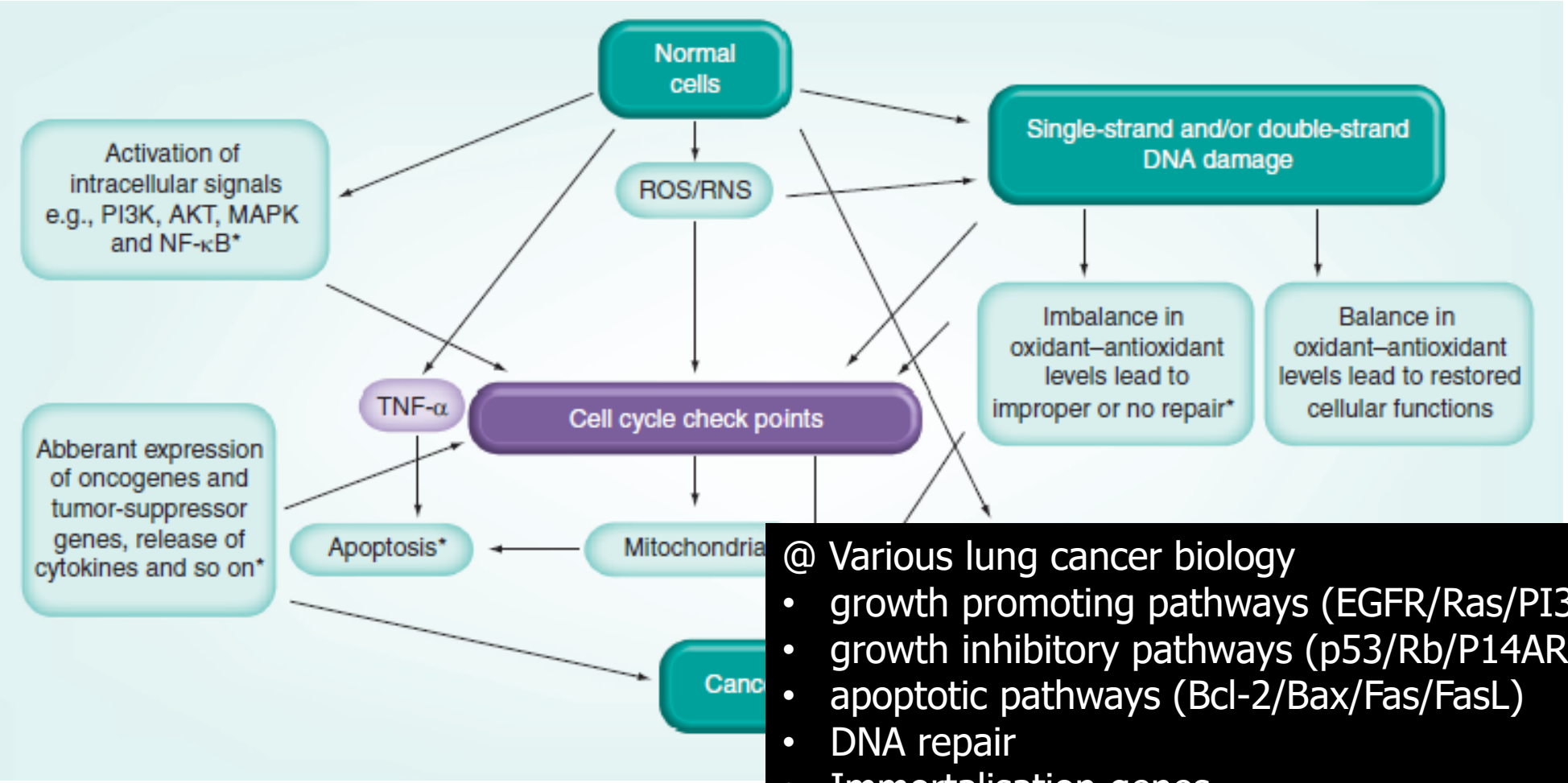
Table 2. Changes in chromosomes and genes related to tobacco-associated lung carcinogenesis.

Chromosome, gene or pathway	Aberration	Smoking-related carcinogenic association	Ref.
Chromosome 3	LOH at 3pl4	*FHIT* exon loss	[121]
Chromosome 9	Allelic losses on chromosomes 9p, 9q	Possible downregulation of tumor suppressors	[122]
Chromosome 13	Allelic losses on 13q	Possible downregulation of tumor suppressors	[122]
p16 gene locus	Homozygous deletion, point mutation	Downregulation	[42]
BRAF(7q34)	Mutation	Overexpression	[52]
LKB1(19p13.3)	Deletion and point mutation	Downregulation	[123]
FOXO3(6q21)	Homozygous deletion	Downregulation	[43]
PTEN (10q23.31)	Mutation	Downregulation	[44]
MET (7q 31)	Mutation	Overexpression	[53]
1p, 3p, 5q, 8p, 9p, 11q, 13q, 17p, and 18q	LOH	Possible downregulation of tumor suppressors	[19]
9p21	LOH	Possible downregulation of tumor suppressors	[42]
P53(17p13.1)	Mutation	Abnormal protein accumulation	[124]
3p21	LOH	Possible downregulation of tumor suppressors	[125]
FHIT, *RASSF1A* and *RUNX3*. APC(3p14.2; 3p21.3; 1p36; and 5q21-q22, respectively)	Promoter methylation	Possible downregulation of tumor suppressors	[126,127]
KRAS(12p12.1)	Mutation	Overexpression, constitutive activation	[124,73]
MGMT(10q26)	Promoter methylation	Downregulation	[127]
HtrA3(4p16.1)	Promoter methylation	Downregulation	[128]
P16/CDKN2A(9p21)	Promoter methylation	Downregulation	[129]
TSLC1/IGSF4(11q23.2)	Promoter methylation	Downregulation	[130]

LOH: Loss of heterozygosity.

Expert Rev. Mol. Diagn. 2012

Cigarette smoking and development of lung cancer



@ Various lung cancer biology
- growth promoting pathways (EGFR/Ras/PI3Kinase)
- growth inhibitory pathways (p53/Rb/P14ARF, STK11)
- apoptotic pathways (Bcl-2/Bax/Fas/FasL)
- DNA repair
- Immortalisation genes

Expert Rev. Mol. Diagn. 2012

Risk Factors_Cigarette smoking

TABLE 46-2. Age-Specific Lung Cancer Mortality Rates (Per 100,000) among Men and Women 60 to 69 Years of Age with Comparable Smoking Levels in the American Cancer Society's Cancer Prevention Study II (CPS-II)

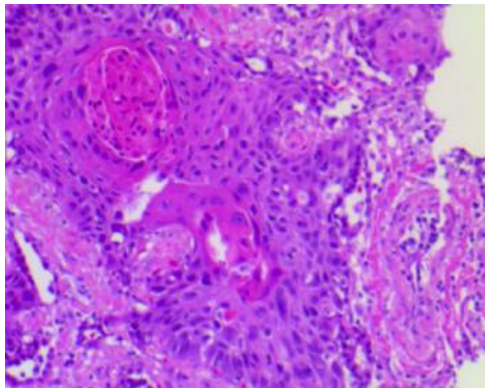
		SMOKED 20 CIGARETTES PER DAY FOR		SMOKED 40 CIGARETTES PER DAY FOR	
Group	Never Smokers	30 Years	40 Years	30 Years	40 Years
Men	11.9	224.3	486.8	572.8	606.6
Women	9.8	200.8	264.4	257.7	552.8

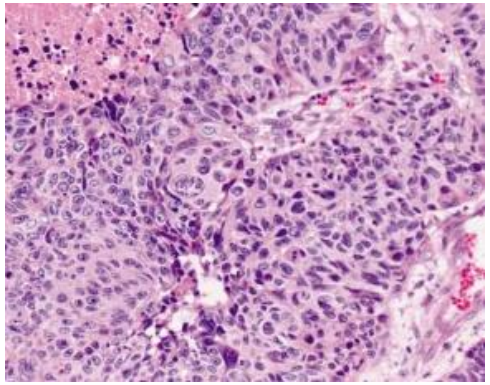
TABLE 46-3. Risk of Lung Cancer among Ex-Smokers Relative to Never Smokers According to Length of Time Since Smoking Cessation and Number of Cigarettes Formerly Smoked among a Cohort of U.S. Veterans

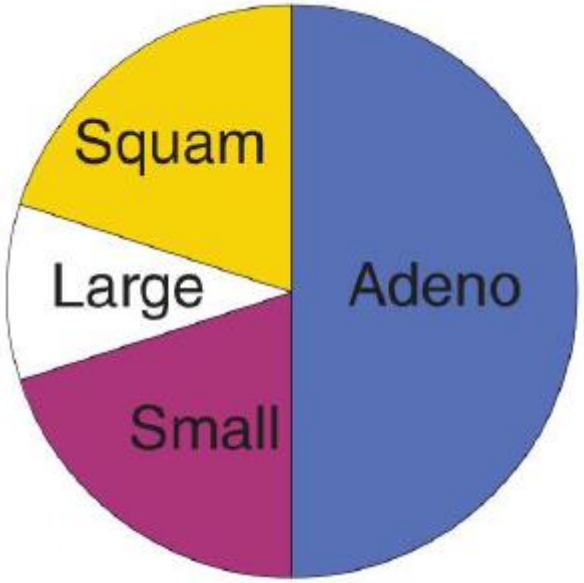
	CIGARETTES SMOKED PER DAY				
Years Since Smoked	1–9	10–20	21–39	40	Total
<5	7.6*	12.5	20.6	26.9	16.1
5–9	3.6	5.1	11.5	13.6	7.8
10–19	2.2	4.3	6.8	7.8	5.1
20–29	1.7	3.3	3.4	5.9	3.3
30–39	0.5	2.1	2.8	4.5	2.0
≥40	1.1	1.6	1.8	2.3	1.5

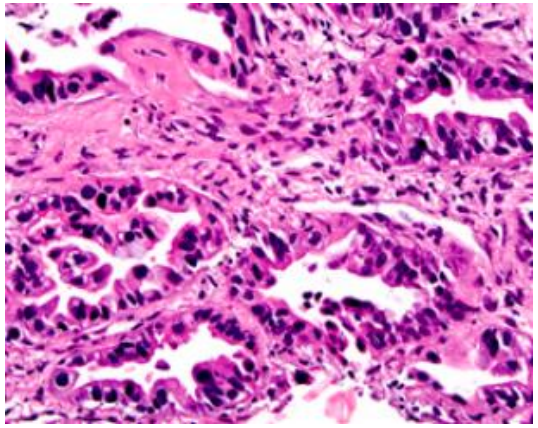
Murray & Nadel's Textbook of Respiratory Medicine 6th ed.

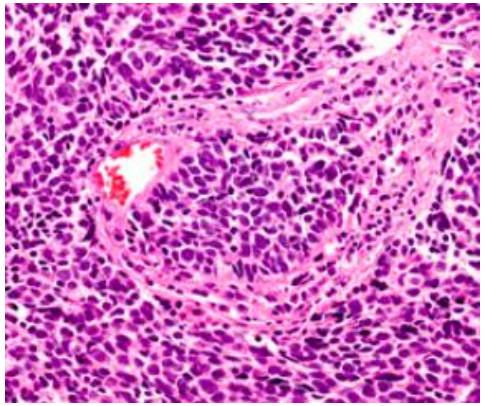
Traditional Histologic View





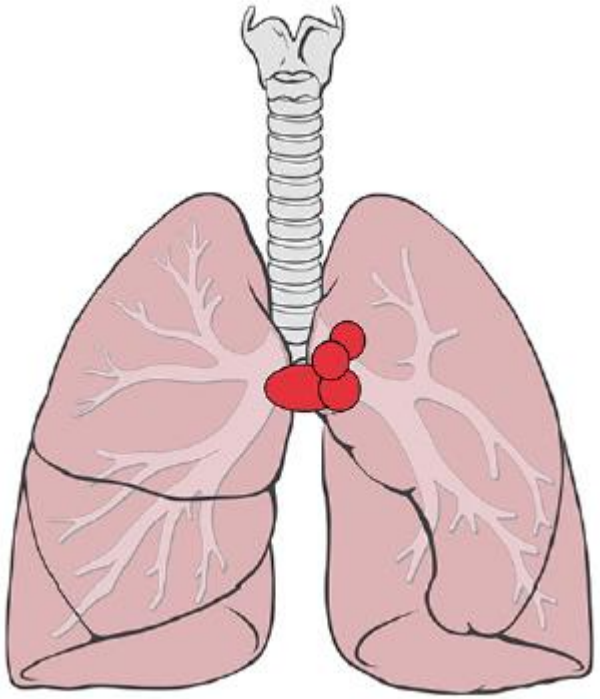


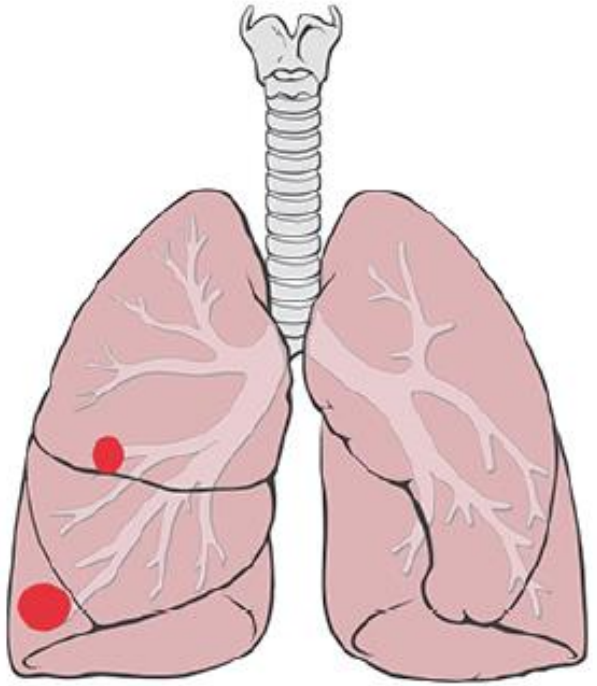


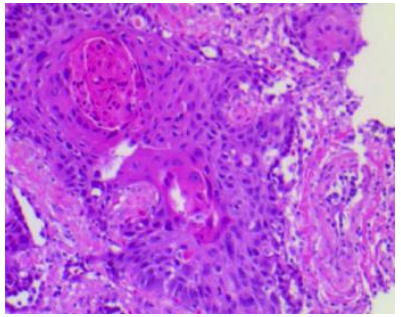


- **Small cell lung cancer** (13-15%)
- **Non-small cell lung cancer**
  - Squamous cell carcinoma
  - Adenocarcinoma (most common)
  - Large-cell carcinoma

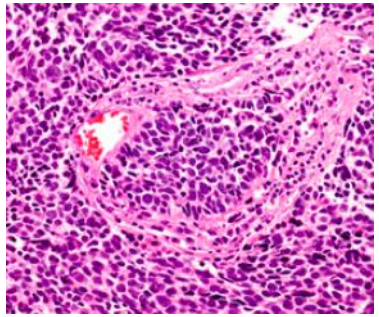
Harrison 19th



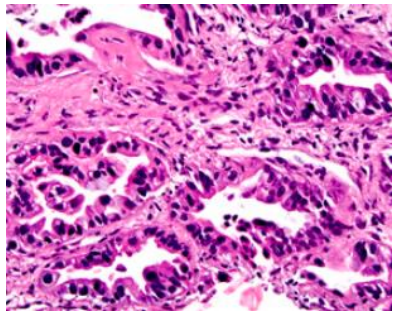




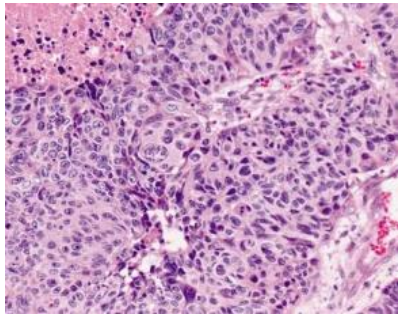
Squamous



Small cell



Adeno



Large cell

Cigarette smoking and histologic subtype of lung cancer

- eight states in the USA
- aged 50–71 years
- 279,214 men and 184,623 women

	Men				Women			
	Person-years	n	Age-standardised* incidence rates/10^5 person-years (95% CI)	Multivariate† adjusted HRs (95% CI)	Person-years	n	Age-standardised* incidence rates/10^5 person-years (95% CI)	Multivariate† adjusted HRs (95% CI)
Adenocarcinoma‡	1996369	1574	78·3 (74·4–82·2)	..	1338587	988	74·4 (69·8–79·0)	..
Never smoked cigarettes, pipes, or cigars	498237	63	12·8 (9·6–16·0)	1·0 (reference)	597856	102	17·0 (13·7–20·3)	1·0 (reference)
Former cigarette smoker ≤1 pack/day	586015	301	48·7 (43·2–54·2)	3·9 (3·0–5·1)	357043	205	56·9 (49·1–64·7)	3·2 (2·5–4·1)
Former cigarette smoker >1 pack/day	560112	686	118·5 (109·6–127·4)	9·2 (7·1–12·0)	161319	221	140·2 (121·7–158·7)	7·9 (6·2–10·0)
Current cigarette smoker ≤1 pack/day	139634	268	203·9 (179·3–228·5)	14·0 (10·6–18·5)	162866	294	188·4 (166·7–210·2)	10·2 (8·1–12·8)
Current cigarette smoker >1 pack/day	102223	238	259·5 (225·1–293·9)	17·6 (13·2–23·5)	59048	166	302·1(254·8–349·4)	16·4 (12·7–21·1)
Small-cell carcinoma‡	1996369	571	28·4 (26·1–30·7)	..	1338587	369	27·8 (25·0–30·7)	..
Never smoked cigarettes, pipes, or cigars	498237	7	1·4 (0·4–2·5)	1·0 (reference)	597856	7	1·2 (0·3–2·0)	1·0 (reference)
Former cigarette smoker ≤1 pack/day	586015	61	10·1 (7·5–12·6)	6·3 (2·9–13·9)	357043	38	10·5 (7·2–13·9)	9·2 (4·1–20·7)
Former cigarette smoker >1 pack/day	560112	181	31·1 (26·5–35·6)	18·6 (8·7–39·8)	161319	59	37·6 (28·0–47·3)	31·7 (14·5–69·6)
Current cigarette smoker ≤1 pack/day	139634	151	116·4 (97·7–135·1)	65·2 (30·4–139·8)	162866	153	101·4 (85·2–117·6)	83·4 (39·0–178·6)
Current cigarette smoker >1 pack/day	102223	165	184·4 (155·1–213·6)	98·2 (45·7–210·9)	59048	112	207·5 (167·9–247·1)	168·4 (77·9–364·3)
Squamous-cell carcinoma‡	1996369	921	45·8 (42·8–48·7)	..	1338587	317	24·0 (21·3–26·6)	..
Never smoked cigarettes, pipes, or cigars	498237	7	1·5 (0·4–2·6)	1·0 (reference)	597856	5	0·8 (0·1–1·6)	1·0 (reference)
Former cigarette smoker ≤1 pack/day	586015	131	21·1 (17·4–24·7)	13·0 (6·0–27·8)	357043	54	15·0 (11·0–19·0)	19·2 (7·7–48·0)
Former cigarette smoker >1 pack/day	560112	359	61·8 (55·4–68·2)	36·0 (17·0–76·3)	161319	71	45·4 (34·8–56·0)	57·2 (23·0–141·9)
Current cigarette smoker ≤1 pack/day	139634	200	154·9 (133·3–176·5)	83·1 (39·0–177·1)	162866	116	76·5 (62·5–90·6)	83·1 (33·8–204·3)
Current cigarette smoker >1 pack/day	102223	219	247·6 (213·6–281·6)	128·2 (60·1–273·6)	59048	70	138·7 (105·5–171·9)	139·8 (56·0–349·1)
Undifferentiated carcinoma‡	1996369	255	12·7 (11·1–14·2)	..	1338587	131	9·9 (8·2–11·6)	..
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Former cigarette smoker ≤1 pack/day	586015	37	6·0 (4·1–8·0)	6·2 (2·4–15·8)	357043	22	6·1 (3·5–8·6)	3·8 (1·8–8·0)
Former cigarette smoker >1 pack/day	560112	101	17·4 (14·0–20·8)	17·0 (6·9–42·1)	161319	30	19·0 (12·2–25·8)	11·5 (5·6–23·6)
Current cigarette smoker ≤1 pack/day	139634	48	36·7 (26·3–47·2)	31·0 (12·2–78·6)	162866	51	32·8 (23·7–41·9)	18·4 (9·2–36·7)
Current cigarette smoker >1 pack/day	102223	59	67·8 (50·0–85·6)	52·3 (20·7–132·1)	59048	18	32·7 (17·0–48·5)	18·0 (8·1–39·9)

Lancet Oncol 2008

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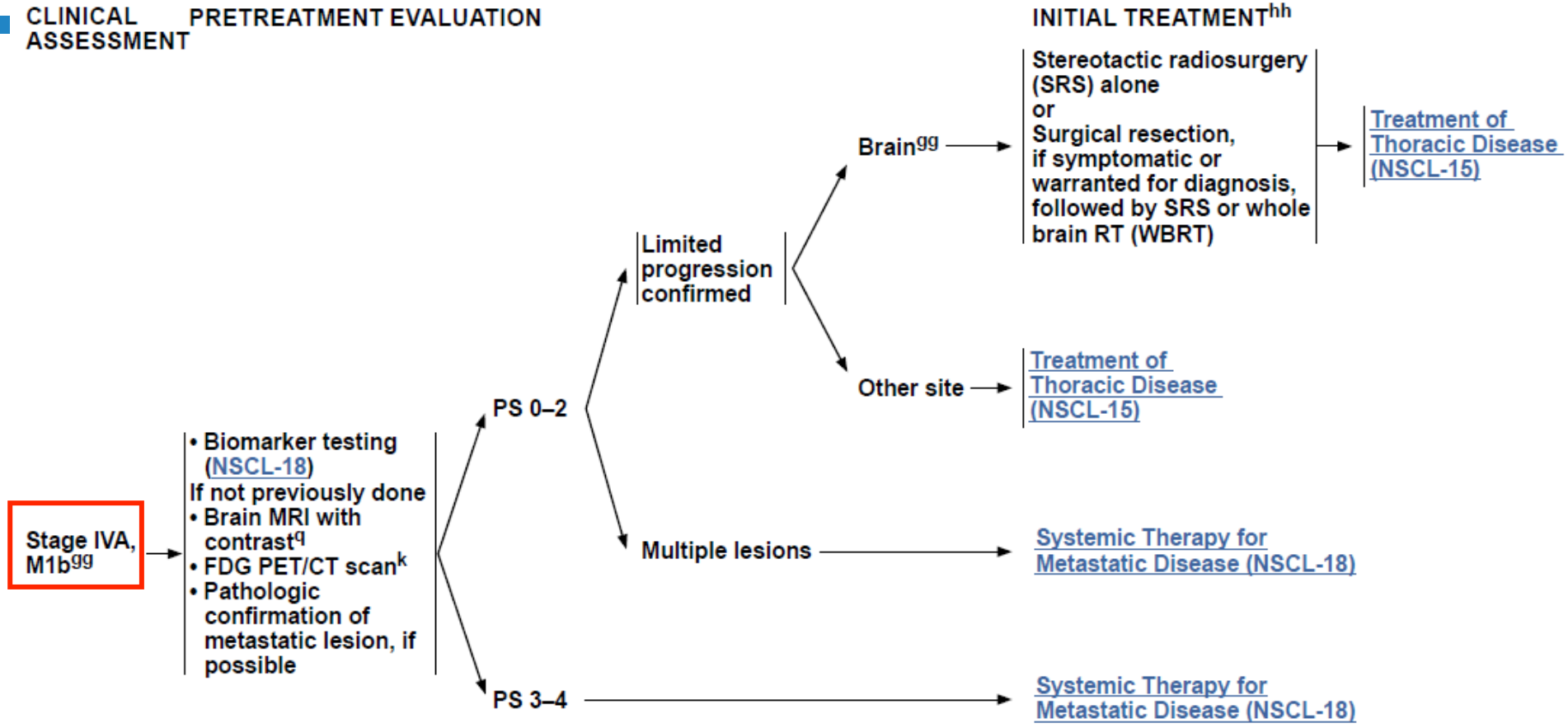
Current cigarette smoker >1 pack/day	102223	219	247·6 (213·6–281·6)	128·2 (60·1–273·6)	59048	70	138·7 (105·5–171·9)	139·8 (56·0–349·1)
Undifferentiated carcinoma‡	1996369	255	12·7 (11·1–14·2)	..	1338587	131	9·9 (8·2–11·6)	..
Never smoked cigarettes, pipes, or cigars	498237	5	1·0 (0·1–2·0)	1·0 (reference)	597856	10	1·7 (0·6–2·7)	1·0 (reference)
Former cigarette smoker ≤1 pack/day	586015	37	6·0 (4·1–8·0)	6·2 (2·4–15·8)	357043	22	6·1 (3·5–8·6)	3·8 (1·8–8·0)
Former cigarette smoker >1 pack/day	560112	101	17·4 (14·0–20·8)	17·0 (6·9–42·1)	161319	30	19·0 (12·2–25·8)	11·5 (5·6–23·6)
Current cigarette smoker ≤1 pack/day	139634	48	36·7 (26·3–47·2)	31·0 (12·2–78·6)	162866	51	32·8 (23·7–41·9)	18·4 (9·2–36·7)
Current cigarette smoker >1 pack/day	102223	59	67·8 (50·0–85·6)	52·3 (20·7–132·1)	59048	18	32·7 (17·0–48·5)	18·0 (8·1–39·9)

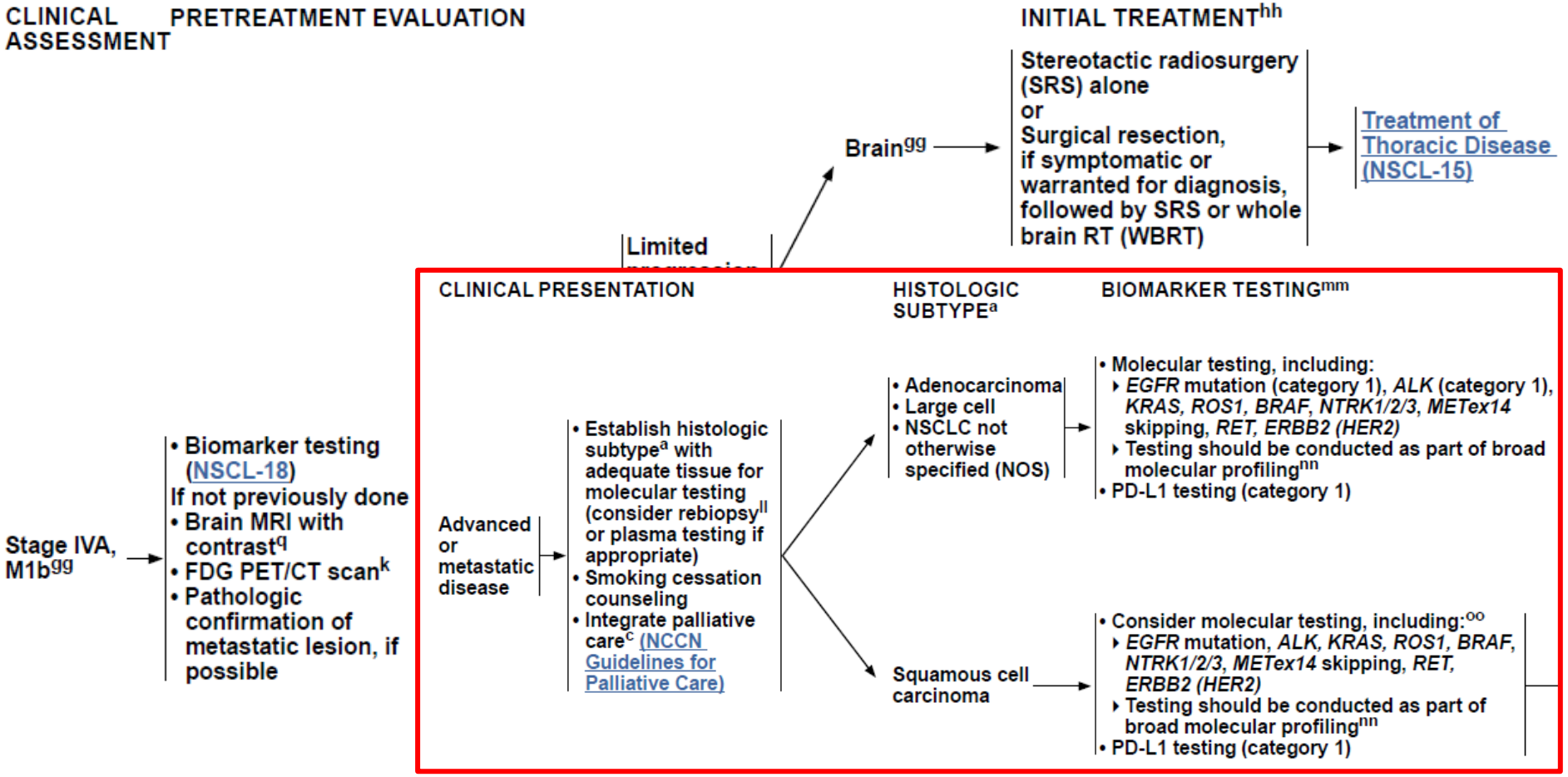
Lancet Oncol 2008

Today

- Smoking as a risk factor of lung cancer
  - **Smoking and oncogenic mutation of lung cancer**
- Impact of smoking on treatment outcome in lung cancer patients
  - Targeted therapy
  - Immunotherapy
- E-cigarette and lung cancer
- Effect of smoking cessation on lung cancer and mortality



[k] PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[q] If MRI is not possible, CT of head with contrast.
[gg] Including selected patients with stage M1c and limited number and volume of metastatic lesions amenable to definitive local therapy. Clinical trials have included up to 3 to 5 progressing sites.
[hh] NCCN Guidelines for Central Nervous System Cancers.



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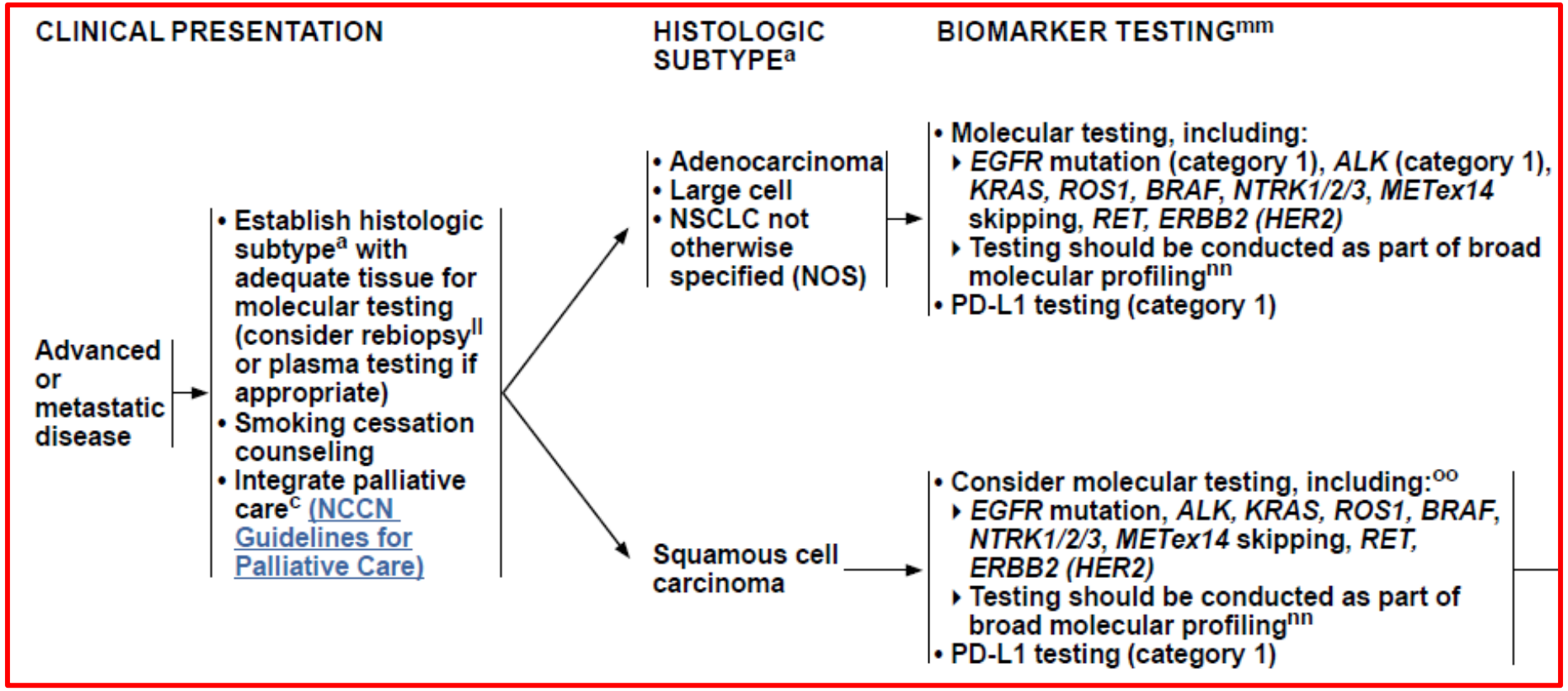
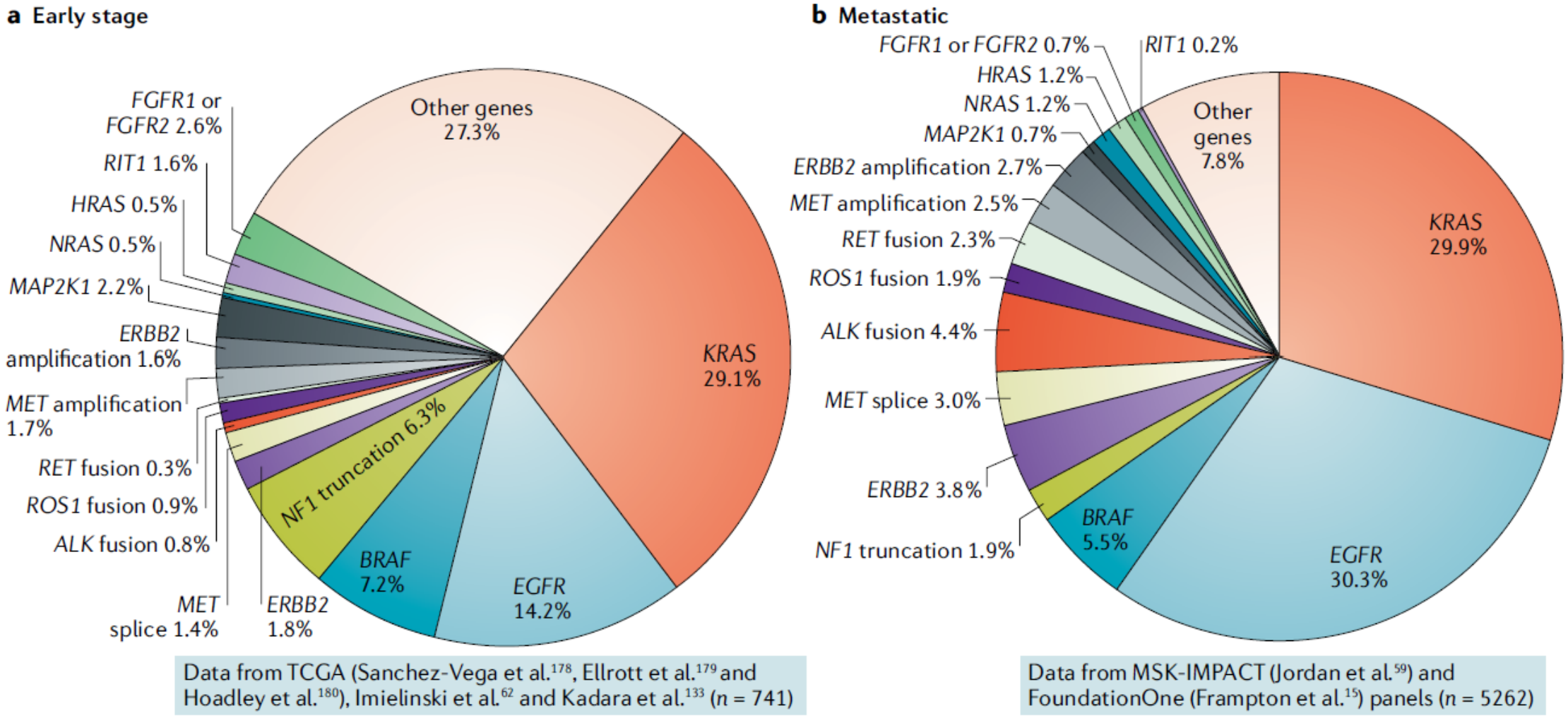
Biomarker testing in advanced NSCLC



Biomarker testing in advanced NSCLC

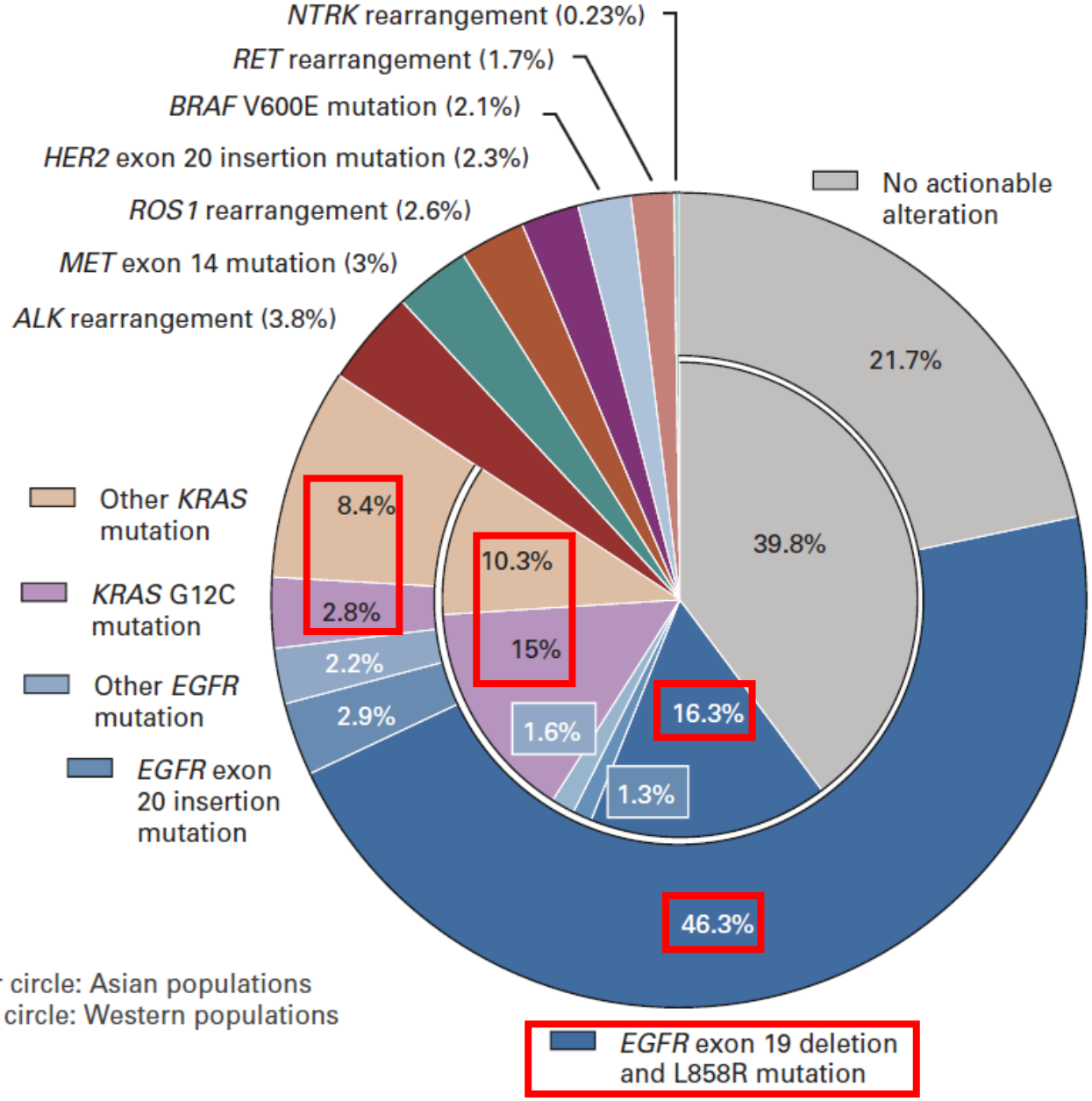
EGFR exon 19 deletion or exon 21 L858R mutation positive	NSCL-20
EGFR S768I, L861Q, and/or G719X mutation positive	NSCL-23
EGFR exon 20 insertion mutation positive	NSCL-24
KRAS G12C mutation positive	NSCL-25
ALK rearrangement positive	NSCL-26
ROS1 rearrangement positive	NSCL-29
BRAF V600E mutation positive	NSCL-31
NTRK1/2/3 gene fusion positive	NSCL-32
METex14 skipping mutation positive	NSCL-33
RET rearrangement positive	NSCL-34
ERBB2 (HER2) mutation positive	NSCL-35
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

Single oncogenic driver paradigm of lung adenocarcinoma molecular classification



Nat Rev Cancer 2019

Targetable oncogenic driver molecular alterations in lung adenocarcinoma



Outer circle: Asian populations
Inner circle: Western populations

J Clin Oncol 2022

KRAS and smoking

- Most mutations in KRAS affect codons 12, 13, 61, and 146
- In NSCLC, mostly codon 12 → The most common G12C and G12V

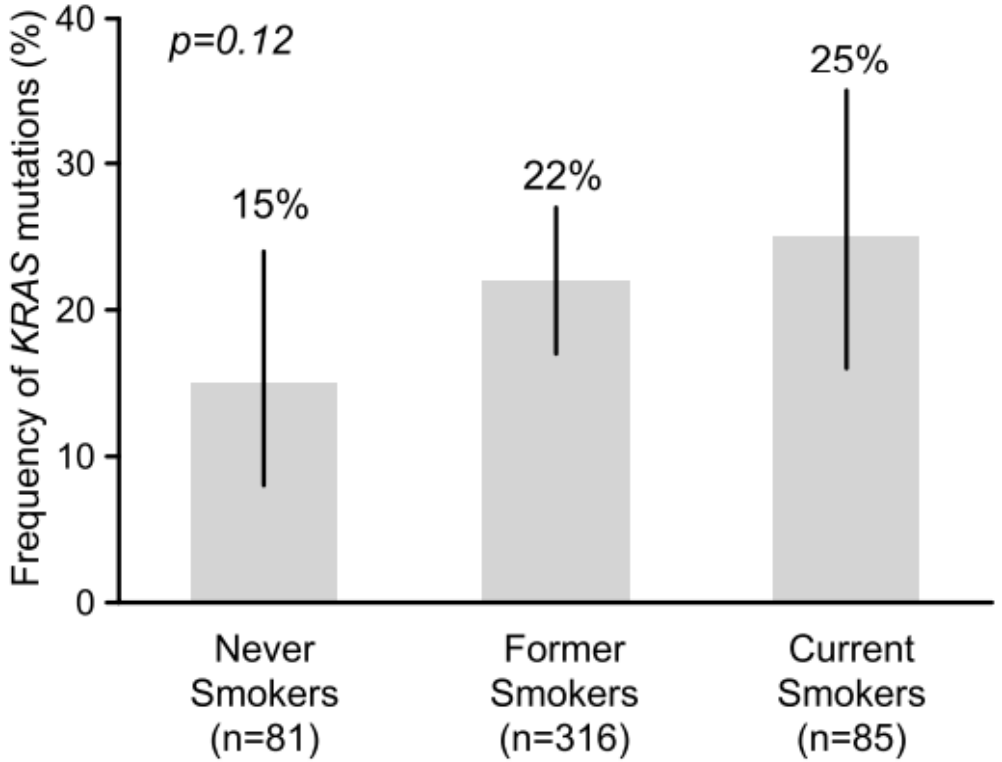
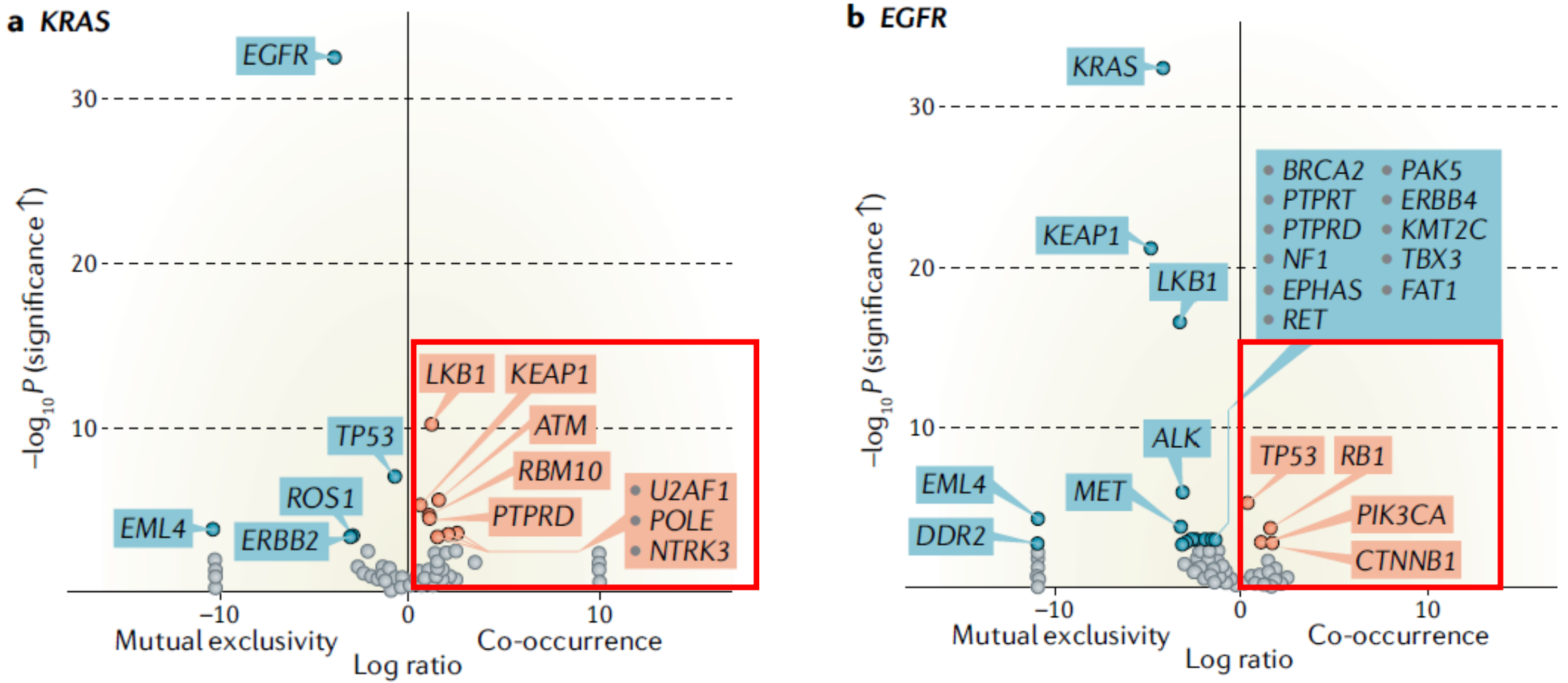


Table 3. *KRAS* mutation type as a function of smoking history

KRAS		Former/current	Never	Total
Mutation	**Nucleotide**			
G12A	G**G**T→G**C**T	13	0	13
G12C	**G**GT→**T**GT	38	0	38
G12V	G**G**T→G**T**T	20	1	21
G13C	**G**GC→**T**GC	2	0	2
G13D	G**G**C→G**A**C	1	0	1
G12D	G**G**T→G**A**T	15	10	25
G12S	**G**GT→**A**GT	1	1	2
Total		90	12	

Clin Cancer Res 2008

Co-occurring genomic alterations in KRAS-mutant lung adenocarcinoma



LKB1 (also known as STK11)

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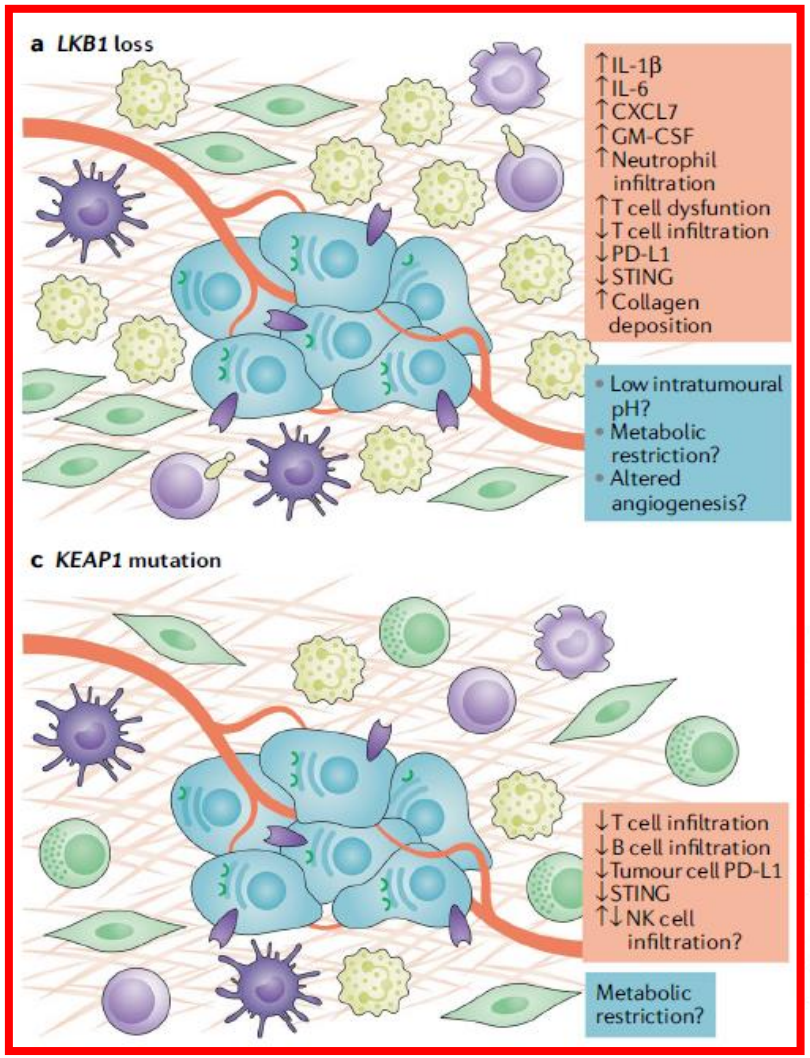
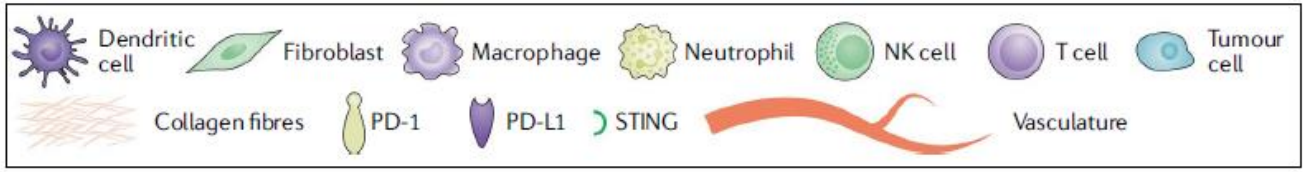
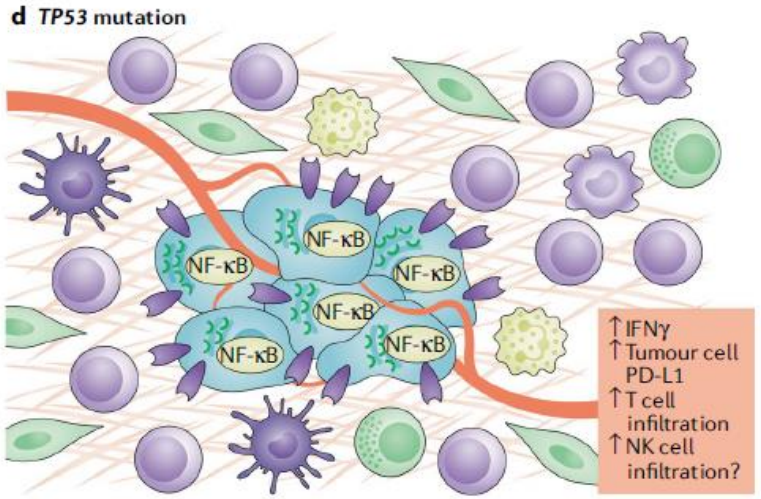
Nat Rev Cancer 2019

Impact of co-mutations on microenvironment of mKRAS lung adenocarcinoma

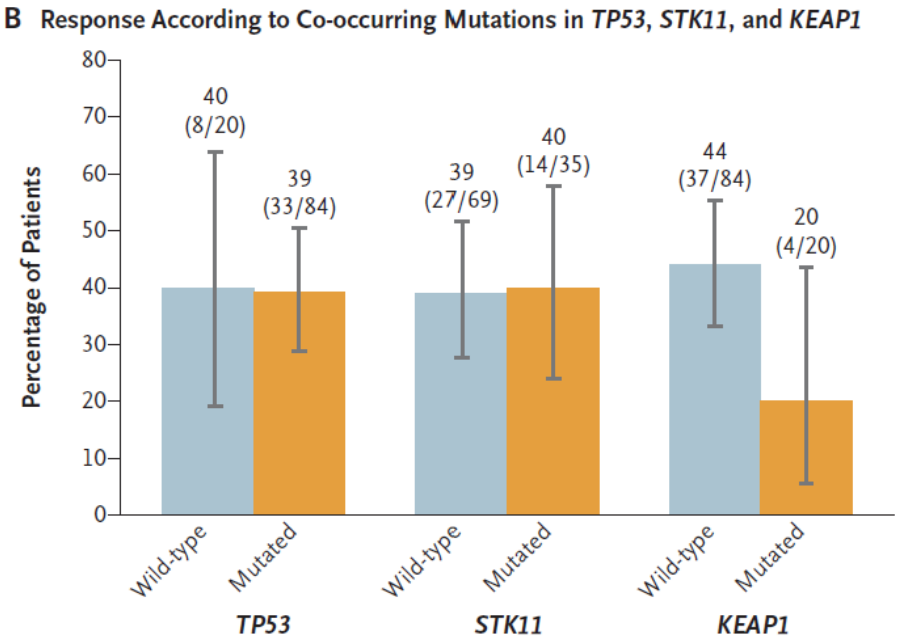




Immune desert
(non-inflamed, cold tumor)



CodeBreaK100: 2L Sotorasib



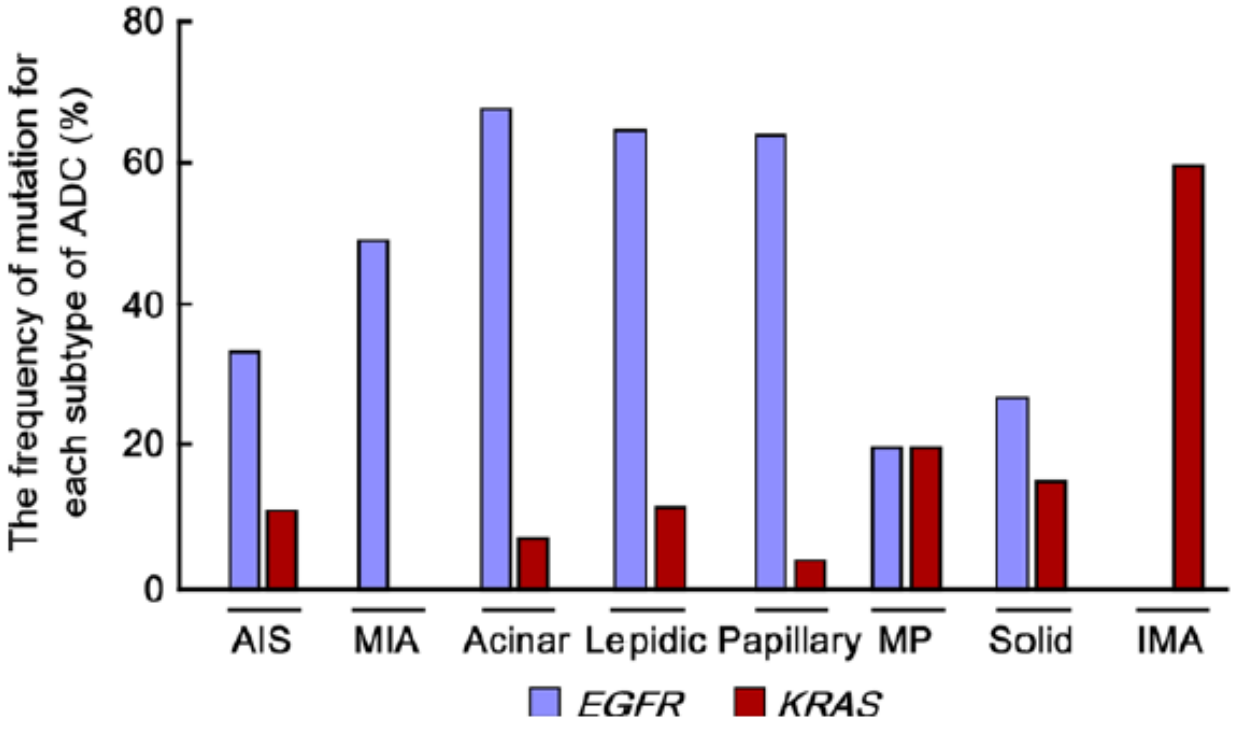
Nat Rev Cancer 2019

Correlation of EGFR and KRAS with histopathologic subtypes of adenocarcinoma

Table 3. Correlation of *EGFR* and *KRAS* with histopathologic subtypes of new adenocarcinoma classification

Features	*EGFR* mutation			*KRAS* mutation		
	Wild type (%)	Mutant (%)	*P*†	Wild type (%)	Mutant (%)	*P*†
AIS	6 (66.7)	3 (33.3)	0.148	8 (88.9)	1 (11.1)	0.255
MIA	16 (50.0)	16 (50.0)	0.250	32 (100.0)	0 (0)	0.998
Acinar	36 (32.4)	75 (67.6)	0.001	103 (92.8)	8 (7.2)	0.446
Lepidic	6 (35.3)	11 (64.7)	0.517	15 (88.2)	2 (11.8)	0.637
Papillary	9 (36.0)	16 (64.0)	0.313	24 (96.0)	1 (4.0)	0.347
MP	8 (80.0)	2 (20.0)	0.210	8 (80.0)	2 (20.0)	0.554
Solid	19 (73.1)	7 (26.9)	0.023	22 (84.6)	4 (15.4)	0.723
IMA	5 (100.0)	0 (0.0)	0.999	2 (40.0)	3 (60.0)	0.013

†Logistic model adjusted for age, gender and smoking status. AIS, adenocarcinoma in situ; IMA, invasive mucinous adenocarcinoma; MIA, minimally invasive adenocarcinoma; MP, micropapillary adenocarcinoma.



Cancer Sci 2017

KRAS^{G12C}: clinical trials

KRYSTAL-1: 2L Adagrasib

Characteristic	Adagrasib (N=116)
Median age (range) — yr	64 (25 to 89)
Female sex — no. (%)	65 (56.0)
Race or ethnic group — no. (%)†	
White	97 (83.6)
Black	9 (7.8)
Asian	5 (4.3)
American Indian or Alaskan Native	1 (0.9)
Other	4 (3.4)
Smoking history — no. (%)	
Never smoked	5 (4.3)
Current smoker	11 (9.5)
Former smoker	100 (86.2)
Histologic type — no. (%)	
Adenocarcinoma	113 (97.4)
Squamous	3 (2.6)

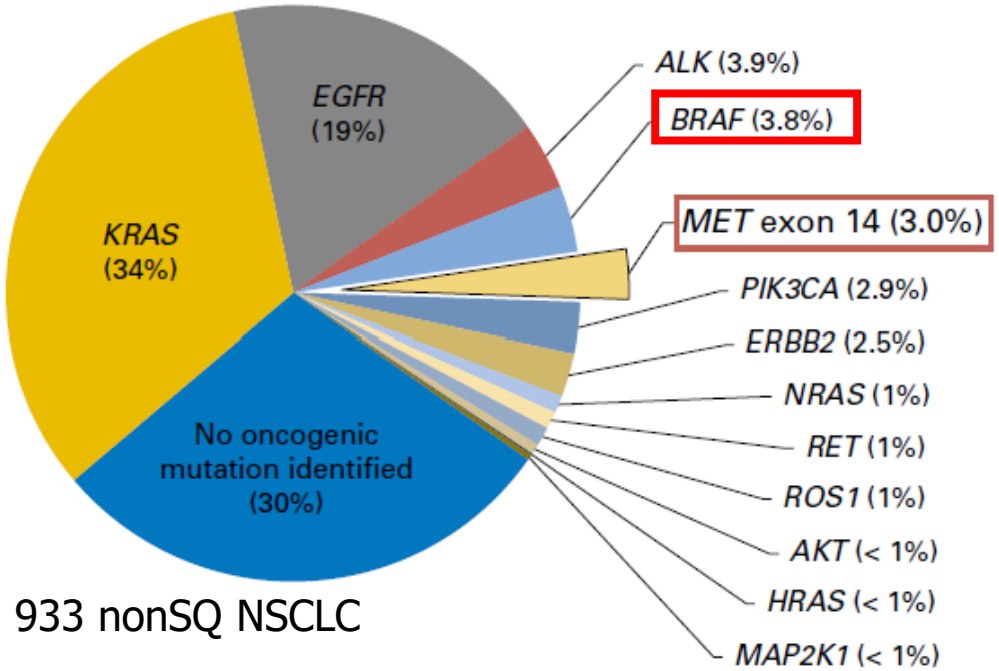
N Engl J Med 2022

CodeBreaK100: 2L Sotorasib

Characteristic	Patients (N=126)
Median age (range) — yr	63.5 (37–80)
Female sex — no. (%)	63 (50.0)
Race — no. (%)†	
White	103 (81.7)
Asian	19 (15.1)
Black	2 (1.6)
Other	2 (1.6)
Smoking history — no. (%)	
Never smoked	6 (4.8)
Current smoker	15 (11.9)
Former smoker	102 (81.0)
Missing data	3 (2.4)
Histologic subtype — no. (%)	
Squamous-cell carcinoma	1 (0.8)
Adenocarcinoma	120 (95.2)
Large-cell carcinoma	3 (2.4)
Bronchoalveolar carcinoma	2 (1.6)

N Engl J Med 2021

BRAF-V600E



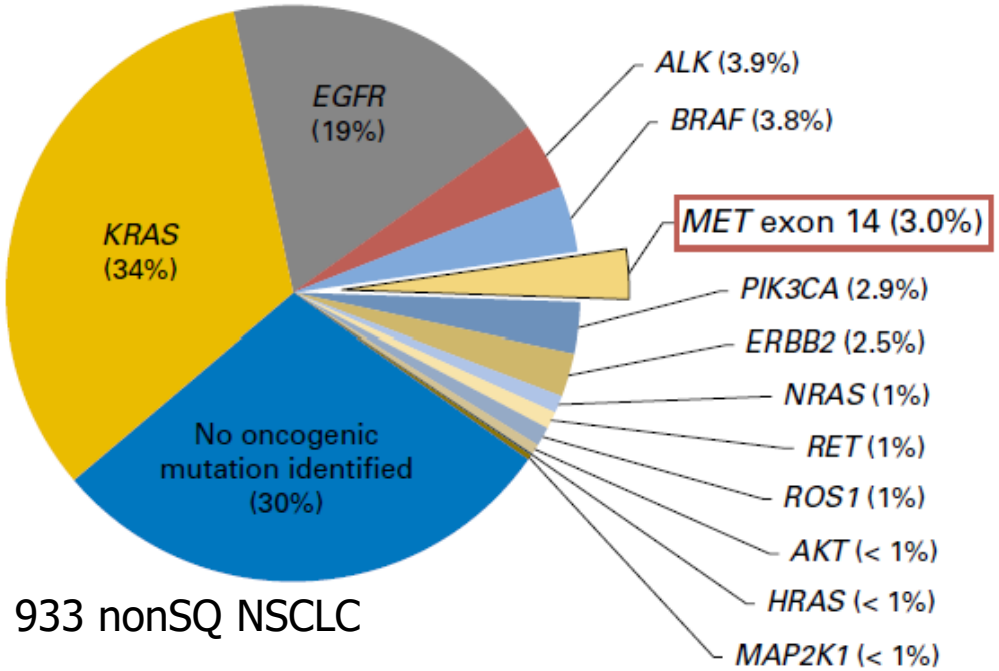
933 nonSQ NSCLC

Characteristic	Pretreated n = 57	Treatment Naive n = 36	Total, N = 93
Age (y)			
Median (min, max)	64.0 (41, 88)	67.0 (44, 91)	65.0 (41, 91)
Sex, n (%)			
Female	28 (49)	22 (61)	50 (54)
Male	29 (51)	14 (39)	43 (46)
Race, n (%)			
White	49 (86)	30 (83)	79 (85)
Asian	4 (7)	3 (8)	7 (8)
Black or African American	2 (4)	1 (3)	3 (3)
Native Hawaiian or other Pacific Islander	1 (2)	1 (3)	2 (2)
Other	1 (2)	1 (3)	2 (2)
Smoking history, n (%)			
Never smoked	16 (28)	10 (28)	26 (28)
Current smoker	6 (11)	5 (14)	11 (12)
Former smoker	35 (61)	21 (58)	56 (60)
Histology, n (%)			
Adenocarcinoma	53 (93)	32 (89)	85 (91)
Adenosquamous carcinoma (predominantly adenocarcinoma)	1 (2)	1 (3)	2 (2)
Adenosquamous carcinoma (predominantly squamous cell carcinoma)	–	1 (3)	1 (1)
Bronchioloalveolar	2 (4)	–	2 (2)
Large cell carcinoma	1(3)	1 (3)	2 (2)
NSCLC without other precision	–	1 (3)	1 (1)

J Thorac Oncol 2022

MET ex14 skipping mutation and smoking

- occurs mostly in **older** patients, those with a **history of smoking**
- has been associated with a poor prognosis.



933 nonSQ NSCLC

Characteristic	*MET* Exon 14 (n = 28)	*EGFR* (n = 99)	*KRAS* (n = 169)
Median age (range), years	72.5 (59-84)	61 (30-93)	65 (42-93)
Sex			
Male	9 (32)	30 (30)	62 (37)
Female	19 (68)	69 (70)	107 (63)
Smoking history, pack-years*			
Never-smoker	10 (36)	57 (58)	6 (4)
≤ 10	3 (11)	10 (10)	11 (7)
> 10	15 (53)	28 (28)	152 (90)
Race			
White, non-Hispanic	28 (100)	79 (80)	157 (93)
Asian	0 (0)	15 (15)	0 (0)
Black	0 (0)	1 (1)	5 (3)
White, Hispanic	0 (0)	3 (3)	3 (2)
Unknown	0 (0)	1 (1)	4 (2)
Histology			
Adenocarcinoma	18 (64)	92 (93)	150 (89)
Pleomorphic with adenocarcinoma component	4 (14)	0 (0)	3 (2)
NSCLC, poorly differentiated	5 (18)	4 (4)	10 (6)
Squamous	0 (0)	2 (2)	5 (3)
Adenosquamous	1 (4)	1 (1)	1 (1)
Stage at diagnosis			
I	13 (46)	9 (9)	12 (7)
II	2 (7)	3 (3)	12 (7)
III	4 (14)	9 (9)	44 (26)
IV	9 (32)	78 (79)	101 (60)

J Thorac Oncol 2022

MET ex14 skipping: clinical trials

VISION: Tepotinib

Characteristic	Liquid Biopsy (N = 66)	Tissue Biopsy (N = 60)	Combined Biopsy (N = 99)
Median age (range) –	74 (49–88)	74 (41–94)	74 (41–94)
Sex — no. (%)			
Male	32 (48)	39 (65)	54 (55)
Female	34 (52)	21 (35)	45 (45)
Race — no. (%)†			
Asian	11 (17)	15 (25)	21 (21)
White	52 (79)	44 (73)	74 (75)
Smoking history — n			
Yes	28 (42)	30 (50)	46 (46)
No	34 (52)	22 (37)	45 (45)
Histologic subtype —			
Adenocarcinoma	58 (88)	56 (93)	89 (90)
Squamous	6 (9)	3 (5)	7 (7)
Sarcomatoid	1 (2)	0	1 (1)

N Engl J Med 2020

GEOMETRY: Capmatinib

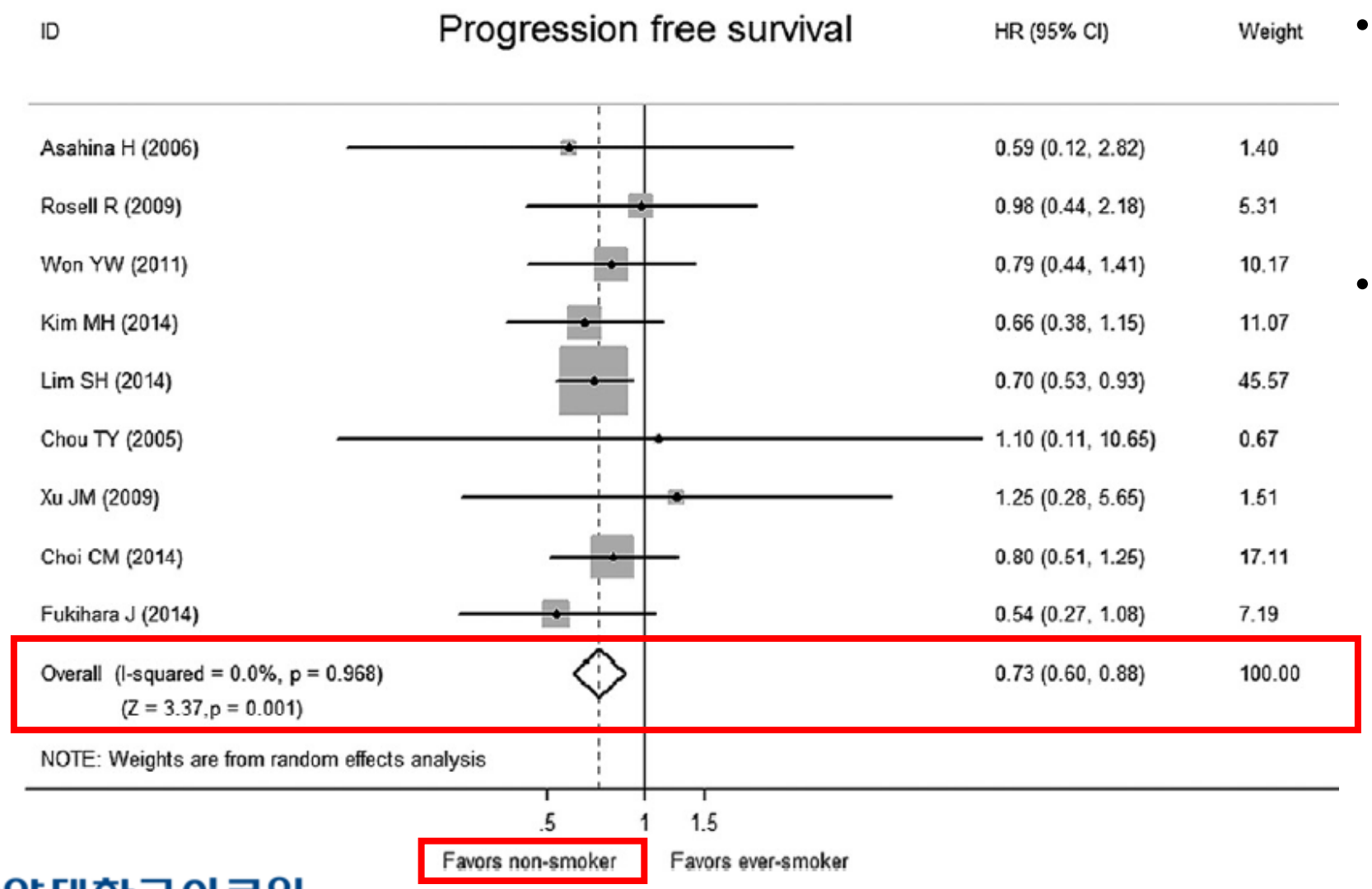
Characteristic	NSCLC with *MET* Exon 14 Skipping Mutation		NSCLC with *MET* Amplification		
	Cohort 4 (N = 69)	Cohort 5b (N = 28)	Cohort 1a (N = 69)	Cohort 1b (N = 42)	Cohort 2 (N = 54)
Age					
Median (range) — yr	71 (49–90)	71 (57–86)	61 (33–76)	60 (36–76)	64 (39–84)
≥65 yr — no. (%)	55 (80)	25 (89)	28 (41)	13 (31)	24 (44)
Female sex — no. (%)	40 (58)	18 (64)	15 (22)	21 (50)	15 (28)
Smoking history — no. (%)					
Never smoked	40 (58)	18 (64)	5 (7)	7 (17)	11 (20)
Former smoking	27 (39)	9 (32)	54 (78)	29 (69)	34 (63)
Current smoking	2 (3)	1 (4)	10 (14)	6 (14)	9 (17)
Histologic findings — no. (%)					
Adenocarcinoma	53 (77)	25 (89)	57 (83)	35 (83)	48 (89)
Squamous-cell carcinoma	6 (9)	2 (7)	7 (10)	2 (5)	4 (7)
Large-cell carcinoma	1 (1)	0	2 (3)	1 (2)	0
Other	9 (13)	1 (4)	3 (4)	4 (10)	2 (4)

N Engl J Med 2020

Today

- Smoking as a risk factor of lung cancer
  - Smoking and oncogenic mutation of lung cancer
- **Impact of smoking on treatment outcome in lung cancer patients**
  - Targeted therapy
  - Immunotherapy
- E-cigarette and lung cancer
- Effect of smoking cessation on lung cancer and mortality

Impact of Smoking Status on EGFR-TKI Efficacy in mEGFR NSCLC



- For advanced mEGFR NSCLC, nonsmoking is associated with longer PFS than ever smoking after EGFR-TKIs treatment.
- Smoking history should be considered an essential factor in studies regarding EGFR-targeted agents toward EGFR-mutant patients.

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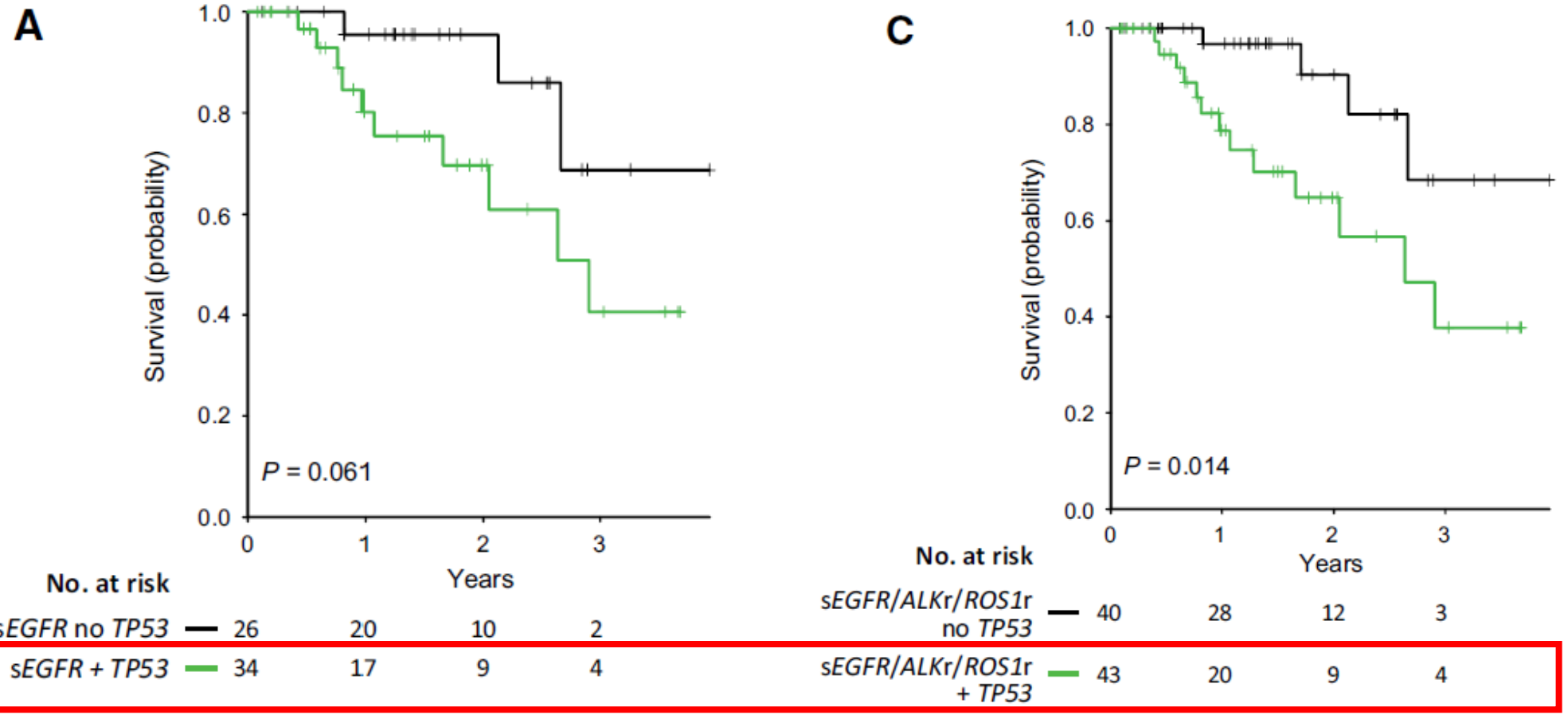
Clinical Lung Cancer **2015**

Smoking and TP53 Mutations in Lung Adenocarcinoma with Targetable Mutations



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Clin Cancer Res 2018

Smoking History as a Potential Predictor of ICI Efficacy in adv NSCLC

- 644 advanced NSCLC treated with ICI monotherapy (Apr 2013- Sep 2020)
- Dana-Farber Cancer Institute and Brigham and Women's Hospital

Table 1. Baseline clinicopathological characteristics (N = 644)

Characteristics	Never smoker (n = 105)	Former smoker (n = 375)	Current smoker (n = 164)	P[a]
Age, median (range), y	63 (25-87)	69 (35-92)	63 (38-88)	<.001
Gender, No. (%)				.80
Female	60 (57.1)	207 (55.2)	88 (53.0)	
Male	45 (42.9)	168 (44.8)	77 (47.0)	
Histology, No. (%)				.27
Nonsquamous cell carcinoma	97 (92.4)	332 (88.5)	141 (86.0)	
Squamous cell carcinoma	8 (7.6)	43 (11.5)	23 (14.0)	
ECOG PS[b], No. (%)				.48
0-1	82 (78.1)	298 (79.5)	123 (75.0)	
≥2	22 (21.0)	74 (19.7)	40 (24.4)	
Unknown	1 (1.0)	3 (0.8)	1 (0.6)	
PD-L1 TPS[c], No. (%)				.07
Negative	20 (19.0)	48 (12.8)	12 (7.3)	
1%-49%	23 (21.9)	86 (22.9)	41 (25.0)	
≥50%	30 (28.6)	137 (36.5)	56 (34.1)	
Unknown	32 (30.5)	104 (27.7)	55 (33.5)	
Lines of therapy[d], No. (%)				<.001
1	18 (17.1)	139 (37.1)	59 (36.0)	
≥2	87 (82.9)	236 (62.9)	105 (64.0)	
Median pack-years[e] (IQR)	0 (0)	28 (25)	40 (26.3)	<.001
Median TMB (IQR), (mut/Mb)	7.6 (6.1)	9.9 (6.8)	12.2 (7.7)	<.001

- OncoPanel NGS
- 22C3 (DAKO), SP263 (Ventana) and E1L3N (Danvers)

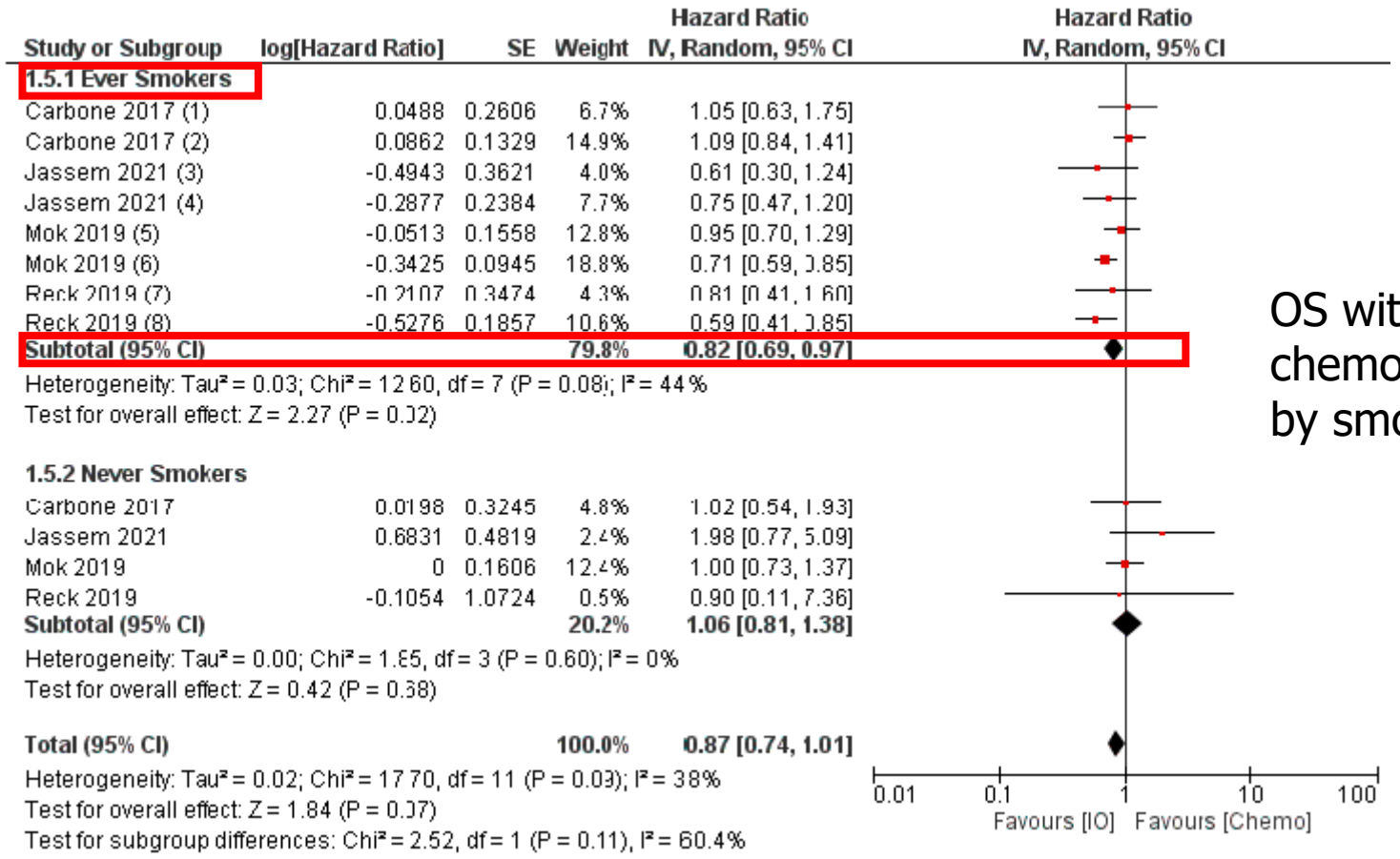
JNCI J Natl Cancer Inst 2021

Smoking History as a Potential Predictor of ICI Efficacy in adv NSCLC

	ORR		PFS		OS	
	Multivariable analysis		Multivariable analysis		Multivariable analysis	
Parameters	OR (95% CI)[c]	P	HR[e] (95% CI)	P	HR[e] (95% CI)	P
Smoker						
Former vs never smoker	2.07 (1.08 to 4.25)	.04	0.74 (0.59 to 0.93)	.01	0.85 (0.66 to 1.11)	.23
Current vs never smoker	3.04 (1.52 to 6.47)	.003	0.60 (0.46 to 0.79)	<.001	0.78 (0.58 to 1.04)	.10
Age	1.01 (0.99 to 1.03)	.22	0.99 (0.98 to 1.00)	.07	1.00 (0.99 to 1.01)	.77
Male vs female	0.79 (0.53 to 1.18)	.25	1.14 (0.96 to 1.34)	.13	1.19 (0.99 to 1.44)	.07
Squamous vs nonsquamous	1.34 (0.72 to 2.39)	.34	1.04 (0.81 to 1.35)	.75	1.15 (0.87 to 1.52)	.34
ECOG PS						
≥2 vs 0-1	0.30 (0.16 to 0.54)	<.001	2.04 (1.67 to 2.49)	<.001	2.98 (2.39 to 3.71)	<.001
Unknown vs 0-1	0.64 (0.03 to 4.77)	.70	0.75 (0.31,1.83)	.53	0.42 (0.10 to 1.69)	.22
PD-L1 TPS						
≥50% vs negative	4.00 (1.84 to 9.70)	<.001	0.55 (0.41 to 0.73)	<.001	0.63 (0.46 to 0.88)	.006
1%-49% vs negative	1.44 (0.63 to 3.64)	.41	0.90 (0.68 to 1.18)	.44	0.99 (0.73 to 1.35)	.95
Unknown vs negative	2.15 (0.98 to 5.26)	.07	0.82 (0.62 to 1.07)	.15	0.97 (0.72 to 1.30)	.82
Doubling pack-years	1.21 (1.09 to 1.36)	<.001	0.92 (0.88 to 0.95)	<.001	0.94 (0.90 to 0.99)	.01

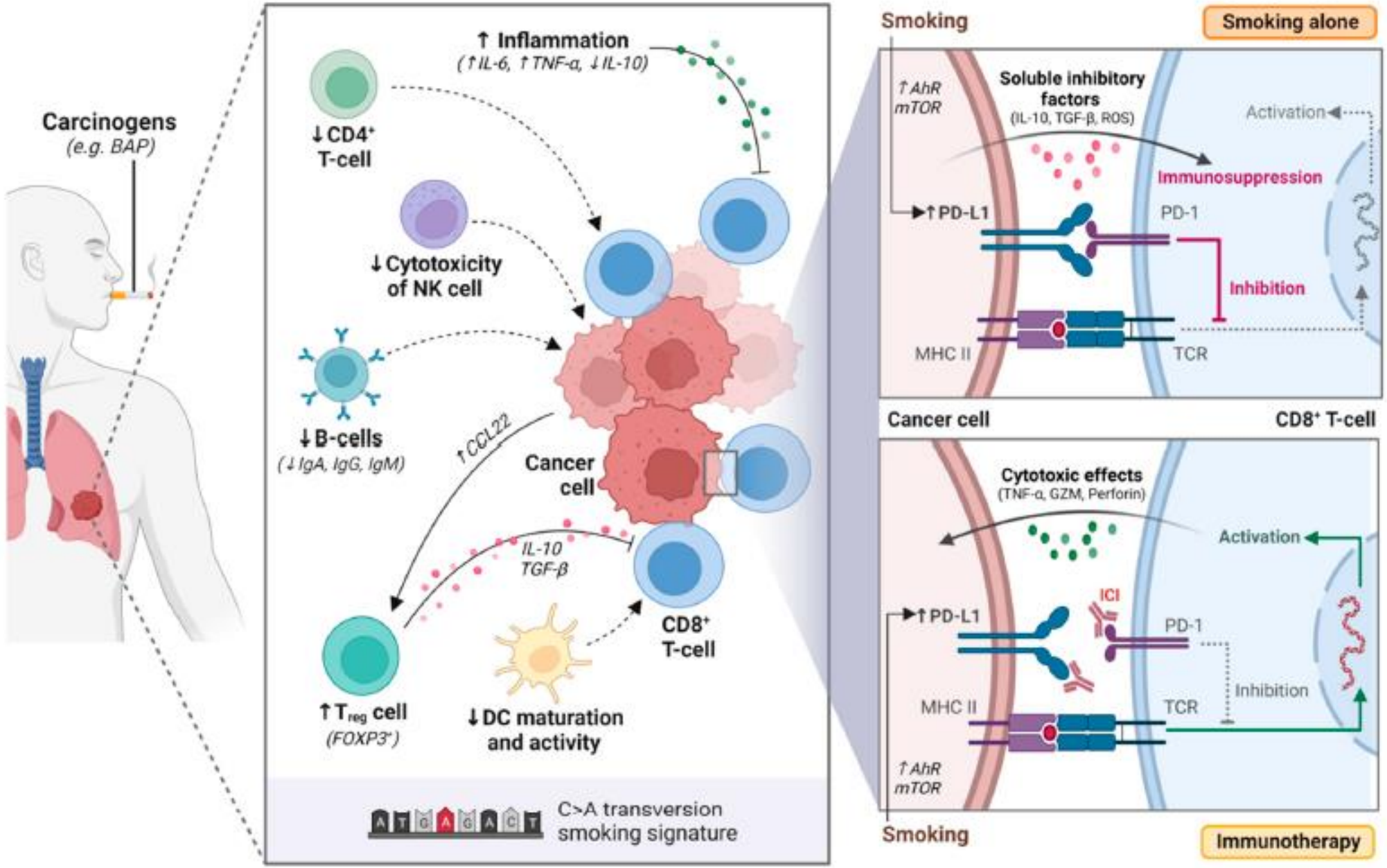
Smoking and response ICI in NSCLC : Meta-ananlysis

- reviewed the literature on the association of tobacco and tumor biology as it relates to ICIs
- reviewed the association of tobacco use on outcomes among ph III RCTs involving ICIs in NSCLC



OS with 1L immunotherapy or chemotherapy
by smoking status at study entry

Curr Oncol 2022



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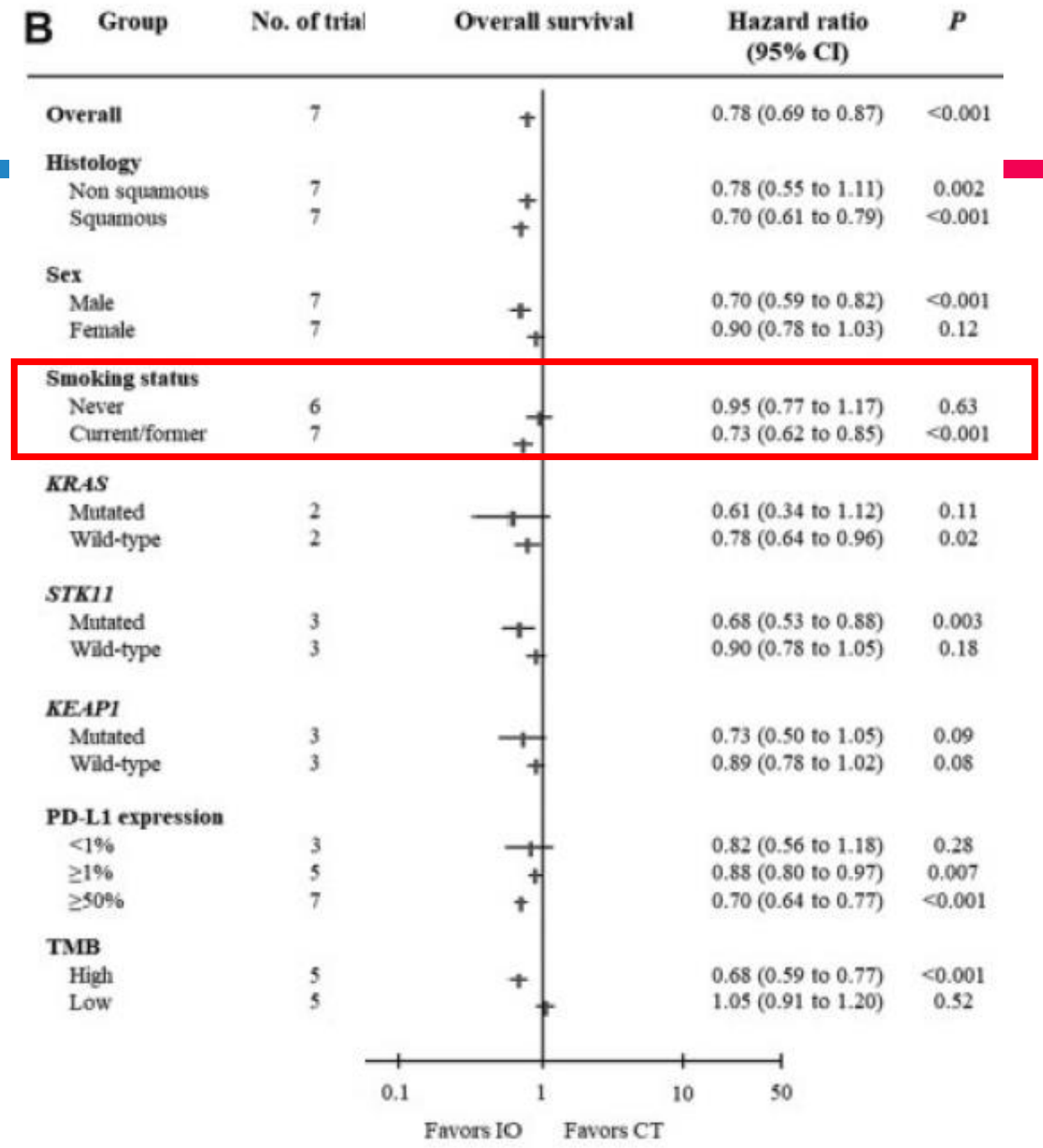
Predictors of survival to IO/ ChemoIO in NSCLC : Meta

- reviewed RCTs investigating IO alone or with CT, vs CT alone (1L setting) in adv NSCLC

- female sex, no smoking history,
- negative PD-L1 expression,
- low TMB

→ correlated with unsatisfactory outcomes

* OS
IO alone vs chemotherapy



JNCI 2023

Predictors of survival to IO/ ChemoIO in NSCLC : Meta

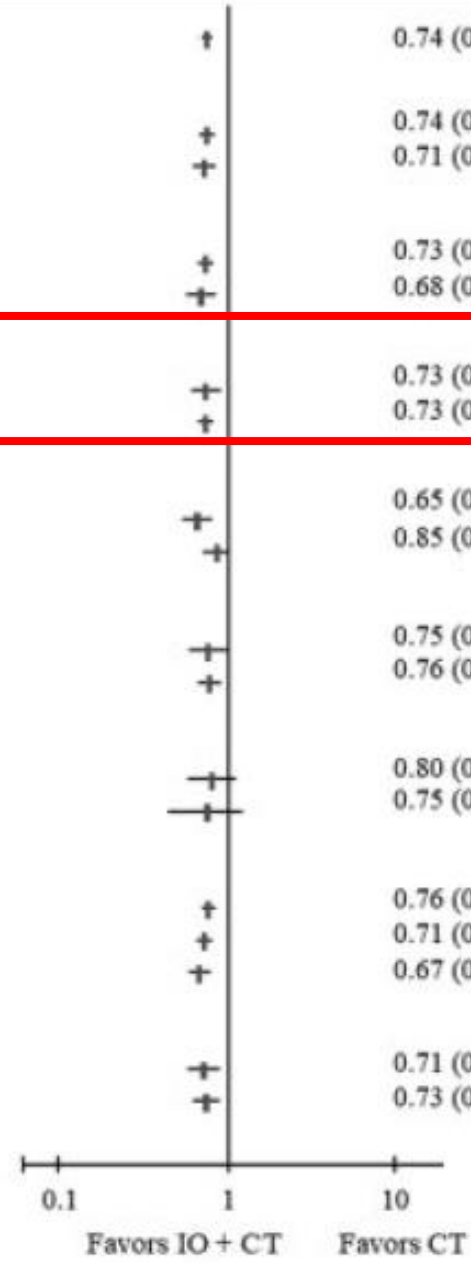
- reviewed RCTs investigating IO alone or with CT, vs CT alone (1L setting) in adv NSCLC

- IO+Chemotherapy improved OS
  in female, never smoker, low PDL1, low TMB

* OS
IO + chemotherapy vs chemotherapy

B

Group	No. of trials	Hazard ratio (95% CI)	P
Overall	17	0.74 (0.69 to 0.79)	<0.001
Histology			
Non squamous	11	0.74 (0.67 to 0.82)	<0.001
Squamous	8	0.71 (0.61 to 0.83)	<0.001
Sex			
Male	12	0.73 (0.66 to 0.80)	<0.001
Female	12	0.68 (0.56 to 0.83)	<0.001
Smoking status			
Never	11	0.73 (0.60 to 0.89)	0.002
Current/former	11	0.73 (0.66 to 0.80)	<0.001
KRAS			
Mutated	4	0.65 (0.53 to 0.78)	<0.001
Wild-type	4	0.85 (0.71 to 1.01)	0.06
STK11			
Mutated	4	0.75 (0.59 to 0.97)	0.03
Wild-type	3	0.76 (0.66 to 0.89)	<0.001
KEAP1			
Mutated	4	0.80 (0.57 to 1.10)	0.17
Wild-type	3	0.75 (0.46 to 1.21)	0.23
PD-L1 expression			
<1%	15	0.76 (0.69 to 0.83)	<0.001
≥1%	10	0.71 (0.65 to 0.78)	<0.001
≥50%	11	0.67 (0.58 to 0.77)	<0.001
TMB			
High	4	0.71 (0.57 to 0.88)	0.002
Low	4	0.73 (0.61 to 0.88)	<0.001



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Today

- Smoking as a risk factor of lung cancer
  - Smoking and oncogenic mutation of lung cancer
- Impact of smoking on treatment outcome in lung cancer patients
  - Targeted therapy
  - Immunotherapy
- **E-cigarette and lung cancer**
- Effect of smoking cessation on lung cancer and mortality

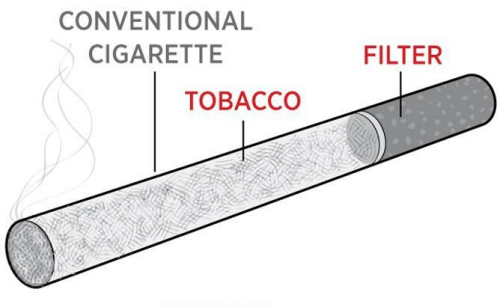
액상형 전자담배

- **니코틴이 들어있는 액상**을 가열(heat)하여
  기화(aerosol)시켜 흡입할 수 있게 하는
  배터리로 작동하는 기구(battery-operated devices).

- Electronic Nicotine Delivery Systems (ENDS)

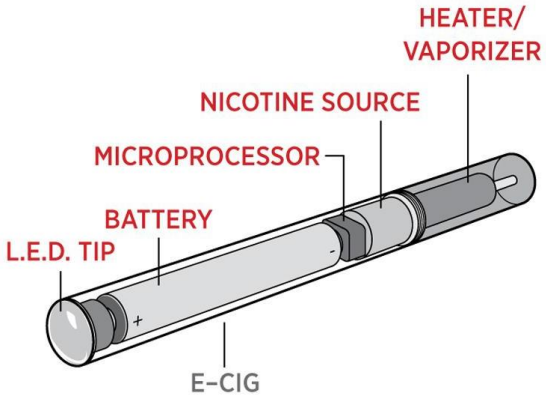
* 참고) 궐련형 전자담배

연초(궐련) vs. 액상형 전자담배 vs. 가열담배



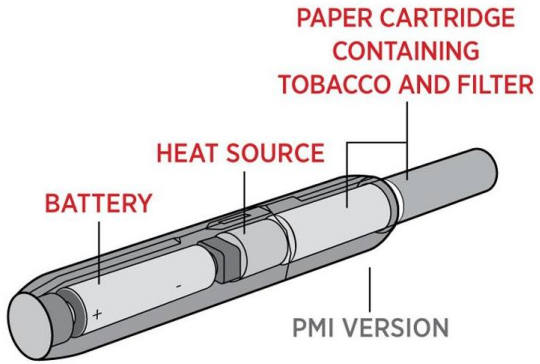
궐련 (Cigarette)

Smoking



액상형 전자담배 (e-Cigarette)

Vapour → Vaping



궐련형 전자담배
➔ 가열담배
= noncombusted cigarette
= Heated tobacco
= Heat-not-burn tobacco

Smoking

E-Cigarettes vs. Nicotine-Replacement Therapy

- 886 adults attending U.K. National Health Service stop-smoking services
- up to 3 months, or an e-cigarette starter pack (2nd G refillable e-cigarette with one bottle of nicotine e-liquid)
  + weekly behavioral support for at least 4 weeks
- primary outcome : sustained abstinence for 1 year (52wks)

* E-Cigarette Group

Vs. Nicotine-Replacement Group

- patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs

- Funded by the National Institute for Health Research and Cancer Research UK

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N Engl J Med 2019;380:629-37

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Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI)†	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46)‡
Secondary outcomes				
Abstinence between wk 26 and wk 52 — no. (%)	93 (21.2)	53 (11.9)	1.79 (1.32–2.44)	1.82 (1.34–2.47)§
Abstinence at 4 wk after target quit date — no. (%)	192 (43.8)	134 (30.0)	1.45 (1.22–1.74)	1.43 (1.20–1.71)¶
Abstinence at 26 wk after target quit date — no. (%)	155 (35.4)	112 (25.1)	1.40 (1.14–1.72)	1.36 (1.15–1.67)‡
Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)	44/345 (12.8)	29/393 (7.4)	1.75 (1.12–2.72)	1.73 (1.11–2.69)‖

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N Engl J Med 2019

액상형 전자담배

- 인체 유해성 vs. 가능성 (존재 이유)

VS.

E-cigarettes and lung cancer

	Clinical studies	Animal studies	Cell line studies
Cancer	N/A	• Tumorigenic transformation in mouse bladder and lung tissues[85] • Increased levels of CYP family genes, activators of PAHs and DNA damage in a rat lung cancer model[25]	• High rates of apoptosis and necrosis in HNSCC cells[82] • Increased expression of double strand DNA break marker γ-H2AX in HNSCC cells[82] • Decreased DNA repair proteins in bronchial epithelial cells[85] • Increase of EMT markers in lung cancer epithelial cells[26] • Increased CSC properties of lung cancer epithelial cells[26]

- Links between electronic cigarette vaping and lung cancer have been found in cell line or animal model

Toxicol Rep 2022

Today

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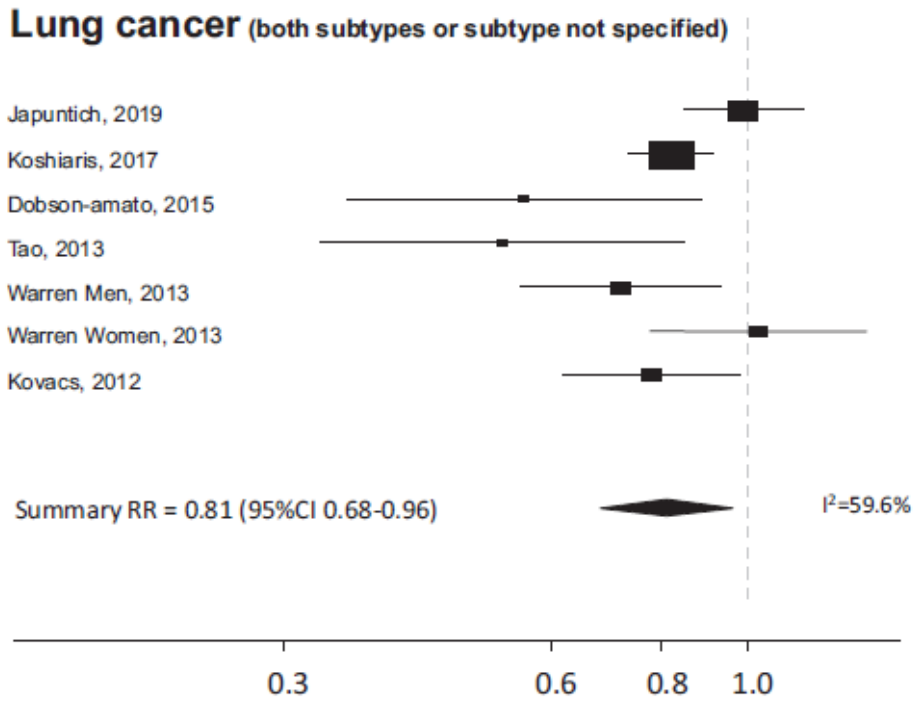
Quitting Smoking At/Around Diagnosis Improves Overall Survival



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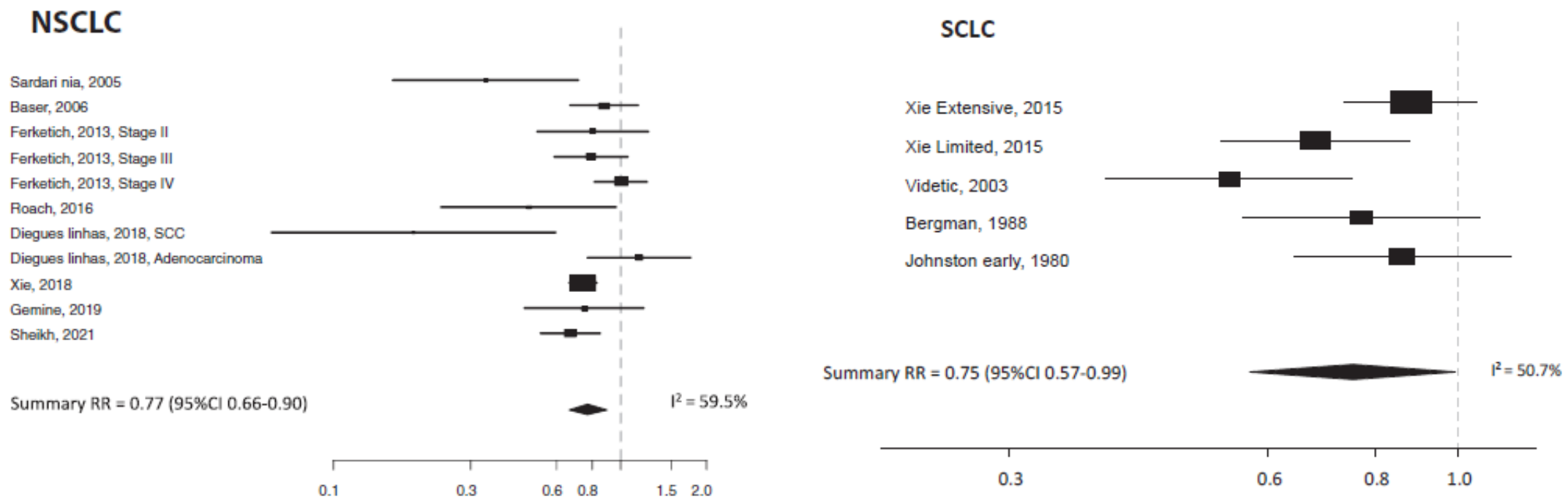
J Thorac Oncol 2022

Quitting Smoking At/Around Diagnosis Improves Overall Survival



- Quitting smoking at/around Dx is associated with a beneficial effect on survival of f LC patients

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J Thorac Oncol 2022

Summary

- Lung cancer (LC) remains a disease with poor prognosis despite recent advances in treatments
- Cigarette smoking is, by far, the most important modifiable risk factor for LC occurrence
- Only, 10–15% of lung cancer patients have never smoked.

- Recently, never smoker lung cancer has become an important issue, though, smoking-related lung cancer is still important.

- Smoking may be associated with certain genomic alterations in lung cancer patients (KRAS) and can have a significant impact on lung cancer treatment outcome.

- The relationship between e-cigarettes and lung cancer needs further research.

- Importantly, smoking is preventable. Thus, efforts to reduce smoking rates can lead to a significant decrease in lung cancer outcome.

Thank you for your attention

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