Early detection
of
Lung cancer

화순전남대병원 호흡기 내과 오형주

Improvement of lung cancer survival

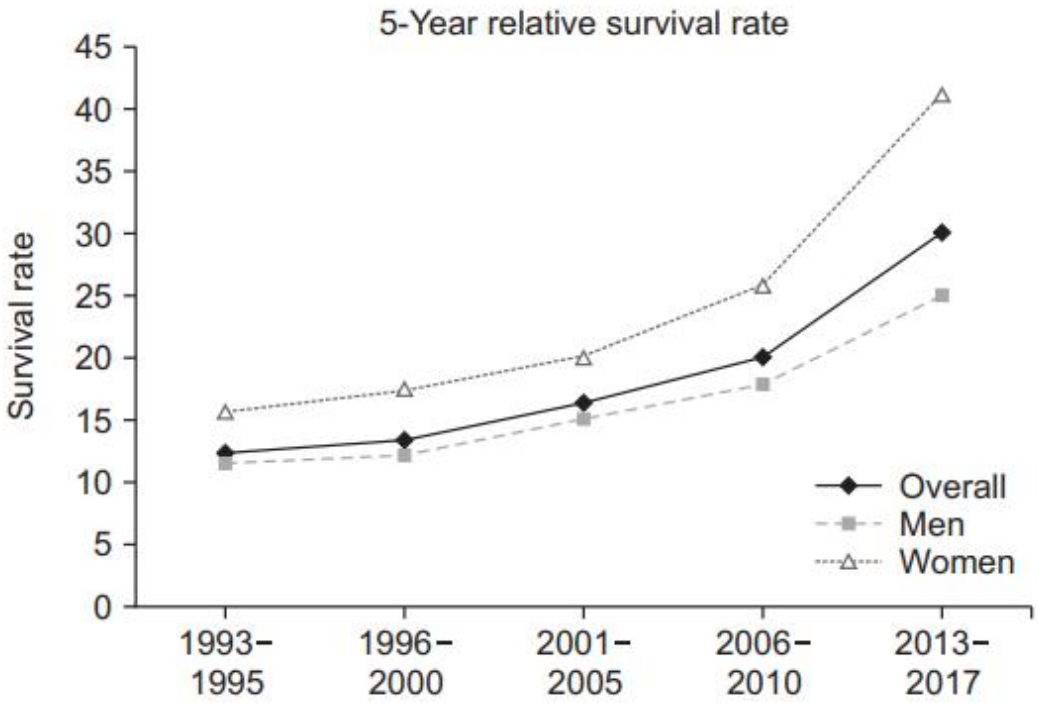
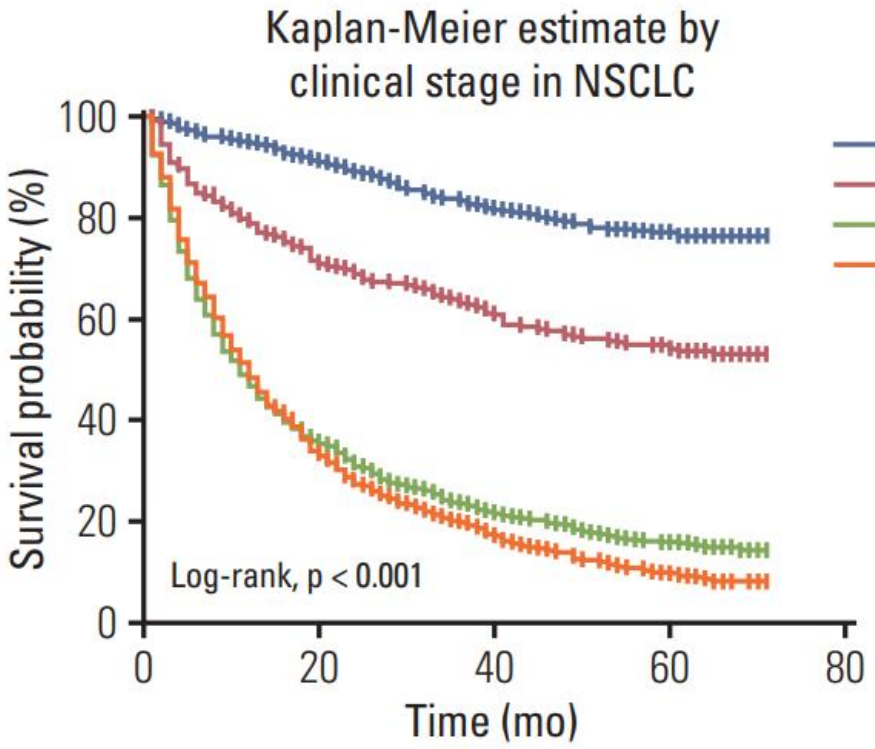


Figure 4. Trend in 5-year relative survival rate of lung cancer in Korea.

- ✓ Sharp decline in tabaco use
- ✓ New treatment in late stage of lung cancer
- ✓ Early cancer detection

Tuberc Respir Dis (Seoul). 2021 Apr;84(2):89-95.

Five-year overall survival of lung cancer by stage



✓ 5-year survival rate

- Stage 1 • 82%
- Stage 2 • 59%
- Stage 3 • 16%
- Stage 4 • 10%

Durvalumab after CCRT (PD-L1>1%, PACIFIC trial)

42.9% vs 33.4%

Pembrolizumab + Ctx

19.4% vs 11.3% in nonSQ NSCLC (Keynote-189)

18.4% vs 9.7% in SQ NSCLC (Keynote-407)

EGFR mutants with TKI

12~14.6% in retrospective data

Overall survival of NSCLC
2,657 patients with lung cancer who were diagnosed in **South Korea in 2015**.

Lancet Reg Health Eur. 2023 Feb 6;27:100592
J Thorac Oncol. 2016 Apr;11(4):556-65.
Cancer Res Treat. 2023;55(1):103-111

Stage Shift Improves Lung Cancer Survival

From 2006 to 2019, a total of 17,298 patients in the National **Taiwan** University Hospital (NTUH) database

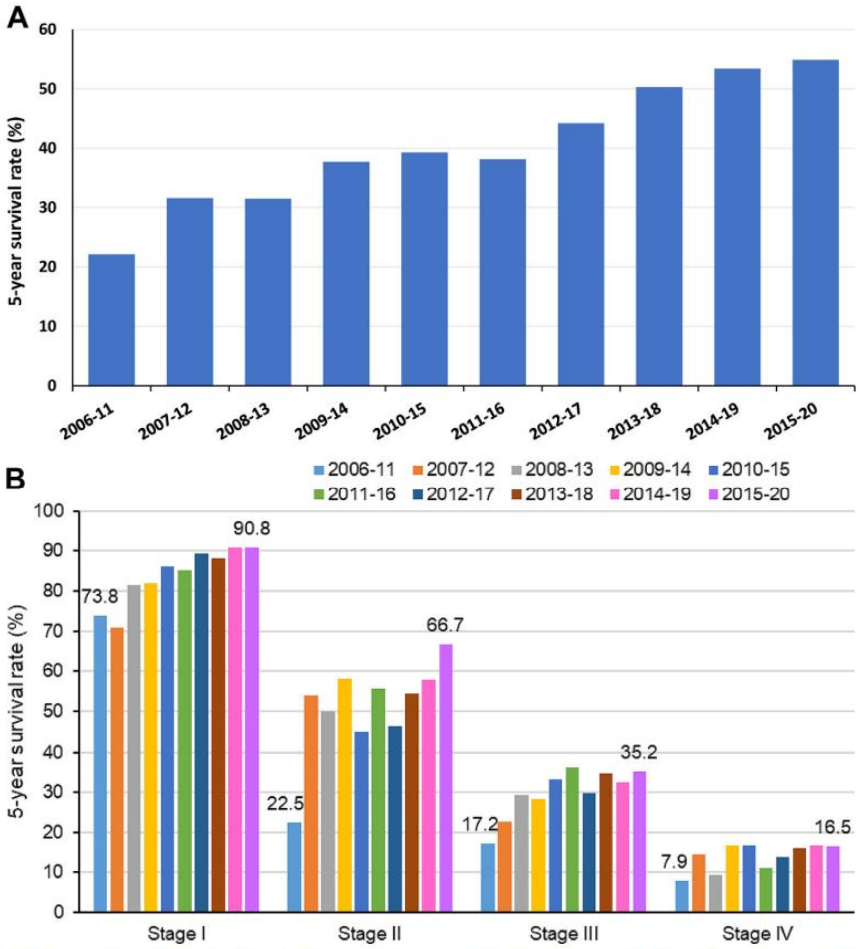


Figure 5. Change in localized (stage 0/I/II) and advanced (stage III/IV) lung cancer from 2006 to 2019 in NTUH.

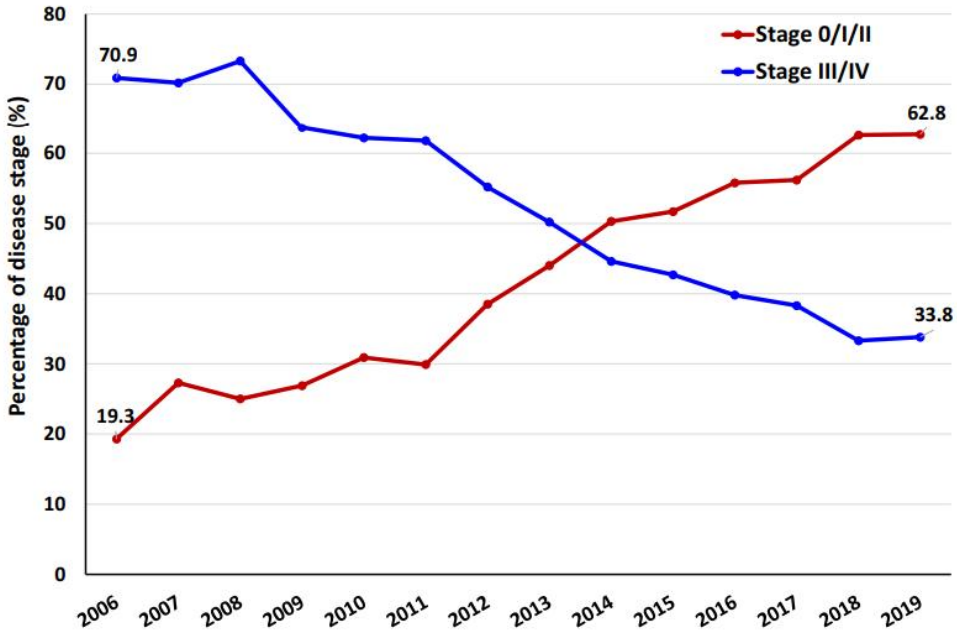


Figure 4. Improvement of 5-year survival rate of lung cancer from 2006 to 2011 to 2015 to 2020 in NTUH.

Journal of Thoracic Oncology, Volume 18, Issue 1,2023,

Stage Shift Improves Lung Cancer Survival

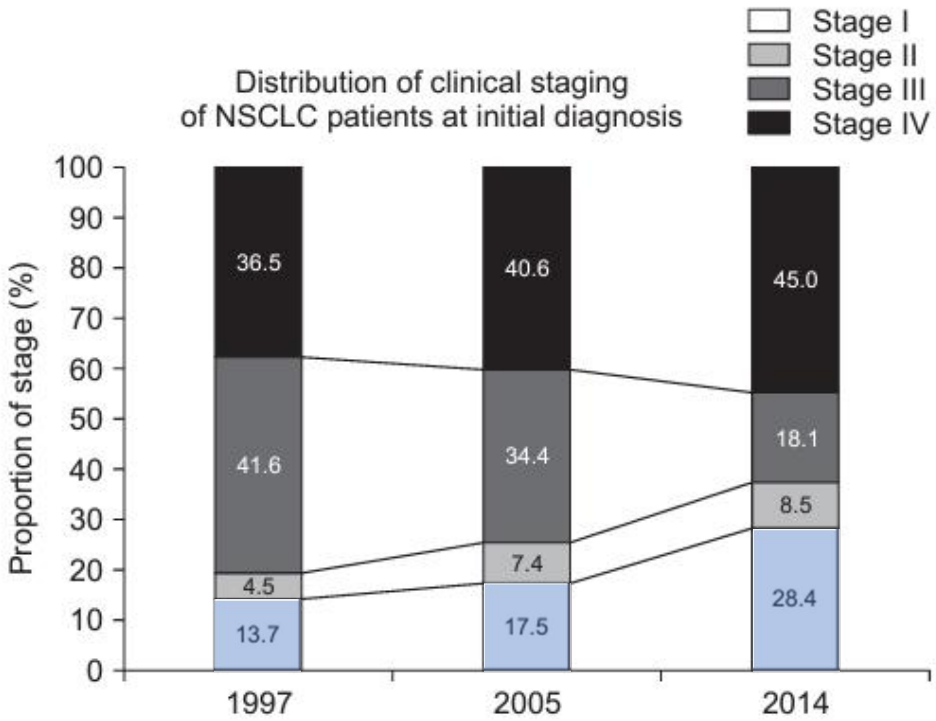
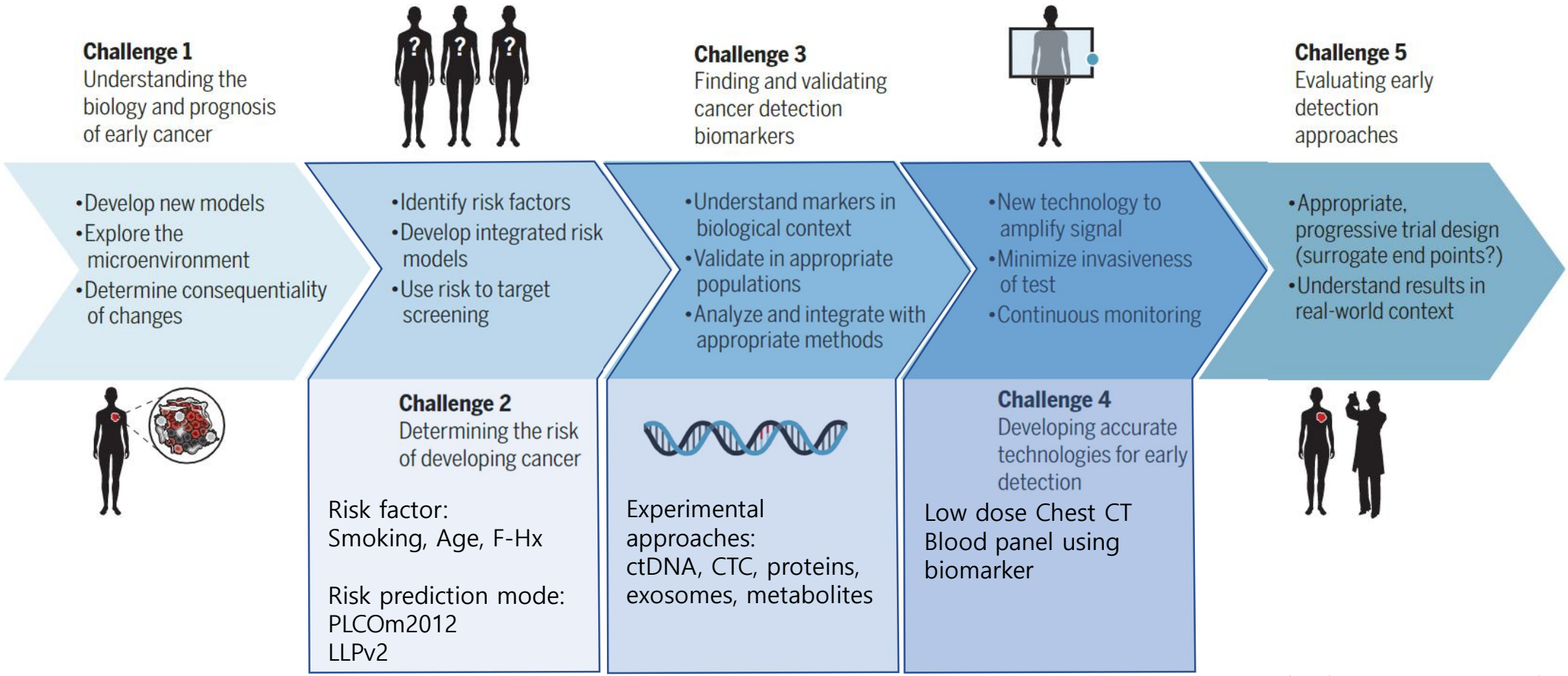


Figure 3. Distribution of clinical staging of non–small cell lung cancer (NSCLC) patients at initial diagnosis.

✓ How can we detect more early lung cancer?

Tuberc Respir Dis (Seoul). 2021 Apr;84(

The early detection of cancer – challenge and ways forward



Crosbyet al.,Science375, 1244 (2022)18 March 2022

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- **Updated biologics & risk factors for lung cancer**
- **Lung cancer prediction model**
- **Biomarkers of lung cancer**

Risk factors of lung cancer: Smoking & Age

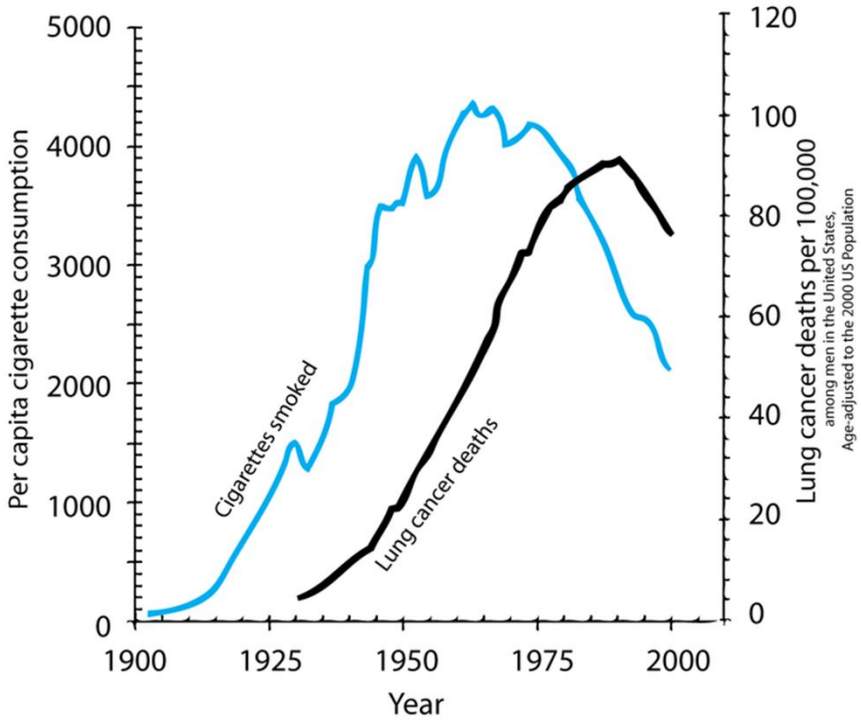


Table 2 Sex-specific pooled relative risks (RR) and ratio of relative risks (RRR) for lung cancer associated with smoking

	RR in women	RR in men	RRR
Age adjusted			
Former versus never	2.82 (2.25 to 3.54)	3.01 (2.23 to 4.08)	0.88 (0.69 to 1.14)
Current versus not	7.48 (5.29 to 10.60)	8.78 (6.13 to 12.57)	0.81 (0.62 to 1.04)
Multiple adjusted			
Former versus never	3.14 (2.45 to 4.03)	3.13 (2.06 to 4.76)	0.89 (0.69 to 1.13)
Current versus not	6.99 (5.09 to 9.59)	7.33 (4.90 to 10.96)	0.92 (0.72 to 1.16)
Maximum adjusted			
Former versus never	2.92 (2.35 to 3.63)	3.08 (2.31 to 4.11)	0.86 (0.71 to 1.05)
Current versus not	7.32 (5.58 to 9.61)	8.05 (5.90 to 10.98)	0.89 (0.73 to 1.08)
Cigarettes per day among current smokers versus never (maximum available adjusted)			
10 or less	5.30 (3.52 to 7.97)	4.97 (2.74 to 9.03)	0.99 (0.65 to 1.52)
10 to 19	10.67 (7.43 to 15.33)	8.93 (4.90 to 16.28)	1.11 (0.75 to 1.64)
20 or more	17.09 (12.11 to 24.11)	14.61 (8.33 to 25.59)	0.94 (0.69 to 1.30)

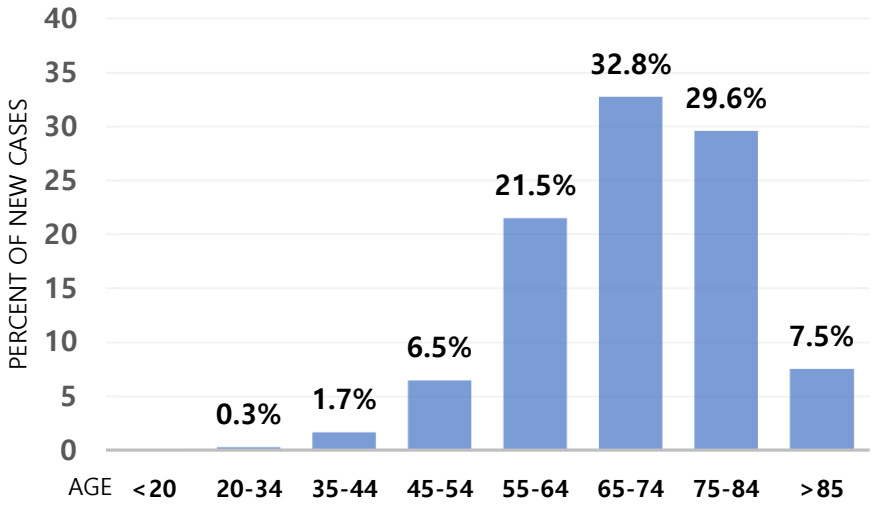
Multiple adjusted includes anything that adjusted for more than just age. Maximum available adjustment refers to the most adjustments provided in the study. For some studies, this would have been age adjusted whereas other studies adjusted for more factors than age only (ie, multiple adjusted). These covariates are listed in table 1.

Meta-analysis of data from 29 studies representing 99 cohort studies, 7 million individuals and >50 000 incident lung cancer cases

Cancer smoking lung cancer correlation from NIH
BMJ Open. 2018 Oct 3;8(10):e021611.

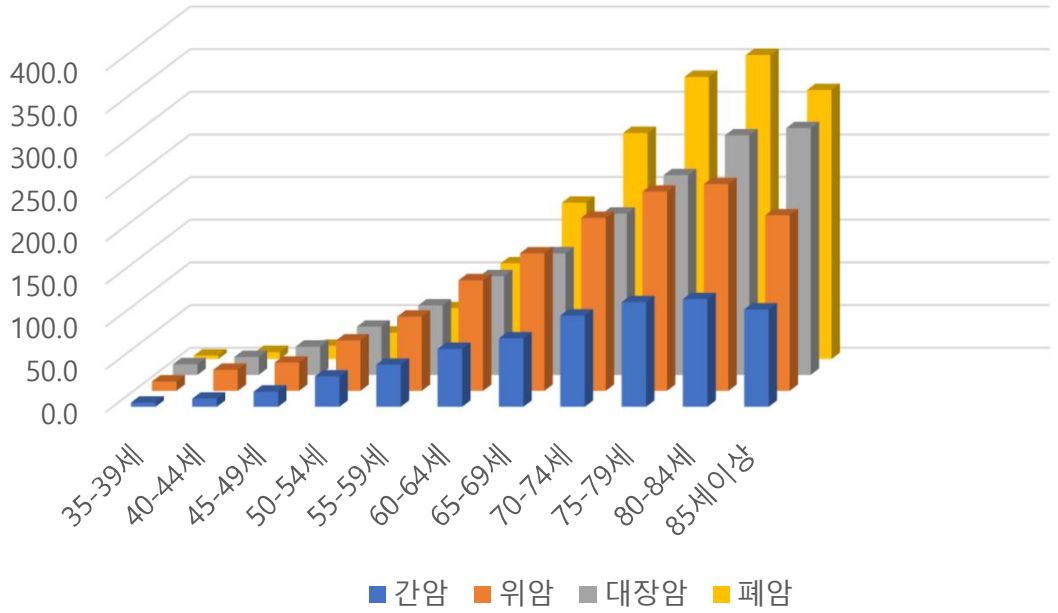
Risk factors of lung cancer: Smoking & Age

폐암 진단 연령



90% case: >50 year-old, Median age at diagnosis: 71

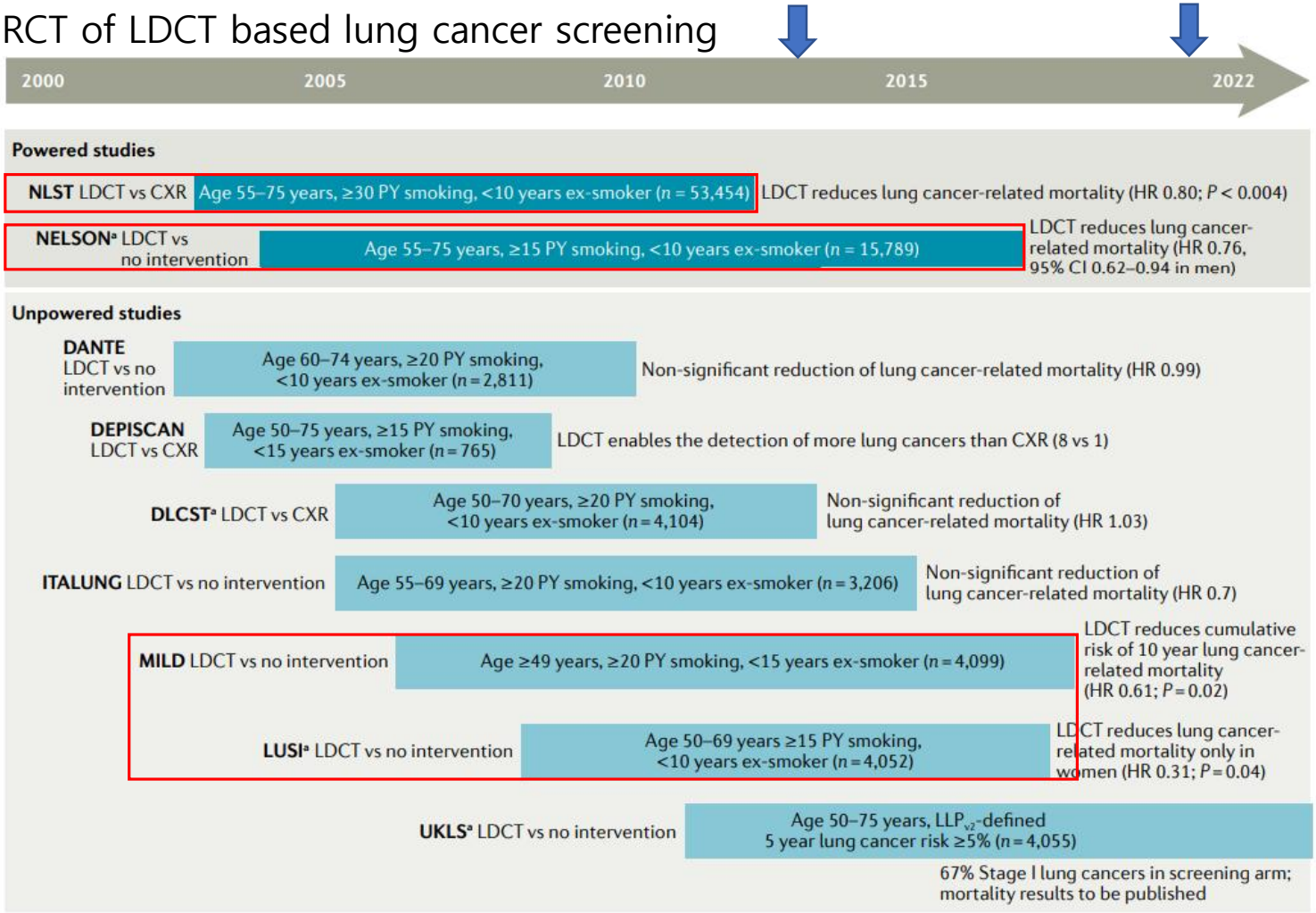
연령병 암 조 발생률



Cancer smoking lung cancer correlation from NIH
국가 통계포털(KOSIS), https://kosis.kr/

Risk factors of lung cancer: Smoking & Age

RCT of LDCT based lung cancer screening



2013 USPSTF

Age 55-80
Smoking ≥30PYS
Quit <15 years

2021 USPSTF

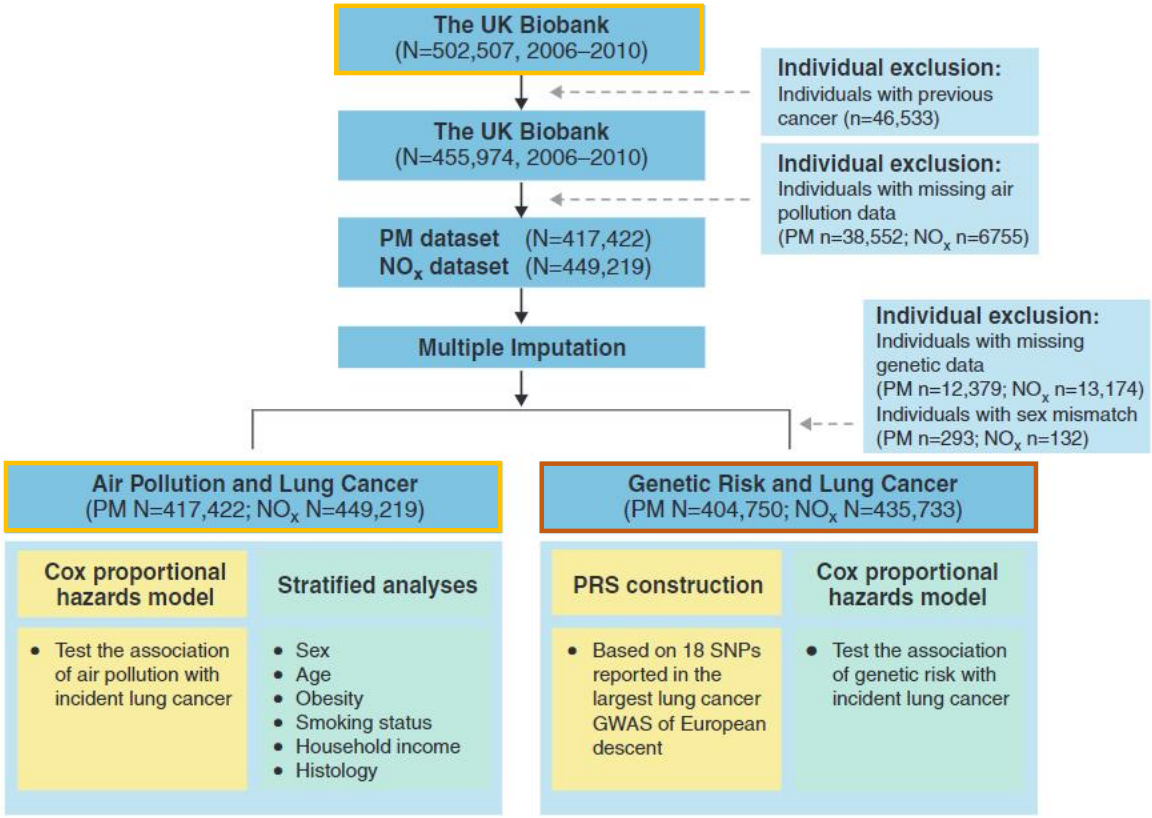
Age **50**-80
Smoking ≥**20**PYS
Quit <15 years

USPSTF: United States Preventive Services Taskforce, 미국예방정책국특별위원회

Nat Rev Clin Oncol. 2021 Mar;18(3):135-151.

Risk factors of lung cancer – Air pollution

UK biobank: more than 500,000 participants, aged 40-69 years from 2006 to 2010
ESCAPE project: Development of Land Use Regression Models for PM2.5, PM10 and PMcoarse in 20 European Study Areas



Study design and workflow. GWAS= genome-wide association study

Table 1. Population Characteristics Included in the Study

Characteristic	PM Data Set ($n = 417,422$)	NO_x Data Set ($n = 449,219$)
Sex, %		
Male	46.8 ($n = 195,366$)	46.7 ($n = 209,741$)
Female	53.2 ($n = 222,056$)	53.3 ($n = 239,478$)
Age, y, mean (SD)	56.2 (8.11)	56.2 (8.10)
Age, %		
<60 y	58.1 ($n = 242,548$)	58.3 ($n = 261,827$)
⩾60 y	41.9 ($n = 174,874$)	41.7 ($n = 187,392$)
BMI, kg/m^2, mean (SD)	27.5 (4.80)	27.4 (4.80)
BMI, %		
Normal (<25 kg/m^2)	32.8 ($n = 136,154$)	32.9 ($n = 146,650$)
Overweight (25–29.9 kg/m^2)	42.6 ($n = 176,787$)	42.6 ($n = 190,259$)
Obesity (⩾30 kg/m^2)	24.6 ($n = 101,869$)	24.5 ($n = 109,573$)
Missing value	2,612	2,737
Education level, %		
Degree level or professional education	47.3 ($n = 193,422$)	47.6 ($n = 209,563$)
Other levels	52.7 ($n = 215,258$)	52.4 ($n = 230,568$)
Missing value	8,742	9,088
Household income, %		
Less than £31,000	47.6 ($n = 168,258$)	47.4 ($n = 180,557$)
£31,000 and above	52.4 ($n = 185,019$)	52.6 ($n = 200,591$)
Missing value	64,145	68,071
Smoking status, %		
Never-smoker	55.1 ($n = 228,851$)	55.2 ($n = 246,664$)
Current or former smoker	44.9 ($n = 186,112$)	44.8 ($n = 199,959$)
Missing value	2,459	2,596
Pack-years of smoking, mean (SD)	8.1 (15.57)	8.1 (15.66)
Missing value	65,091	69,399
Lung cancer cases,%	0.4 ($n = 1,812$)	0.4 ($n = 2,020$)

Definition of abbreviations: BMI = body mass index; NO_x = nitrogen oxides; PM = particulate matter.

Am J Respir Crit Care Med. 2021 Oct 1;204(7):817-825.

Risk factors of lung cancer – Air pollution

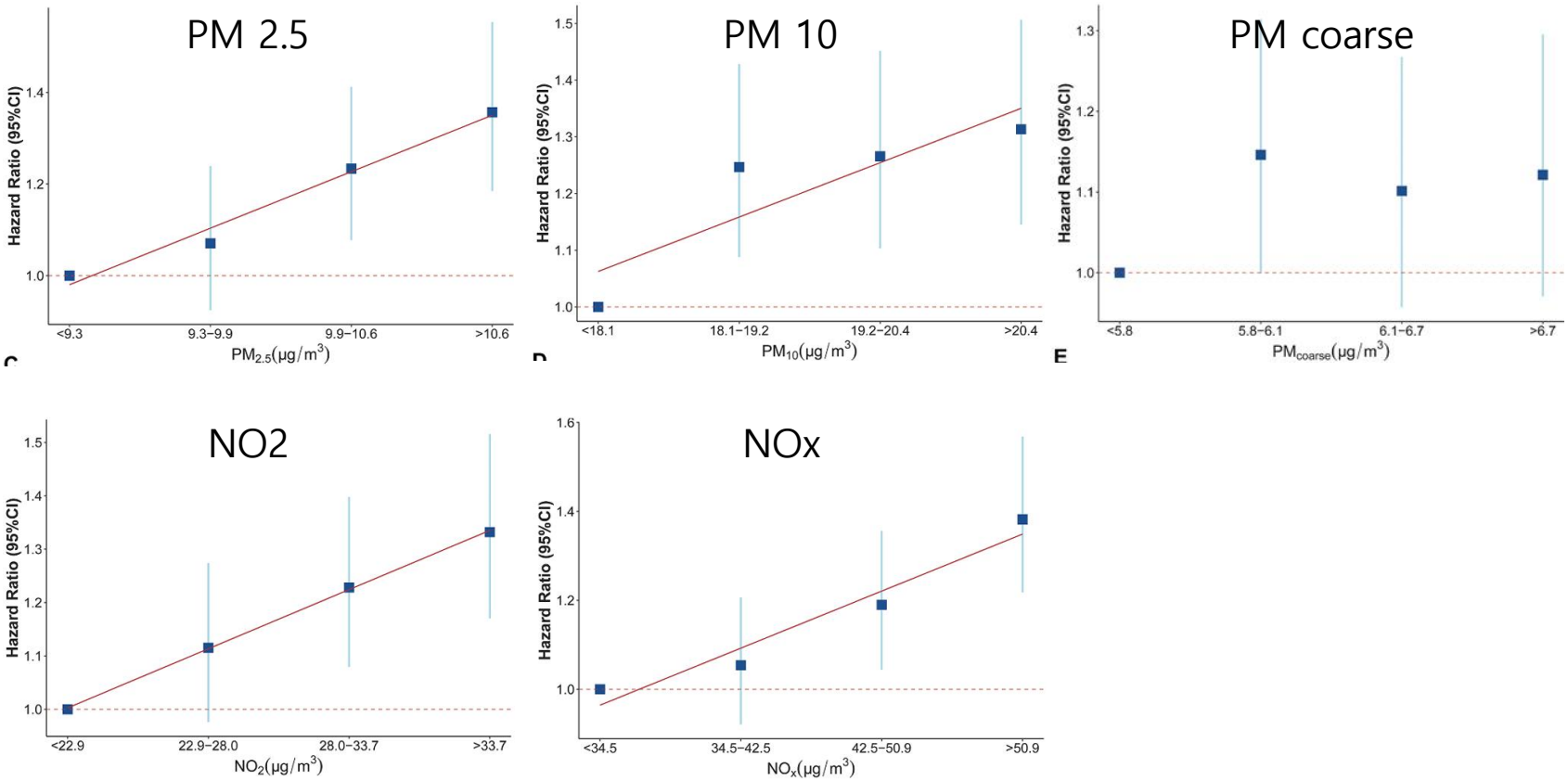


Figure E1. Risk of lung cancer according to quartiles of ambient air pollution exposure

Am J Respir Crit Care Med. 2021 Oct 1;204(7):817-825.

Risk factors of lung cancer – Genomic profile

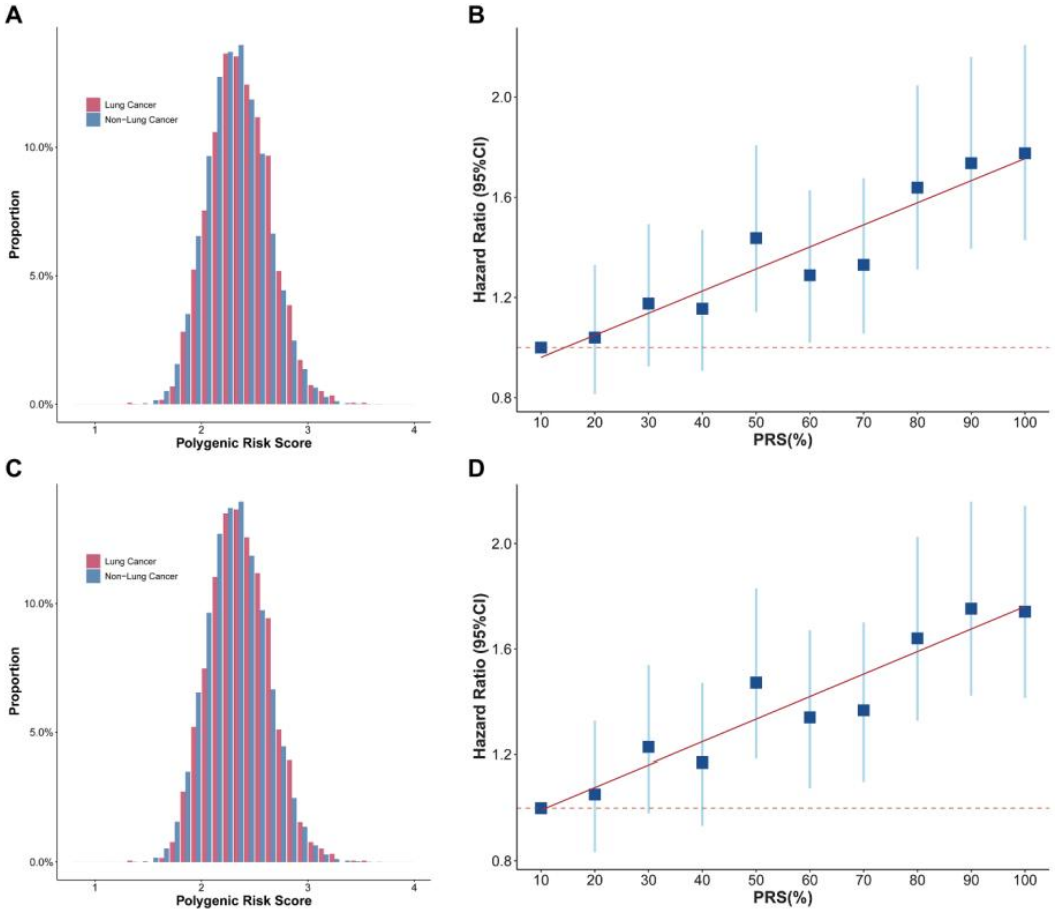
Table E10. Summary results of 18 SNPs used for polygenic risk score in the study of McKay et al. (2017)

No.	Chr.	SNP ID	Position (bp)	Allele A	Allele B	EAF	OR(95%CI)	Beta
1	1	rs71658797	77967507	T	A	0.103	1.14(1.09-1.18)	0.128
2	3	rs13080835	189357199	T	G	0.507	1.06(1.03-1.08)	0.057
3	5	rs7705526	1285974	C	A	0.340	1.12(1.10-1.15)	0.117
4	6	rs116822326	31434111	A	G	0.161	1.15(1.12-1.19)	0.140
5	6	rs6920364	167376466	G	C	0.456	1.07(1.05-1.10)	0.068
6	8	rs11780471	27344719	A	G	0.940	1.15(1.10-1.21)	0.141
7	8	rs4236709	32410110	A	G	0.216	1.07(1.04-1.10)	0.064
8	9	rs885518	21830157	A	G	0.103	1.09(1.05-1.13)	0.088
9	10	rs11591710	105687632	A	C	0.137	1.07(1.04-1.11)	0.070
10	11	rs1056562	118125625	C	T	0.476	1.07(1.04-1.09)	0.066
11	12	rs7953330	998819	C	G	0.688	1.09(1.06-1.12)	0.087
12	13	rs11571833	32972626	A	T	0.011	1.50(1.24-1.82)	0.472
13	15	rs55781567	78857986	C	G	0.367	1.30(1.27-1.33)	0.260
14	15	rs77468143	49376624	G	T	0.746	1.09(1.06-1.12)	0.083
15	15	rs66759488	47577451	G	A	0.362	1.07(1.04-1.10)	0.068
16	19	rs56113850	41353107	T	C	0.560	1.13(1.10-1.16)	0.123
17	20	rs41309931	62326579	G	T	0.115	1.08(1.04-1.12)	0.081
18	22	rs17879961	29121087	G	A	0.006	1.66(1.42-1.94)	0.506

Definition of abbreviations: SNP, single nucleotide polymorphism; EAF, effect allele frequency; OR, odds ratio; CI, confidence interval.

Polygenic risk score (PRS) = $\sum j\ M = 1\ \beta j \times SNPj$

Figure E2. Distribution of polygenic risk score and association of PRS with incident lung cancer



Am J Respir Crit Care Med. 2021 Oct 1;204(7):817-825.

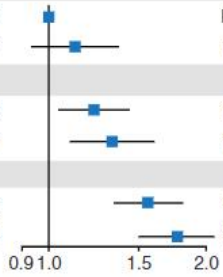
Risk factors of lung cancer – Air pollution & Genomic profile

A:$PM_{2.5}$

Subgroup	No.of Events/ Total No.	Incidence/ 100,000 person-yr	Hazard Ratio (95% CI)	*P* Value
Low Genetic Risk				
Low $PM_{2.5}$ pollution	229/71,660	45.72	Reference	Reference
High $PM_{2.5}$ pollution	225/63,143	50.63	0.99 (0.82–1.19)	0.892
Intermediate Genetic Risk				
Low $PM_{2.5}$ pollution	237/71,644	47.30	1.03 (0.86–1.23)	0.769
High $PM_{2.5}$ pollution	318/63,237	71.53	1.38 (1.16–1.63)	2.50×10^{-4}
High Genetic Risk				
Low $PM_{2.5}$ pollution	320/72,144	63.42	1.36 (1.14–1.61)	4.35×10^{-4}
High $PM_{2.5}$ pollution	409/62,922	92.25	1.71 (1.45–2.02)	1.28×10^{-10}

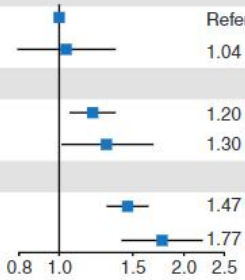
B:PM_{10}

Subgroup	No.of Events/ Total No.	Incidence/ 100,000 person-yr	Hazard Ratio (95% CI)	*P* Value
Low Genetic Risk				
Low PM_{10} pollution	297/91,463	45.95	Reference	Reference
High PM_{10} pollution	157/43,340	52.52	1.13 (0.93–1.38)	0.207
Intermediate Genetic Risk				
Low PM_{10} pollution	372/91,952	57.29	1.23 (1.05–1.43)	0.009
High PM_{10} pollution	183/42,929	61.77	1.34 (1.11–1.61)	0.002
High Genetic Risk				
Low PM_{10} pollution	472/92,511	72.19	1.53 (1.32–1.77)	8.88×10^{-9}
High PM_{10} pollution	257/42,555	87.38	1.77 (1.50–2.10)	3.92×10^{-11}



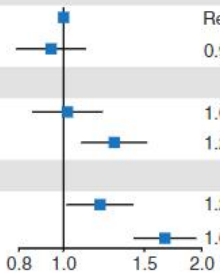
C:NO_2

Subgroup	No.of Events/ Total No.	Incidence/ 100,000 person-yr	Hazard Ratio (95% CI)	*P* Value
Low Genetic Risk				
Low NO_2 pollution	461/129,301	50.20	Reference	Reference
High NO_2 pollution	54/15,813	51.05	1.04 (0.78–1.38)	0.789
Intermediate Genetic Risk				
Low NO_2 pollution	556/129,378	60.53	1.20 (1.06–1.35)	0.005
High NO_2 pollution	67/15,841	63.18	1.30 (1.01–1.69)	0.045
High Genetic Risk				
Low NO_2 pollution	705/130,285	76.12	1.47 (1.31–1.66)	1.40×10^{-10}
High NO_2 pollution	98/15,115	96.92	1.77 (1.42–2.22)	6.55×10^{-7}



D:NO_x

Subgroup	No.of Events/ Total No.	Incidence/ 100,000 person-yr	Hazard Ratio (95% CI)	*P* Value
Low Genetic Risk				
Low NO_x pollution	252/72,284	49.32	Reference	Reference
High NO_x pollution	263/72,830	51.25	0.94 (0.79–1.12)	0.471
Intermediate Genetic Risk				
Low NO_x pollution	258/72,301	50.47	1.02 (0.86–1.21)	0.819
High NO_x pollution	365/72,918	71.09	1.29 (1.10–1.52)	0.002
High Genetic Risk				
Low NO_x pollution	311/73,234	60.04	1.20 (1.01–1.41)	0.034
High NO_x pollution	492/72,166	96.60	1.67 (1.43–1.95)	5.84×10^{-11}



Am J Respir Crit Care Med. 2021 Oct 1;204(7):817-825.

Risk factors of lung cancer – Air pollution & Genomic profile

‡Defined by WHO guideline value of $PM_{2.5}$: low (<10 $\mu g/m^3$) and high (≥10 $\mu g/m^3$).
§Defined by WHO guideline value of PM_{10}: low (<20 $\mu g/m^3$) and high (≥20 $\mu g/m^3$).
‖Defined by WHO guideline value of NO_2: low (<40 $\mu g/m^3$) and high (≥40 $\mu g/m^3$).
¶Defined by the median of NO_x: low (<42.39 $\mu g/m^3$) and high (≥42.39 $\mu g/m^3$).

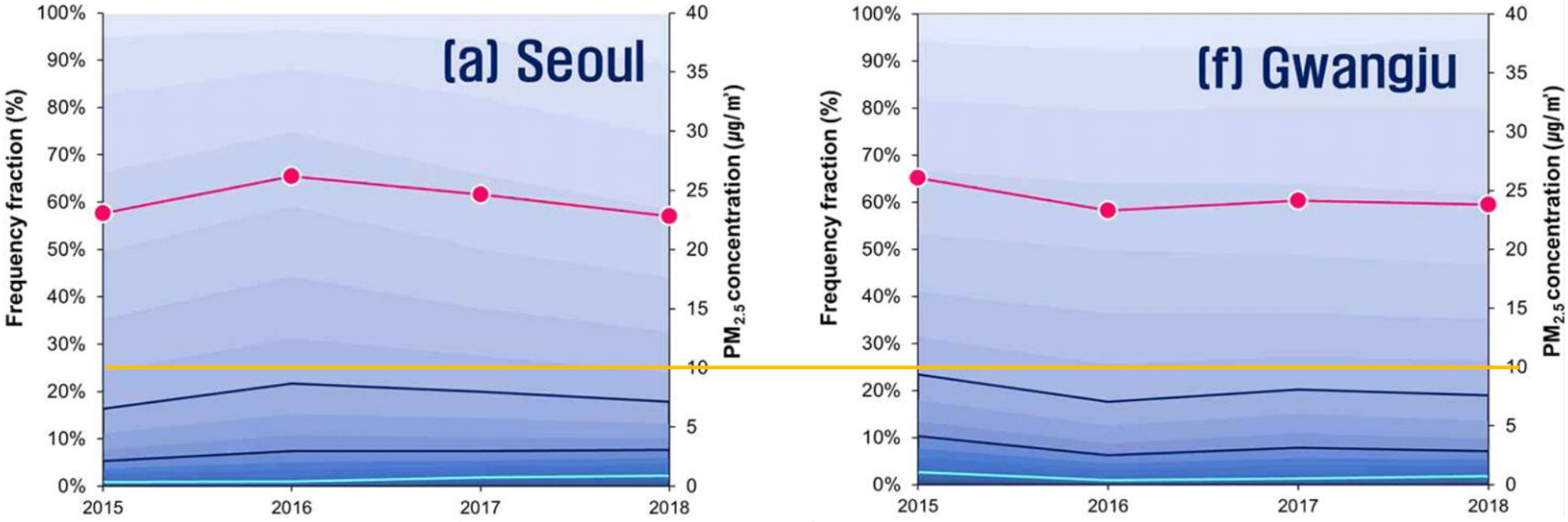


Fig. 1. Annual mean $PM_{2.5}$ concentration (first bold line with circle markers) and annual $PM_{2.5}$ frequency fraction by the concentration level in each region, respectively (second and third bold lines (dark), and fourth line (light) for $PM_{2.5}$: 〉 35, 〉 50, and 〉 75 ㎍/㎥) (raw data: KECO, 2019).

Particle and Aerosol Research Part. Aerosol Res. Vol. 15, No. 2: June 2019 pp. 45-56

Risk factors of lung cancer – Indoor air pollution

Biobank recruited 512,715 adults aged 30–79 years from 10 regions in China during 2004–2008. Self-reported never-smoking participants (N=323,794) were followed up to December 31, 2016

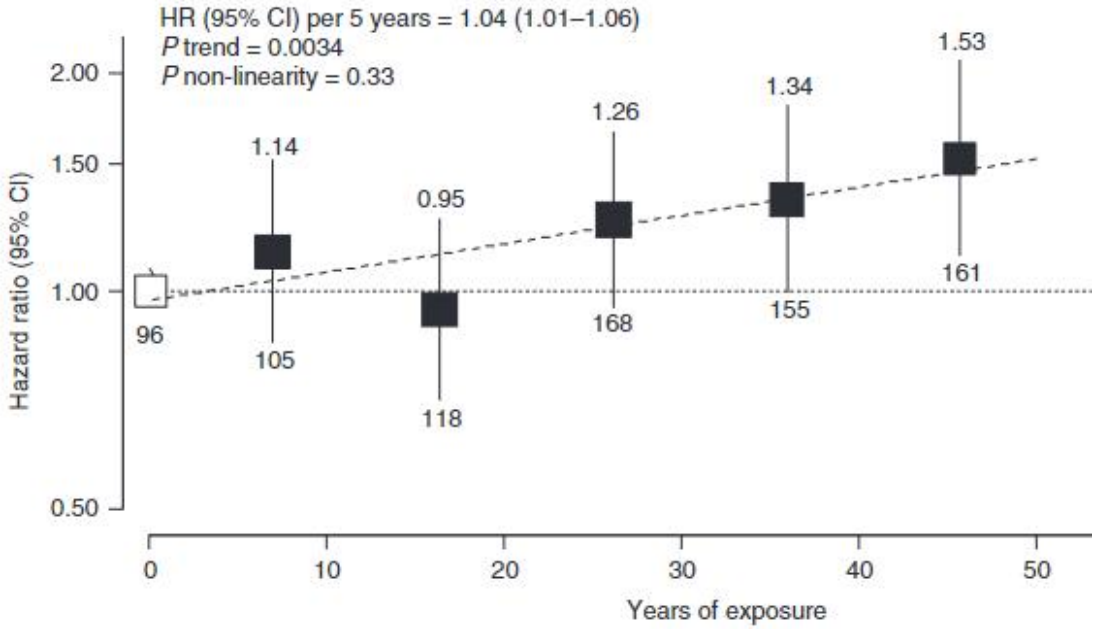
Characteristics	All Participants (*n* = 323,794)	Exposure to Household Air Pollution			Exposure to Secondhand Tobacco Smoke		
		Never Exposed (*n* = 49,236)	Ever Exposed (*n* = 274,558)	*P* Value*	Never Exposed (*n* = 29,245)	Ever Exposed (*n* = 294,549)	*P* Value*
Proportion of all participants, %	100	15.2	84.8	—	9.0	91.0	—
Mean age at baseline (SD), yr	51.5 (10.6)	48.9 (10.5)	51.9 (10.5)	<0.0001	55.0 (11.2)	51.1 (10.4)	<0.0001
Mean height at baseline (SD), cm	155.5 (6.9)	157.6 (6.9)	155.1 (6.9)	<0.0001	156.6 (7.6)	155.4 (6.9)	<0.0001
Women, %	88.7	78.0	90.7	<0.0001	80.6	89.5	<0.0001
Rural, %	54.0	27.7	58.7	<0.0001	34.2	55.9	<0.0001
Primary school or lower, %	53.4	33.0	57.1	<0.0001	49.0	53.8	<0.0001
Agricultural or factory worker, %	51.1	34.2	54.2	<0.0001	35.8	52.7	<0.0001
No ventilation in all three residences, %	14.1	3.9	15.9	<0.0001	9.0	14.6	<0.0001
Use of lard, soybean, or rapeseed cooking oil in all three residences, %	22.3	5.6	25.3	<0.0001	17.6	22.8	<0.0001
Normal BMI (22.0–25.0 kg/m^2)†, %	38.4	41.1	38.0	<0.0001	36.7	38.6	<0.0001
Mean BMI (SD), kg/m^2	23.8 (3.4)	23.6 (3.2)	23.9 (3.5)	<0.0001	23.9 (3.5)	23.8 (3.4)	<0.0001
Mean physical activity (SD), MET-h/d	20.5 (13.0)	21.2 (13.8)	20.4 (12.9)	<0.0001	18.1 (13.0)	20.7 (13.0)	<0.0001
Mean cooking solid fuel use (SD), years	16.3 (15.4)	0	19.3 (15.0)	<0.0001	11.9 (15.4)	16.8 (15.4)	<0.0001
Mean slow-burning stove smoky coal use (SD), years	1.5 (5.4)	0	1.7 (5.8)	<0.0001	1.3 (5.4)	1.5 (5.4)	<0.0001
Mean coal-smoky home in winter (SD), years	6.6 (8.1)	0	7.8 (8.2)	<0.0001	6.3 (9.5)	6.7 (8.0)	<0.0001
Ever lived with a person who smoked at home for ≥6 mo, %	79.6	65.7	82.1	<0.0001	0	87.5	<0.0001

*Household air pollution: self-reported domestic solid fuel use

Am J Respir Crit Care Med. 2022 Nov 1;206(9):1153-1162.

Risk factors of lung cancer – Indoor air pollution

Biobank recruited 512,715 adults aged 30–79 years from 10 regions in China during 2004–2008.
Self-reported never-smoking participants (N=323,794) were followed up to December 31, 2016

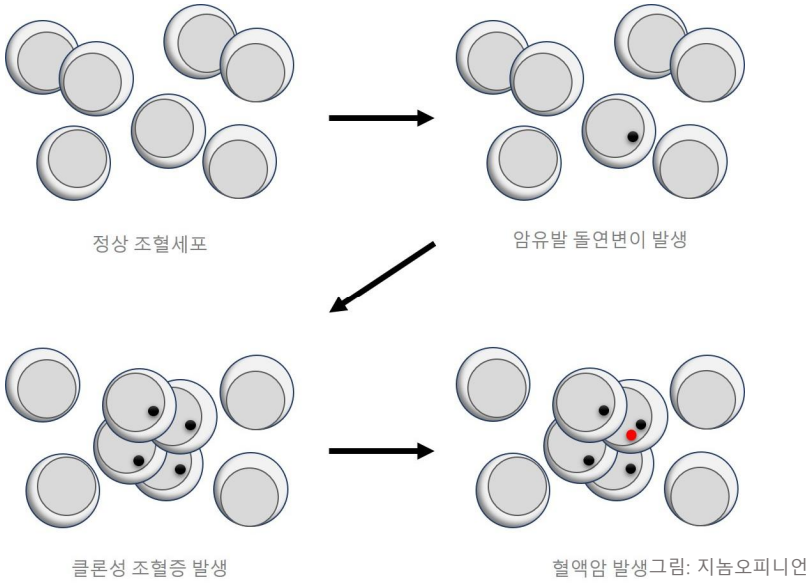


Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancerdeaths among never-smokers by years of exposure to household air pollution in China KadoorieBiobank
HRs were calculated from multivariable analyses

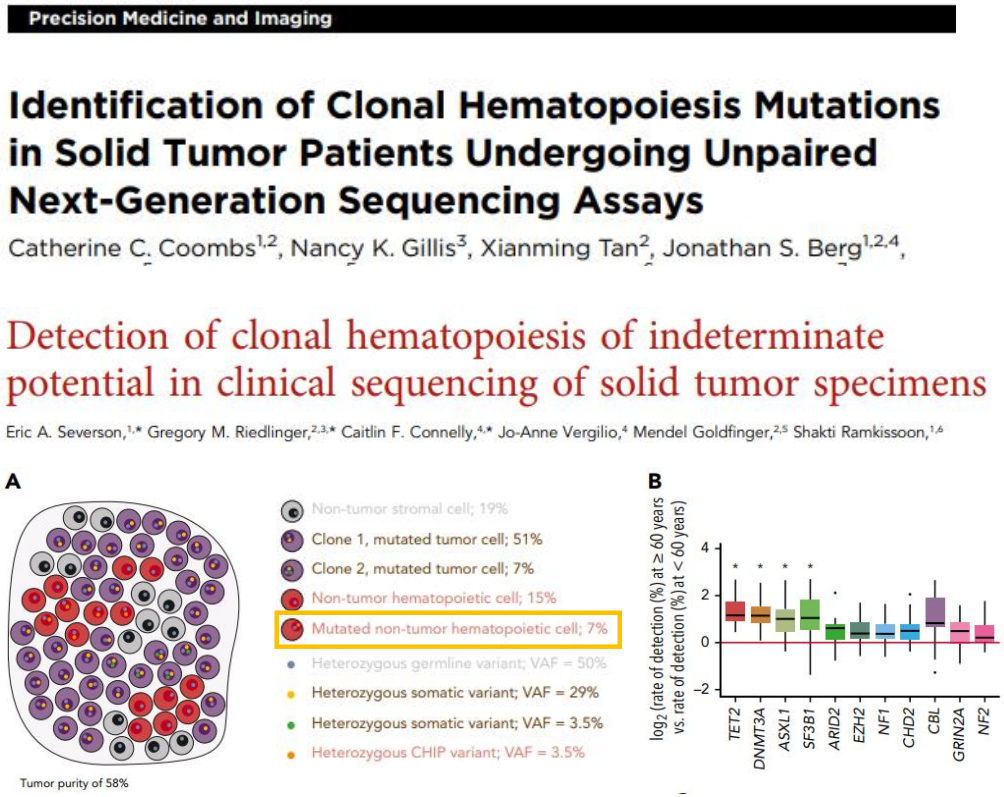
Am J Respir Crit Care Med. 2022 Nov 1;206(9):1153-1162.

Risk factors of lung cancer – Clonal hematopoiesis

Clonal hematopoiesis



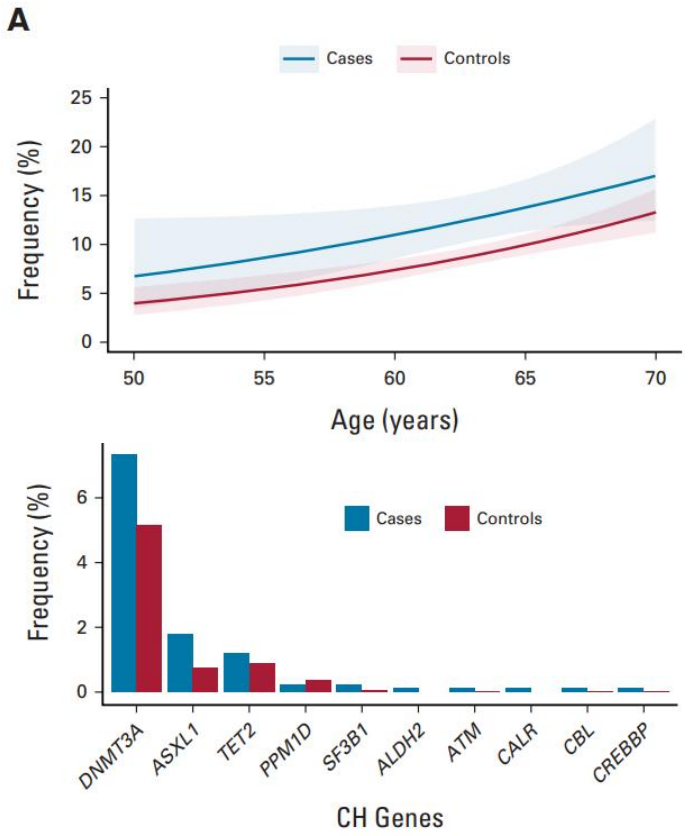
- Often involve genes implicated in hematologic malignancies such as DNMT3A, TET2, and ASXL1
- May have role of inflammatory elements in the tumor microenvironment and cancer pathogenesis



Blood. 2018 May 31;131(22):2501-2505
Clin Cancer Res. 2018 Dec 1;24(23):5918-5924.

Risk factors of lung cancer – Clonal hematopoiesis

UKBB: population-based prospective study of more than half a million participants, **between 2006 and 2010**
Whole-exome sequencing from blood
Lung cancer case: cancer registries and death records provided by the National Health Service Information Centre and the National Health Service Central Register (**July 31, 2019**),



Characteristic	Lung Cancer Status: Cases (n = 832)	Lung Cancer Status: Controls (n = 3,951)
Matching factors		
Age at baseline, years, mean ± SD	61.9 ± 6.20	61.6 ± 6.26
Time from blood draw to diagnosis/index date, years, median (IQR)	6.0 (3.4-8.0)	6.0 (3.4-8.0)
Male, No. (%)	442 (53.1)	2,090 (52.9)
Race, No. (%)		
White	796 (95.7)	3,776 (95.6)
Others	36 (4.3)	175 (4.4)
Smoking status, No. (%)		
Never	121 (14.5)	604 (15.3)
Past	391 (47.0)	1,886 (47.7)
Current	320 (38.5)	1,461 (37.0)
CH status		
Carrier, No. (%)	104 (12.5)	343 (8.7)
1 mutation, No. (%)	97 (93.3)	325 (94.8)
≥ 2 mutations, No. (%)	7 (6.7)	18 (5.2)
VAF, %, mean ± SD	12.1 ± 8.70	11.9 ± 9.62
2% to < 10%, No. (%)	52 (50.0)	199 (58.0)
≥ 10%, No. (%)	52 (50.0)	144 (42.0)

CH carriers: individuals containing one or more of a prespecified list of CH variants with a VAF > 2%

J Clin Oncol. 2023 Mar 1;41(7):1423-1433.

Risk factors of lung cancer – Clonal hematopoiesis

UKBB: population-based prospective study of more than half a million participants, **between 2006 and 2010**
Whole-exome sequencing from blood
Lung cancer case: cancer registries and death records provided by the National Health Service Information Centre and the National Health Service Central Register (**July 31, 2019**),

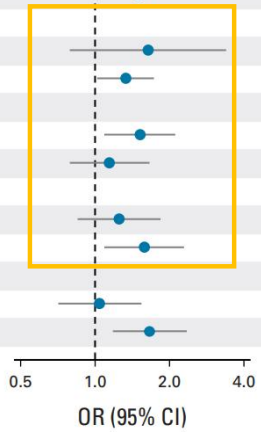
TABLE 2. CH and Risk of Incident Lung Cancer Overall and According to VAF, UK Biobank

Participant	CH Carrier	2% to < 10%
All participants		
No. of cases (%)/controls (%)	104 (12.5)/343 (8.7)	52 (6.3)/199 (5.0)
MV-adjusted OR (95% CI)[a]	1.49 (1.18 to 1.88)	1.28 (0.93 to 1.76)
MV-adjusted OR (95% CI)[b]	1.36 (1.06 to 1.74)	1.17 (0.84 to 1.63)
MV-adjusted OR (95% CI)[c]	1.43 (1.06 to 1.94)	1.19 (0.79 to 1.80)
Participants without history of COPD at/before blood draw[d]		
No. of cases (%)/controls (%)	94 (12.5)/327 (8.6)	49 (6.5)/190 (5.0)
MV-adjusted OR (95% CI)[a]	1.52 (1.19 to 1.94)	1.36 (0.98 to 1.89)
MV-adjusted OR (95% CI)[b]	1.39 (1.07 to 1.79)	1.21 (0.86 to 1.71)

Abbreviations: CH, clonal hematopoiesis; COPD, chronic obstructive pulmonary disease; MV, multivariable; OR, odds
variant allele frequency.
[a]Adjusted for matching factors: age and year at blood draw, sex (female/male), race (White/others), and smoking
[b]Additionally adjusted for pack-years of smoking (continuous), family history of lung cancer (no/yes), and the first 10 prin
[c]Additionally adjusted for COPD at/before blood draw, Forced expiratory volume in 1 second, PRS, and C-reactive
controls. For PRS-related analyses, we have also excluded one individual from each pair of first-degree (or higher) relative
[d]Excluded 216 participants (80 cases and 136 controls) with history of COPD at/before blood draw.

FIG 2. CH and risk of incident lung cancer according to (A) lung cancer risk factors

Subgroup	CH Carrier No. of Cases (%)/Controls (%)	OR (95% CI)	*P* Interaction
Sex			.88
Female	42 (10.8)/153 (8.2)	1.31 (0.90 to 1.91)	
Male	62 (14.0)/190 (9.1)	1.40 (1.01 to 1.95)	
Family history of lung cancer			.88
No	79 (12.0)/289 (8.5)	1.34 (1.01 to 1.77)	
Yes	25 (14.5)/54 (10.0)	1.52 (0.87 to 2.64)	
Smoking status			.84
Never	11 (9.1)/35 (5.8)	1.64 (0.79 to 3.39)	
Past/current	93 (13.1)/308 (9.2)	1.33 (1.02 to 1.73)	
Age at blood draw, years			.58
< 65	59 (11.2)/178 (7.0)	1.52 (1.09 to 2.11)	
≥ 65	45 (14.8)/165 (11.8)	1.14 (0.79 to 1.66)	
PRS			.27
Low (Q1-Q3)	39 (11.4)/178 (8.7)	1.25 (0.85 to 1.84)	
High (Q4-Q5)	52 (13.9)/123 (9.0)	1.58 (1.09 to 2.29)	
CRP			.86
Low (Q1-Q3)	39 (10.4)/200 (8.9)	1.04 (0.71 to 1.54)	
High (Q4-Q5)	62 (14.7)/129 (8.6)	1.66 (1.18 to 2.35)	



J Clin Oncol. 2023 Mar 1;41(7):1423-1433.

Risk factors of lung cancer

Chronic inflammation
- Chronic obstructive pulmonary disease: independent of smoking
- Asthma in never smoker: relative risk of 1.8 (95%CI 1.3-2.3)
- Pulmonary tuberculosis: relative risk of 1.5

Occupational exposure
- Asbestos
- Silica
- Metal: Chromium, Nickel etc

Eur Respir J. 2016 Sep;48(3):889-902.

Contents

- Updated biologic & risk factors for lung cancer
- Lung cancer prediction model
- Biomarkers of lung cancer

Categorical model vs Quantified risk model – ILST

Prospective cohort study, **I**nternational **L**ung **S**creening **T**rial: USPSTF2013 versus PLCOm2012

4 countries (Canada, Australia, UK, Hong Kong), 9 sites

CLINICAL STUDY DESIGN

Protocol and Rationale for the International Lung Screening Trial

Inclusion criteria:

- Age 55 to 80 years
- ECOG performance status 0 or 1
- Current or former* smoker
- Capable of providing consent for LDCT
- **$PLCO_{m2012}$ 6-year risk score ≥ 1.51%**

OR

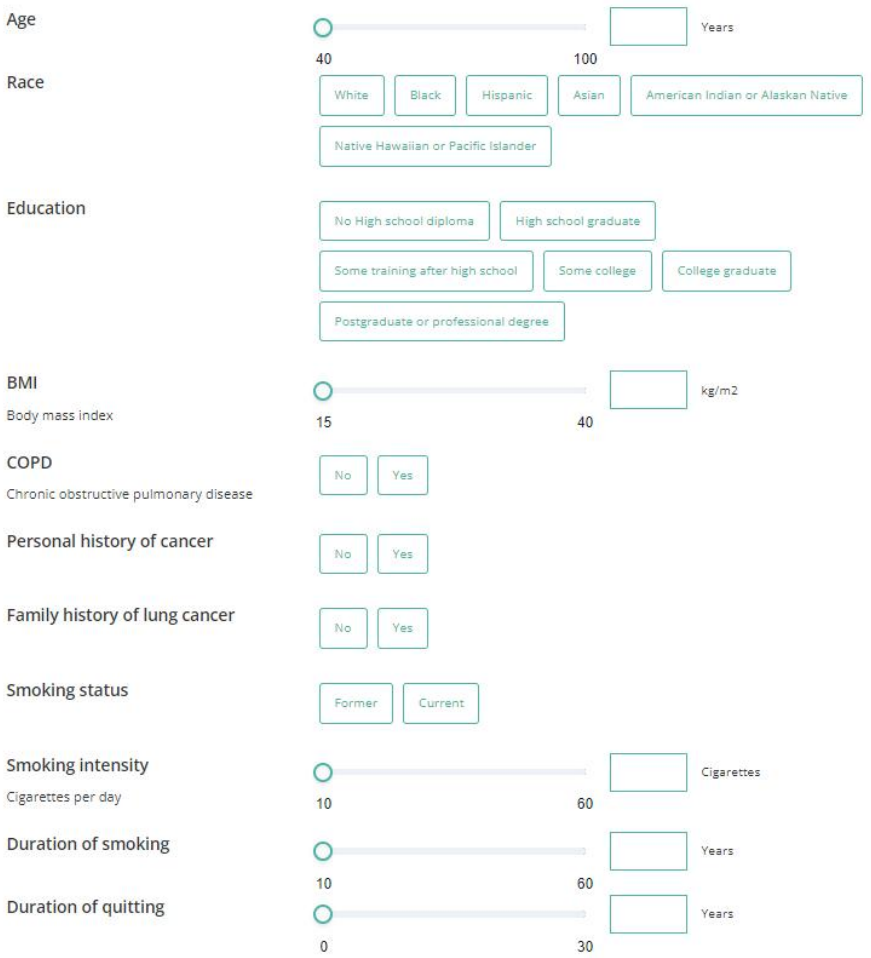
USPSTF screening criteria (≥ 30 pack-years smoking history and quit ≤ 15 years ago)**

*** USPSTF2013 Criteria**

Lancet Oncol. 2022 Jan;23(1):138-148.

Categorical model vs Quantified risk model

PLCOm2012 – Risk prediction model



ORIGINAL ARTICLE

Selection Criteria for Lung-Cancer Screening

Martin C. Tammemägi, Ph.D., Hormuzd A. Katki, Ph.D., William G. Hocking, M.D.,

Table 4. Accuracy of Lung-Cancer Classification According to Alternative Criteria in the PLCO Intervention-Group Smokers.*

Criteria†	Participants with Lung Cancer (N=678)	Participants without Lung Cancer (N=36,654)	Total Participants (N=37,332)	Predictive Value
NLST				
Criteria positive	482 TP (3.4%)	13,662 FP (96.6%)	14,144	PPV, 3.4%
Criteria negative	196 FN (0.8%)	22,992 TN (99.2%)	23,188	NPV, 99.2%
Sensitivity	71.1%			
Specificity		62.7%		
$PLCO_{M2012}$ ‡				
Criteria positive	563 TP (4.0%)	13,581 FP (96%)	14,144	PPV, 4.0%
Criteria negative	115 FN (0.5%)	23,073 TN (99.5%)	23,188	NPV, 99.5%
Sensitivity	83.0%			
Specificity		62.9%		

* FN denotes false negative, FP false positive, NPV negative predictive value, PPV positive predictive value, TN true negative, and TP true positive.
† NLST criteria for study entry included a history of cigarette smoking of at least 30 pack-years and, for former smokers, cessation within the previous 15 years.
‡ According to the $PLCO_{M2012}$ criteria, positivity was defined as a probability of lung cancer that was greater than 1.3455% over a period of 6 years.

N Engl J Med 2013;368:728-36
https://www.evidencio.com/models/show/992

Categorical model vs Quantified risk model – ILST

Prospective cohort study, International Lung Screening Trial: USPSTF2013 versus PLCOm2012

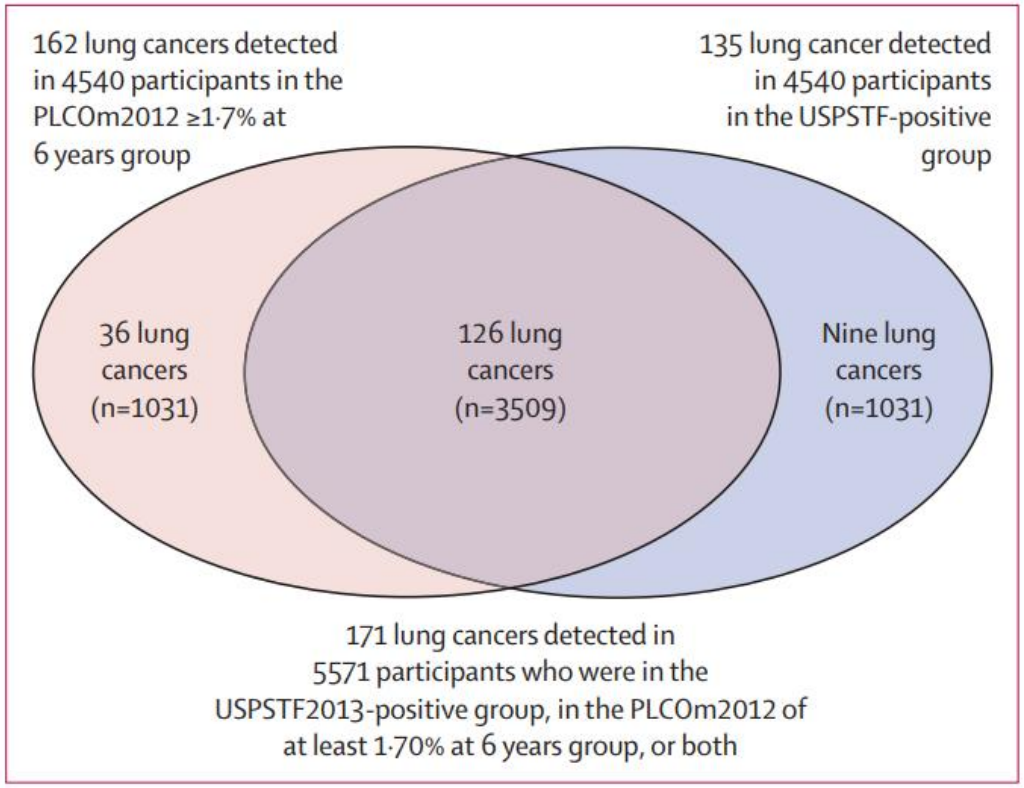


Figure: **Venn diagram describing the distribution of individuals and lung cancer cases by criteria (USPSTF2013 positivity and PLCOm2012 ≥1·7% at 6 years status)**

27 (15·8% [95% CI 10·7–22·1%]; p<0·0001) of 171 more lung cancers were detected by PLCOm2012 than USPSTF criteria. The figure excludes six lung cancers detected in 248 individuals who were USPSTF-negative but were enrolled because they had PLCOm2012 risks at least 1·5% at 6 years and less than 1·70% at 6 years.

Lancet Oncol. 2022 Jan;23(1):138-148.

Categorical model vs Quantified risk model

Prospective cohort study, International Lung Screening Trial: USPSTF2013 versus PLCOm2012

Study Participant Characteristics

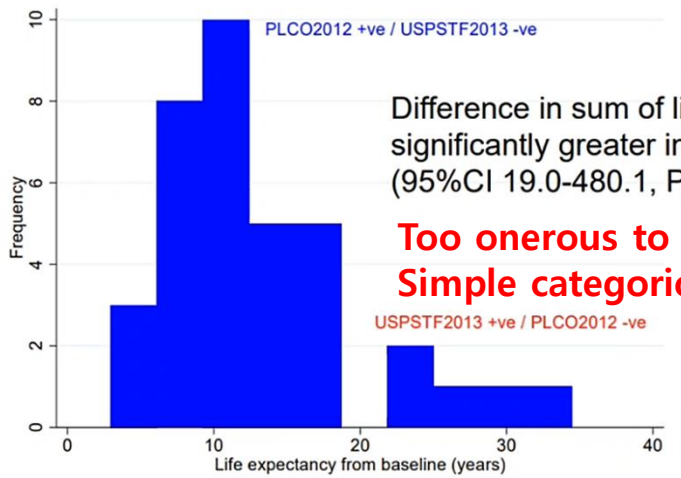
Characteristic	USPSTF2013 Eligible N = 4540	PLCOm2012 ≥1.70%/6y N = 4540	P-value*	Total Sample N = 5819
Sociodemographic				
Age	63.27 (SD 5.65) R55-80	65.68 (SD 5.90) R55-80	$P_{t\text{-}test} < 0.0001$	64.45 (SD 6.15) R55-80
Sex				
Female	2046 (45.1%) [3.13%]	2112 (46.5%) [4.02%]		2717 (46.7%) [3.31%]
Male	2494 (54.9%) [2.45%]	2428 (53.5%) [2.72%]	$P_{exact} = 0.165$	3102 (53.3%) [2.45%]
Education				
Highschool completed or less	2111 (46.5%) [3.60%]	2329 (51.3%) [4.25%]		2707 (46.5%) [3.8%]
Beyond high school	2428 (53.5%) [2.02%]	2211 (48.7%) [2.35%]	$P_{exact} < 0.0001$	3111 (53.5%) [2.03%]
Medical History				
Body mass index (kg/m²)	27.56 (SD 5.29)	26.88 (SD 4.82)	$P_{t\text{-}test} < 0.0001$	27.34 (SD 5.17)
COPD				
No	3469 (76.4%) [2.54%]	3233 (71.2%) [3.28%]		4413 (75.8%) [2.74%]
Yes	1071 (23.6%) [3.45%]	1307 (28.8%) [3.44%]	$P_{exact} < 0.0001$	1406 (24.2%) [3.20%]
Personal history of lung cancer				
No	3062 (89.9%) [2.38%]	2864 (85.3%) [2.97%]		3826 (87.7%) [2.48%]
Yes	342 (10.0%) [2.05%]	492 (14.7%) [2.03%%]	$P_{exact} < 0.0001$	539 (12.3%) [2.04%]
Family history of lung cancer				
No	3550 (78.2%) [2.59%]	3230 (71.1%) [3.28%]		4349 (74.7%) [2.69%]
Yes	990 (21.8%) [3.33%]	1310 (28.9%) [3.44%]	$P_{exact} < 0.0001$	1470 (25.3%) [3.33%]
Comorbidity count ‡ 25th, 50th (median), 75th percentile	0.5, 1, 2	1, 2, 3	$P_{nptrend} < 0.0001$	1, 1, 2

→ Life expectancy 14.8 years 13.9 years

Weibull survival model estimated

Results

Figure. Representative histograms of baseline life-expectancy by PLCOm2012+/ USPSTF- vs USPSTF+/PLCOm2012- in those who develop lung cancer in 6 years of follow-up.



p=0.012). **Conclusion:** In this prospective, multinational, population-based study, the PLCOm2012 approach selects significantly more individuals diagnosed with lung cancer. In spite of selecting individuals who were older and had more comorbidities, the overall weighted balance of life years potentially liveable if lung cancer deaths were averted significantly favours using the PLCOm2012 criteria. **Keywords:**

2021 WCLC, OA19.01, Journal of Thoracic Oncology 16.10 (2021): S881.

Categorical model vs Quantified risk model

Prospective cohort study, International Lung Screening Trial: USPSTF2013 versus PLCOm2012

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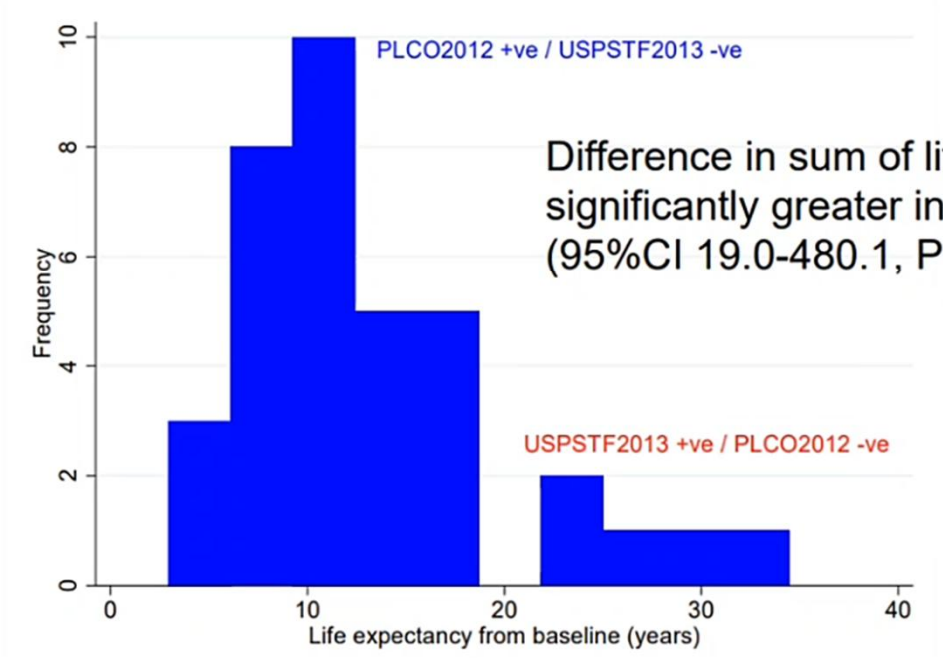


Difference in sum of life expectancy = 247.9 years, significantly greater in PLCOm2012 +ve (95%CI 19.0-480.1, P=0.015).

p=0.012). **Conclusion:** In this prospective, multinational, population-based study, the PLCOm2012 approach selects significantly more individuals diagnosed with lung cancer. In spite of selecting individuals who were older and had more comorbidities, the overall weighted balance of life years potentially liveable if lung cancer deaths were averted significantly favours using the PLCOm2012 criteria. **Keywords:**

Too onerous to implement,
Simple categorical approach is better?

2021 WCLC, OA19.01, Journal of Thoracic Oncology 16.10 (2021): S881

TALENT: Taiwan lung cancer screening for **never smoker** Trial

- From Feb 2015 to Jul 2019
- Prospective, multi center study (17 centers)
- Inclusion criteria
  - 55- 75 years #
  - Never smoker or have less than 10PYS and quitted over 15years
  - **One** of the following risks
    - Family history of lung cancer within third-degree
    - Environmental smoking exposure
    - Chronic lung disease: Tb/COPD
    - Cooking index >110 *
    - Not using ventilator during cooking
  - Negative CXR

Subjects who have family history of lung cancer and were older than index case in family can be recruited in even they are less than 55 years-old

***Index of cooking**=
2/7 x (days of using saute, fry, or deep-fried a week) x (cooking years)

소테(프랑스어: sauté, sautér, 영어: sautéing, sauteing):
아주 센불에서 소량의 기름으로 단시간에 조리하는 기술을 의미하는 용어

TALENT: Taiwan lung cancer screening for never smoker Trial

Table 1. Characteristics of the subjects and first round (T0) results of TALENT study

Characteristic	Number	%
All participants	12,011	100
Sex		
Male	3,143	26.2
Female	8,868	73.8
Age	61.2±6.2yr*	
Male	61.6±6.4yr	
Female	61.1±6.2yr	
Risk factor**		
With family history of lung cancer	6,012	50.1
Without family history of lung cancer	5,999	49.9
Environmental smoking exposure	9,923	82.6
TB/COPD	1,142	9.5
Cooking index≧110	4,395	36.6
Cooking without ventilator	211	1.8

TALENT: Taiwan lung cancer screening for **never smoker** Trial

Table 1. Characteristics of the subjects and first round (T0) results of TALENT study

Characteristic	Number	%
LDCT positive lung nodule***	2,094	17.4
Invasive procedure for lung nodule	392	3.3
Histologic diagnosis		
Adenocarcinoma in situ	57	
Minimally invasive adenocarcinoma	71	
Invasive adenocarcinoma	182	
Adenosquamous carcinoma	1	
Benign lung lesion	77	
Other malignancy	4	
Lung cancer detection rate	311	2.6
Subjects with family history	192	3.2
1st degree	185/5586	3.3
2nd degree	6/367	1.6
3rd degree	1/59	1.7
Subjects without family history	119	2.0

*** Solid or part-solid nodule ≥ 6mm, GGN ≥ 5mm
GGO 47%, Solid 19% Part-solid 34%

NLST: 1.1%, NELSON: 0.9%

96.5% stage 1

3.2%(**192**/6012) vs 2.0%(**119**/5999)
***p*<0.001**

WCLC 2020 ARCHIVE JAN 27, 2021

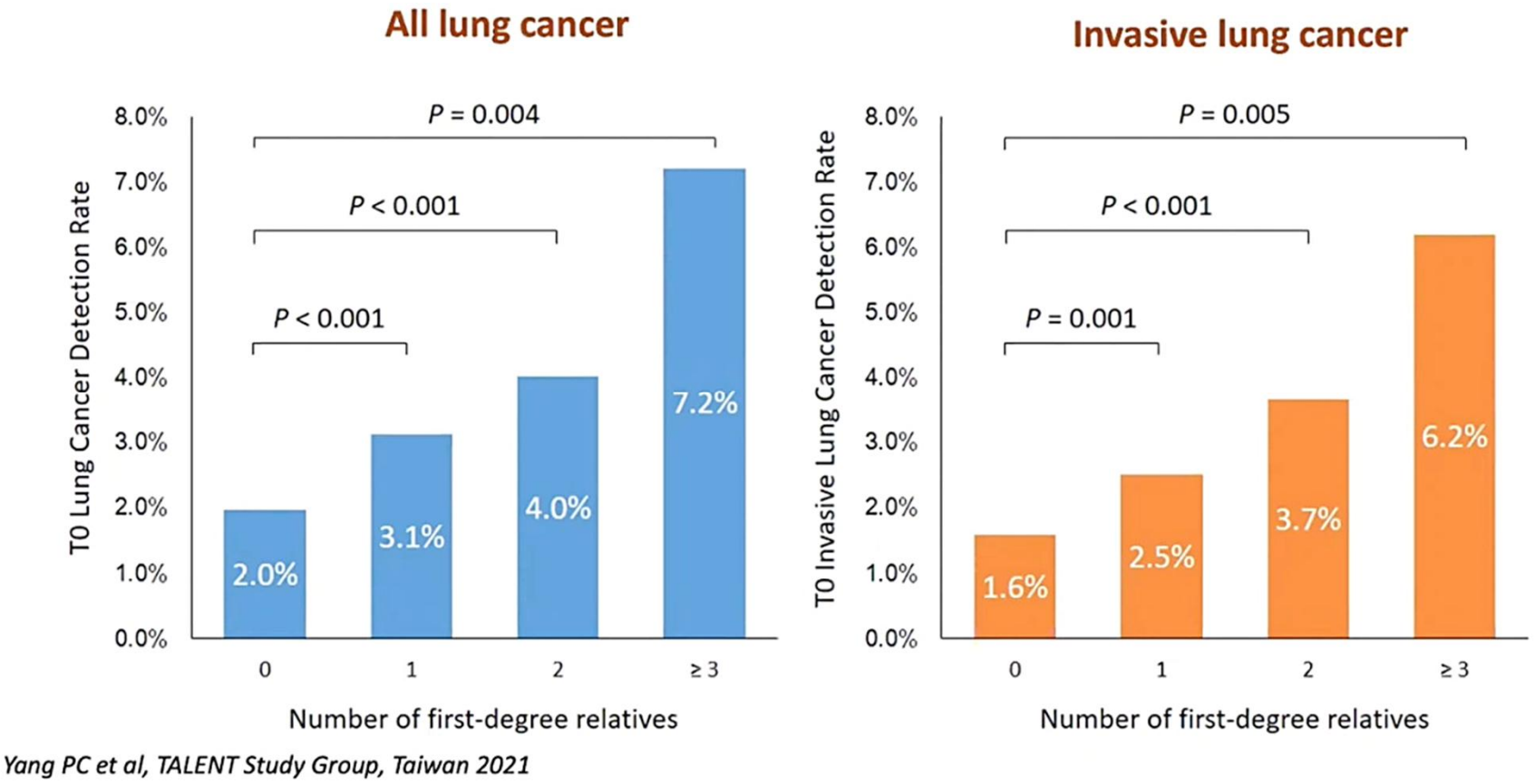
TALENT: Taiwan lung cancer screening for **never smoker** Trial

Prevalence of Lung Cancer in Different Subpopulations

	Absence		Presence		R.R. (95% CI)		p
	n	%	n	%			
Lung cancer family history	**120/6002**	**2.0**	**193/6009**	**3.2**	**1.61**	**(1.28—2.01)**	**< 0.001**
First-degree family	**127/6432**	**2.0**	**186/5579**	**3.3**	**1.69**	**(1.35—2.11)**	**< 0.001**
Father	281/10377	2.7	32/1634	2.0	0.72	(0.50—1.04)	0.077
Mother	**251/10241**	**2.5**	**62/1770**	**3.5**	**1.43**	**(1.09—1.88)**	**0.010**
Brother	**260/10901**	**2.4**	**53/1110**	**4.8**	**2.00**	**(1.50—2.67)**	**< 0.001**
Sister	**244/10367**	**2.4**	**69/1644**	**4.2**	**1.78**	**(1.37—2.32)**	**< 0.001**
Second degree family	307/11645	2.6	6/366	1.6	0.62	(0.28—1.39)	0.238
Third degree family	312/11947	2.6	1/64	1.6	0.60	(0.09—4.20)	1.000
Environmental tobacco exposure	53/1999	2.7	254/9923	2.6	0.97	(0.72—1.29)	0.813
Chronic lung disease history	284/10568	2.7	19/1142	1.7	0.62	(0.39—0.98)	0.038
Cooking index ≥110	209/7591	2.8	104/4395	2.4	0.86	(0.68—1.08)	0.201
Cooking without ventilation	306/11800	2.6	7/211	3.3	1.28	(0.61—2.67)	0.513

Yang PC et al, TALENT Study Group, Taiwan 2021

TALENT: Taiwan lung cancer screening for **never smoker** Trial



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TALENT: Taiwan lung cancer screening for **never smoker** Trial

TALENT vs Other LDCT Lung Cancer Screening Studies

	TALENT			NLST[1]	NELSON[2]	UKLS-pilot[3]	I-ELCAP[4]
	w/ FH	w/o FH	ALL	LDCT arm	LDCT arm	LDCT arm	ALL
Population	Never or light ex- smoker[5]			Smoker	Smoker	Smoker[6]	Mixed[7]
Patient number	6009	6002	12011	26309	7557	1994	31567
LDCT positive rate	17.7%	17.1%	17.4%	27.3%	20.8%[8]	13.3%	26.9%
T0 LC detection rate	**3.2%**	**2.0%**	**2.6%**	**1.1%**	**0.9%**	**1.7%**	**1.1%**
Sensitivity	91.7%	92.5%	92.0%	93.8%	94.6%	97.6%	98.8%
Specificity	84.7%	84.4%	84.6%	73.4%	98.3%	74.6%	87.9%
PPV	**16.6%**	**10.8%**	**13.8%**	3.8%	35.7%	7.6%	9.7%
NPV	99.7%	99.8%	99.7%	99.9%	99.9%	99.9%	100.0%
Stage 0-I (%)	**96.4%**	**96.7%**	**96.5%**	**54.8%**	**63.9%**	**66.7%**	**85%[9]**

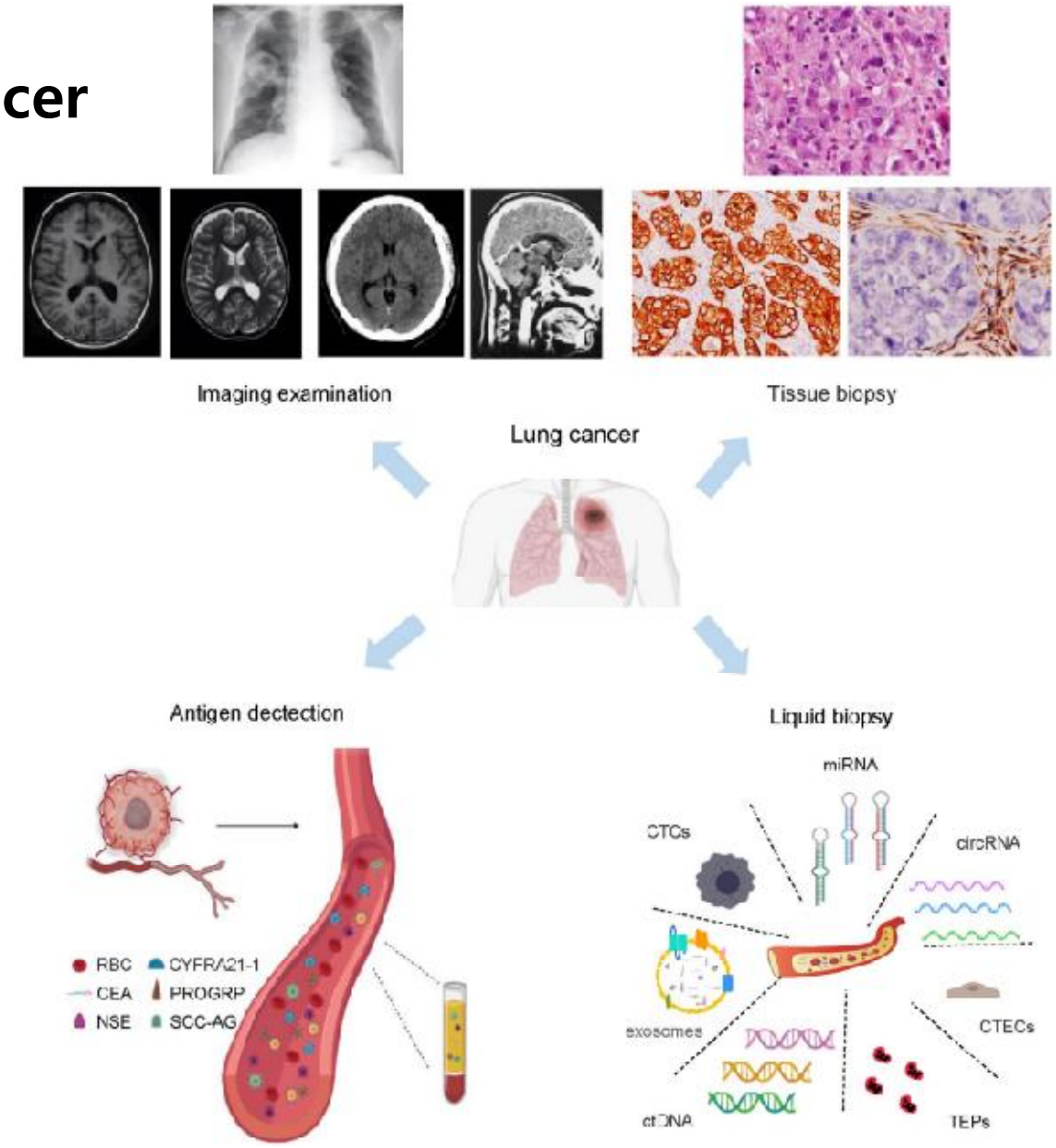
Yang PC et al, TALENT Study Group, Taiwan 2021

Overdiagnosis?
Could reduce lung cancer mortality?

Contents

- Updated biologic & risk factors for lung cancer
- Lung cancer prediction model
- Biomarkers of lung cancer

Diagnosis of lung cancer



Biomarker for lung cancer detection: circulating proteins

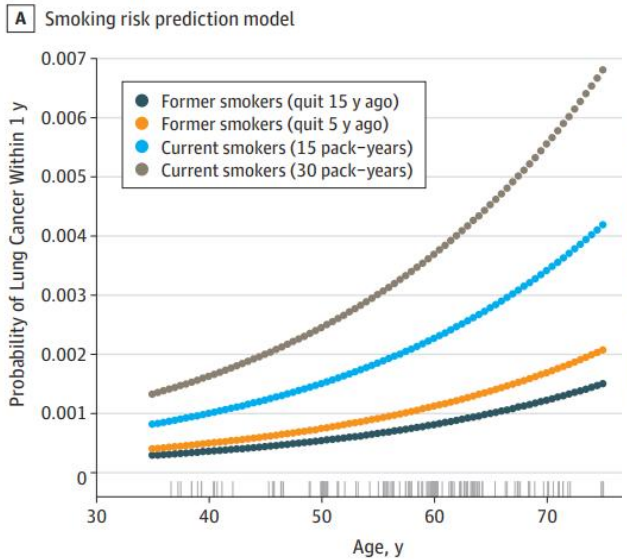
- Four-marker protein panel: **pro-surfactant protein B, CA-125, CEA, Cytokeratin-19 fragment(Cyfra21-1)**

eTable 5. Subject Baseline Characteristics in the Training (CARET)

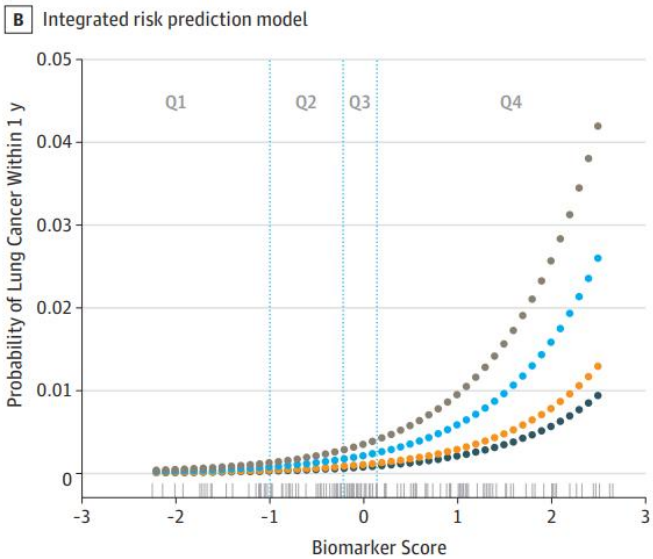
		Training study (CARET)	
	N (%)	**Cases**	**Controls**
Overall		108	216
Sex	Male	75 (69.4)	150 (69.4)
	Female	33 (30.6)	66 (30.6)
Age, years	≤40	-	-
	40-50	2 (1.9)	4 (1.9)
	50-60	35 (32.4)	72 (33.3)
	60-70	69 (63.9)	136 (63.0)
	>70	2 (1.9)	4 (1.9)
Years from BC to diagnosis	0-0.5	40 (37.0)	-
	0.5-1	68 (63.0)	-
	1-2	-	-
Smoking status	Never	-	-
	Former	36 (33.3)	72 (33.3)
	Current	72 (66.7)	144 (66.7)
Histological subtype	ADC	40 (37.0)	-
	SCC	38 (35.2)	-
	Other	30 (27.8)	-
Stage	I and II	26 (24.1)	-
	III and IV	64 (59.3)	-
	Unknown	18 (16.7)	-
Eligible for lung cancer screening (USPSTF)	Not Eligible	29 (26.9)	57 (26.4)
	Eligible	79 (73.1)	159 (73.6)
	N/A	-	-

CARET Study: randomised, double blind, placebo-controlled tiral
The prevention efficacy of beta-carotene & retinol palmitate in person at high risk for lung cancer
N= 18,314, At 6 US centers, enrolled from 1985 to 1994, followed until 2005

108 subjects who subsequently developed **NSCLC within 12 months after blood sampling**



Diagnosis of lung cancer within 1 year: **0.37%**
for a 60-year-old man with 30 PYS smoking Hx



Diagnosis of lung cancer within 1 year in fourth quartile: **1.56%** for a 60-year-old man with 30 PYS smoking Hx

CARET: US Carotene and Retinol Efficacy Trial, EPIC: European Prospective Investigation into Cancer and Nutrition, NSHDS: Northern Sweden Health and Disease Study

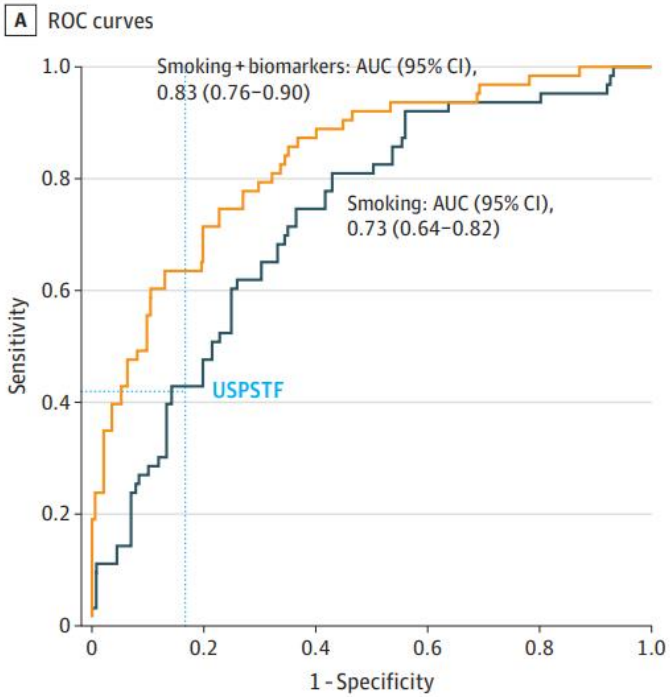
JAMA Oncol. 2018 Oct 1;4(10):e182078.

Biomarker for lung cancer detection: circulating proteins

Validation Set
EPIC study: N= 267,477 from1992 to 1998 from 7 countries
NSHDS: N= 99,404 participants at 2014 in Sweden

		Validation study (EPIC and NSHDS)	
		Diagnostic 0 to 1 year from BC	
	N (%)	Cases	Controls
Overall		67	126
Sex	Male	43 (64.2)	79 (62.7)
	Female	24 (35.8)	47 (37.3)
Age, years	≤40	3 (4.5)	6 (4.8)
	40-50	7 (10.4)	14 (11.1)
	50-60	30 (44.8)	55 (43.7)
	60-70	22 (32.8)	42 (33.3)
	>70	5 (7.5)	9 (7.1)
Years from BC to diagnosis	0-0.5	31 (46.3)	-
	0.5-1	36 (53.7)	-
	1-2	-	-
Smoking status	Never	4 (6)	36 (28.6)
	Former	24 (35.8)	43 (34.1)
	Current	39 (58.2)	47 (37.3)
Histological subtype	ADC	23 (34.3)	-
	SCC	17 (25.4)	-
	Other	27 (40.3)	-
Stage	I and II	11 (16.4)	-
	III and IV	36 (53.7)	-
	Unknown	20 (29.9)	-
Eligible for lung cancer screening (USPSTF)	Not Eligible	40 (59.7)	104 (82.5)
	Eligible	26 (38.8)	20 (15.9)
	N/A	1 (1.5)	2 (1.6)

- USPSTF vs USPSTF + 4MP in Validation cohort



Risk model	AUC	95% CI	Sensitivity at USPSTF Specificity	95% CI	Specificity at USPSTF Sensitivity	95% CI
Smoking[c]	0.73	[0.64-0.82]	0.43	[0.23-0.65]	0.86	[0.72-0.94]
Smoking + Biomarkers[d]	0.83	[0.76-0.90]	0.63	[0.49-0.76]	0.95	[0.85-0.99]

JAMA Oncol. 2018 Oct 1;4(10):e182078.

Biomarker for lung cancer detection: circulating proteins

- PLCOm2012 vs PLCOm2012 + 4MP

PLCO Cancer Screening Trial: Randomised multicenter trial in US aimed at evaluating the impact of early detection procedures for prostate, lung, colorectal and ovarian cancer on disease-specific mortality. Age 55-74, N=155,000, 1993-2001
Ever-smoker: N=42,450
Diagnosed lung cancer within 6 years of study entry with prediagnostic sera available: N=552, specimen N=1229

	Cases[a]		Noncases[a]	
Variable	**No. of Specimens**	**No. of Participants**	**No. of Specimens**	**No. of Participants**
No.	1,299	552	8,709	2,193
Age, mean (SD)		65 (5)		62 (5)
Sex, No. (%)				
Male	851 (66)	354 (64)	4,813 (60)	1,210 (60)
Female	448 (34)	198 (36)	3,896 (40)	983 (40)
Smoking status, No. (%)				
Former	733 (60)	314 (60)	7,196 (80)	1797 (80)
Current	566 (40)	238 (40)	1,513 (20)	396 (20)
PY, No. (%)				
< 10	30 (2)	12 (2)	1,566 (18)	386 (18)
≥ 10 to < 20	75 (6)	31 (6)	1,680 (19)	416 (19)
≥ 20 to < 30	119 (9)	53 (10)	1,259 (14)	314 (14)
≥ 30	1,052 (81)	448 (81)	3,989 (46)	1,021 (47)
Unknown	23 (2)	8 (1)	215 (2)	56 (3)
Stage, No. (%)				
I and II	530 (41)	232 (42)	—	—
III and IV	743 (57)	310 (56)	—	—
Unknown	26 (2)	10 (2)		
Histology, No. (%)				
Adenocarcinoma	496 (40)	211 (40)	—	—
Squamous cell carcinoma	280 (20)	119 (20)	—	—
Small-cell carcinoma	202 (20)	82 (10)	—	—
Others	321 (20)	140 (30)	—	—

J Clin Oncol. 2022 Mar 10;40(8):876-883.

Biomarker for lung cancer detection: circulating proteins

- PLCOm2012 vs PLCOm2012 + 4MP

PLCO Cancer Screening Trial: Randomised multicenter trial in US aimed at evaluating the impact of early detection procedures for prostate, lung, colorectal and ovarian cancer on disease-specific mortality. Age 55-74, N=155,000, 1993-2001
Ever-smoker: N=42,450
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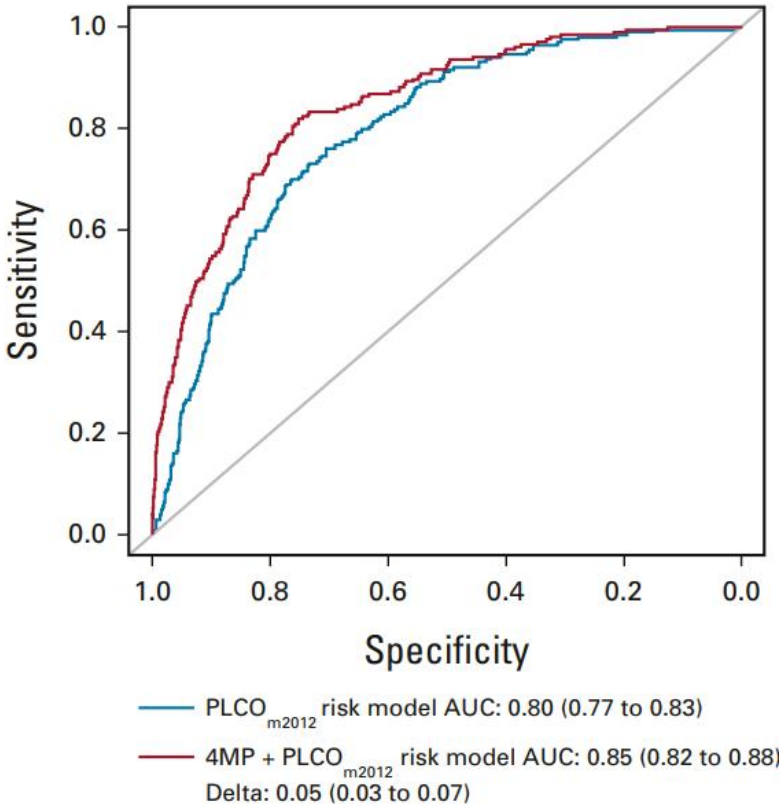


TABLE 2. Accuracy Performances in the Validation Set for the 4MP, $PLCO_{m2012}$, and the Combined Model of 4MP Plus $PLCO_{m2012}$ at Fixed Thresholds of ≥ 1.7% and ≥ 1% 6-Year Risk, to be Comparable With USPSTF2013 and USPSTF2021 Criteria in ESIA10+

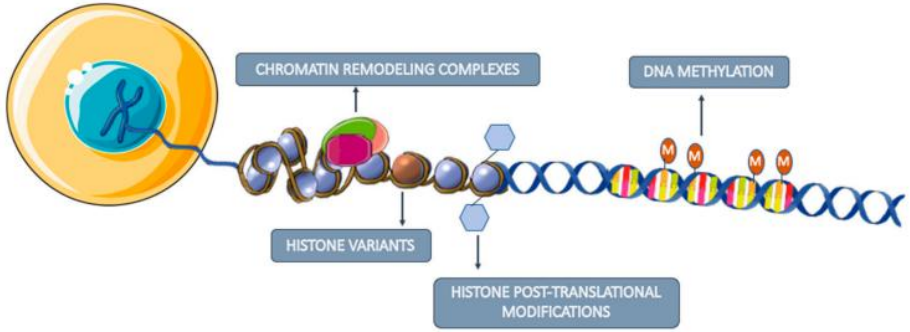
Criteria	N1[a]	N0	1-Year Sensitivity[b]	Specificity	1-Year TP[c]	FP[c]
≥ 1.7% risk threshold					+12.6%	-29.6%
USPSTF2013[d]	119	32,243	0.716	0.564	85	14,061
4MP[e]	119	32,243	0.824	0.632	98	11,866
$PLCO_{m2012}$[f]	119	32,243	0.776	0.654	93	11,145
Combined 4MP + $PLCO_{m2012}$ model[g]	119	32,243	0.835	0.693	100	9,905
≥ 1.0% risk threshold						
USPSTF2021[d]	119	32,243	0.785	0.493	94	16,356
4MP[e]	119	32,243	0.915	0.454	109	17,591
$PLCO_{m2012}$[f]	119	32,243	0.920	0.466	110	17,224
Combined 4MP + $PLCO_{m2012}$ model[g]	119	32,243	0.884	0.562	105	14,122

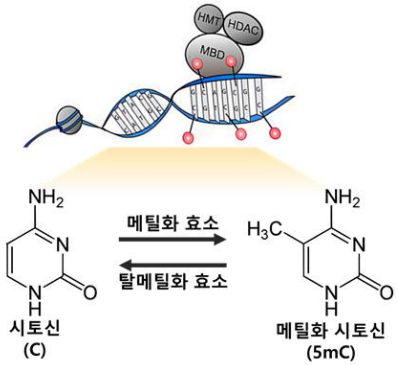
ESIA10+: ever smoker intervention arm 10+ PY group
USPSTF 2013: 55-80 year-old, >30PYs
USPSTF 2021: 50-80 year-old, >20PYs

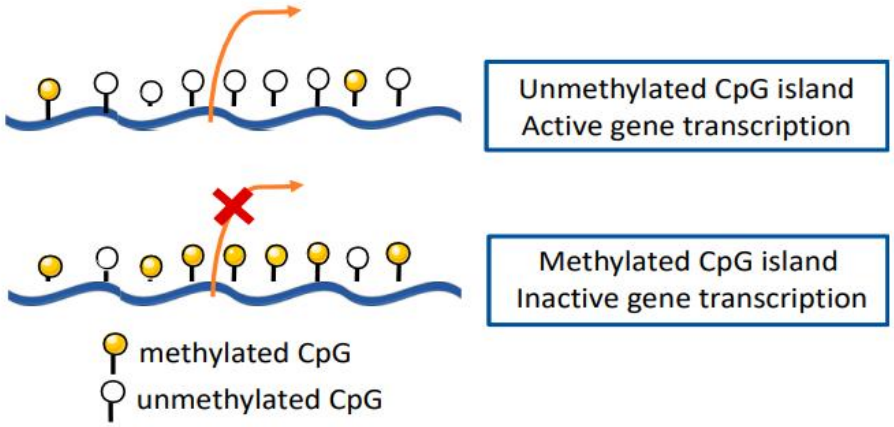
J Clin Oncol. 2022 Mar 10;40(8):876-883.

Biomarker for lung cancer detection: methylation of ctDNA

- DNA methylation and gene expression regulation







Not hypomethylation of oncogenes,
But **activation of tumor supressor genes by hypermethylation,** considered a major contributor to neoplastic transformation

Cells. 2020 Mar 5;9(3):624.

Biomarker for lung cancer detection: methylation of ctDNA

- Circulating cfDNA-based methylation biomarker for lung cancer detection

Lung Cancer						
Genes	**Number of Cases/Controls**	**Sensitivity (%)**	**Specificity (%)**	**Sources**	**Methods**	**References**
APC_{me}	89 LC/50 AC	47	100	Serum/Plasma	qMSP	[33]
$p16^{INK4a}{}_{me}$	35 NSCLC/15 AC	34	100	Plasma	F-MSP	[34]
$MGMT_{me}/p16^{INK4a}{}_{me}/RASSF1A_{me}/DAPK_{me}/RAR\beta_{me}$	91 LC/109 BPD	50	85	Serum	MSP	[47]
$p16^{INK4a}{}_{me}/CDH13_{me}$	61 NSCLC/15 BPD	39	100	Serum	MSP	[48]
$RASSF1A_{me}$	80 LC/50 AC [a]	34	100	Serum	MSP	[49]
$CDH13_{me}/p16^{INK4a}{}_{me}/FHIT_{me}/RAR\beta_{me}/RASSF1A_{me}/ZMYND10_{me}$	63 NSCLC/36 BPD	73	83	Plasma	Two-step MSP	[50]
$KLK10_{me}$	78 NSCLC/50 AC [a]	38	96	Plasma	MSP	[51]
$SFRP1_{me}$	78 NSCLC/50 AC [a]	28	96	Plasma	MSP	[52]
$DLEC1_{me}$	78 NSCLC/50 AC [a]	36	96	Plasma	MSP	[53]
$Kif1a_{me}/DCC_{me}/RAR\beta2_{me}/NISCH_{me}$	70 LC/80 BPD	73	71	Plasma	qMSP	[54]
$APC_{me}/RASSF1A_{me}/CDH13_{me}/KLK10_{me}/DLEC1_{me}$	110 NSCLC [b]/50 AC [a]	84	74	Plasma	MSP	[55]
$APC_{me}/CDH1_{me}/MGMT_{me}/DCC_{me}$ $RASSF1A_{me}/AIM1_{me}$	76 LC/30 AC	84	57	Serum	qMSP	[56]
$SHOX2_{me}$	188 LC/155 AC [a,c]	60	90	Plasma	qMSP	[37]
$TMEFF2_{me}$	316 NSCLC/50 AC	9	100	Serum	Two-step MSP	[57]
$RAR\beta2_{me}$ $RASSF1A_{me}$	60 NSCLC/32 AC	72 66	62 57	Plasma	qMSP	[35]
$SEPT9_{me}$	70 LC/100 AC	44	92	Plasma	qMSP	[43]
$p14ARF_{me}$	107 NSCLC/20 BPD	25	95	Plasma	Two-step MSP	[58]
$DCLK1_{me}$	65 LC/95 AC	49	92	Plasma	qMSP	[42]
$SOX17_{me}$	48 Operable NSCLC/49 AC 74 Advanced NSCLC/49 AC	56 36	98	Plasma	qMSP	[59]
$SHOX2_{me}$	38 LC/31 BPD	81	79	Plasma	qMSP	[38]
$SHOX2_{me}/PTGER4_{me}$ *	50 LC/122 AC [a]	67 90	90 73	Plasma	Multiplex qMSP	[39]

*Conformité Européenne (CE) for In Vitro Diagnostic (IVD) test CE

Cells. 2020 Mar 5;9(3):624.

Biomarker for lung cancer detection: methylation of ctDNA

- Circulating cfDNA-based methylation biomarker for **early lung cancer detection**

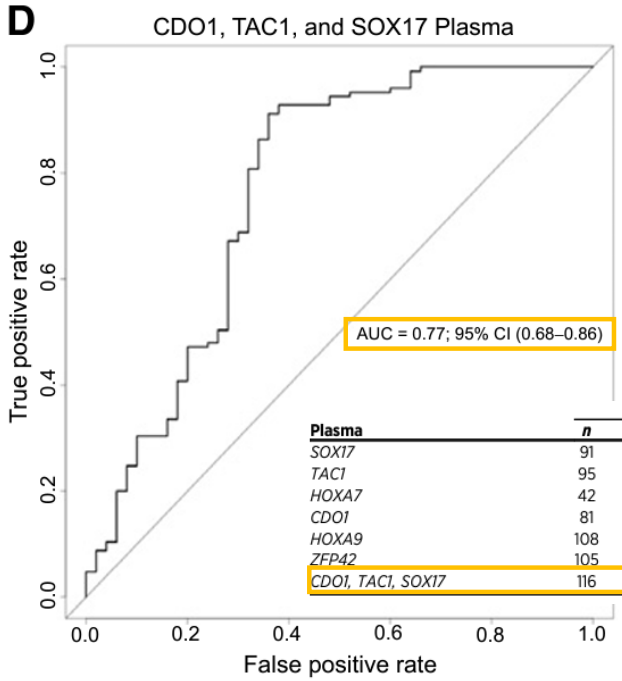
Early Detection of Lung Cancer Using DNA Promoter Hypermethylation in Plasma and Sputum

Alicia Hulbert[1,2], Ignacio Jusue-Torres[3], Alejandro Stark[4], Chen Chen[1,5],

Methylation-specific real-time PCR of cancer specific genes (SOX17, TAC1, HOXA7, CDO1, HOXA9, and ZFP42)

Table 1. Baseline characteristics of the 210 subjects

Patient characteristics	Cancer ($N = 150$)	Control ($N = 60$)	*P*
Age at surgery (IQR), y	68 (62–75)	63 (55–73)	0.007
Gender			
Male (%)	63 (42%)	33 (55%)	0.094
Female (%)	87 (58%)	27 (45%)	
Race			
White (%)	120 (80%)	51 (85%)	0.087
Black (%)	19 (13%)	3 (5%)	
Other (%)	11 (7%)	6 (10%)	
Stage			
IA–IB (%)	136 (91%)	NA	NA
IIA (%)	14 (9%)	NA	
Histology			
Adenocarcinoma (%)	121 (81%)	NA	NA
Squamous cell (%)	26 (17%)	NA	
Adenosquamous (%)	3 (2%)	NA	
Smoking status			
Current (%)	27 (18%)	7 (12%)	0.176
Former (%)	87 (58%)	34 (57%)	
Never (%)	31 (21%)	19 (32%)	
Pack-year (IQR)	30 (10–50)	20 (0–35)	0.010
Nodule size, cm	2 (1.5–3)	1.5 (1.1–3)	0.01
<1	6 (4%)	13 (22%)	0.001
1–2	52 (35%)	19 (32%)	
>2	92 (61%)	28 (47%)	
Nodule volume, cm^3	4.19 (1.77–14–14)	1.6 (0.52–18.12)	0.001



Plasma	Cancer ($N = 125$) *n*	Sensitivity	Control ($N = 50$) *n*	Specificity	PPV	NPV
SOX17	91	73%	8	84%	92%	55%
TAC1	95	76%	11	78%	90%	57%
HOXA7	42	34%	4	92%	91%	36%
CDO1	81	65%	13	74%	86%	46%
HOXA9	108	86%	27	46%	80%	58%
ZFP42	105	84%	23	54%	82%	57%
CDO1, TAC1, SOX17	116	93%	19	62%	86%	78%

Clin Cancer Res. 2017 Apr 15;23(8):1998-2005.

Biomarker for lung cancer detection: methylation of ctDNA

- Circulating cfDNA-based methylation biomarker for **early lung cancer detection**

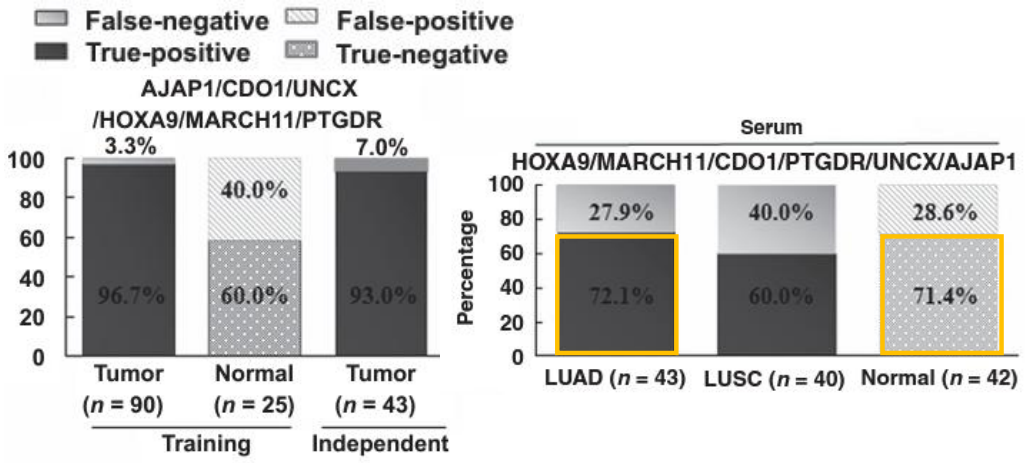
A Panel of Novel Detection and Prognostic Methylated DNA Markers in Primary Non–Small Cell Lung Cancer and Serum DNA

Akira Ooki[1], Zahra Maleki[2], Jun-Chieh J. Tsay[3], Chandra Goparaju[4], Mariana Brait[1],

Methylation panel of 6 genes (CDO1, HOXA9, AJAP1, PTGDR, UNCX, andMARCH11)

Table 1. The clinicopathologic features of cohorts in this study

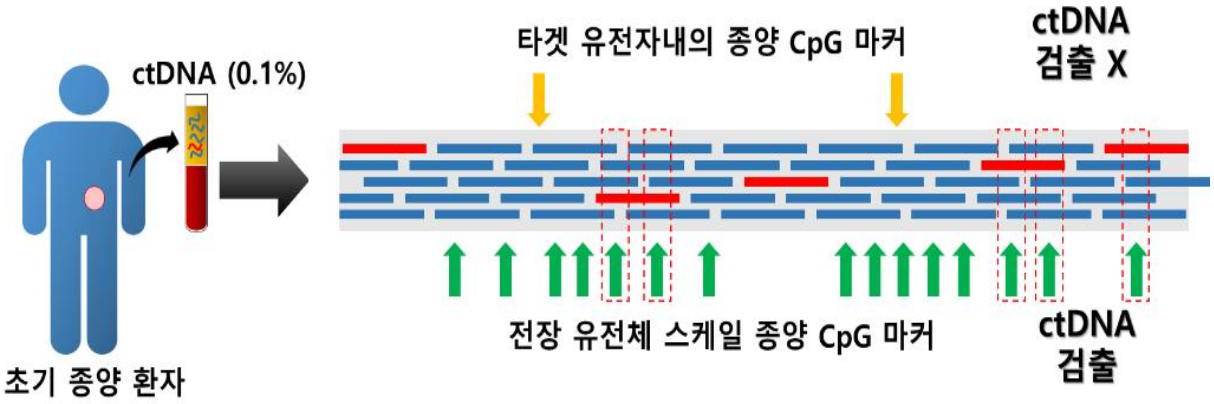
Samples	Primary tumor		Serum		
Patients	Training cohort[a] ($n = 90$)	Validation cohort[b] ($n = 43$)	Stage IA LUAD[b] ($n = 43$)	Stage IA LUSC ($n = 40$)	Control ($n = 42$)
Age (years)					
Mean ± SEM (years)	64.61 ± 1.13	70.02 ± 8.92	70.02 ± 8.92	71.80 ± 9.06	66.65 ± 1.02
Range (years)	41–86	46–88	46–88	49–87	49–76
Race					
Caucasian (%)	60 (80.0)	39 (90.7)	39 (90.7)	36 (90.0)	40 (95.2)
Asian (%)	1 (1.3)	4 (9.3)	4 (9.3)	2 (5.0)	1 (2.4)
Others (%)	14 (18.7)	0 (0.0)	0 (0.0)	2 (5.0)	1 (2.4)
Gender					
Female (%)	37 (49.3)	29 (67.4)	29 (67.4)	17 (42.5)	27 (64.3)
Male (%)	38 (50.7)	14 (32.6)	14 (32.6)	23 (57.5)	15 (35.7)
Smoking history					
Absence (%)	29 (38.7)	16 (37.2)	16 (37.2)	1 (2.5)	12 (28.6)
Presence (%)	46 (61.3)	27 (62.8)	27 (62.8)	39 (97.5)	30 (71.4)
Tumor size					
Mean ± SEM (cm)	3.87 ± 0.21	1.73 ± 0.60	1.73 ± 0.60	1.72 ± 0.73	—
Histology					—
Adenocarcinoma (%)	60 (66.7)	43 (100.0)	43 (100.0)	—	—
Squamous carcinoma (%)	25 (27.8)	—	—	40 (100.0)	—
Large cell carcinoma (%)	5 (5.5)	—	—	—	—
Stage					—
Stage I (%)	31 (41.3)	43 (100.0)	43 (100.0)	40 (100.0)	—
Stage II (%)	22 (29.3)	—	—	—	—
Stage III/IV (%)	22 (29.3)	—	—	—	—
Adjuvant chemotherapy					—
Absence (%)	unknown	43 (100.0)	43 (100.0)	40 (100.0)	—
Recurrence					—
Absence (%)	40 (53.3)	36 (83.7)	36 (83.7)	33 (82.5)	—
Presence (%)	35 (46.7)	7 (16.3)	7 (16.3)	7 (17.5)	—



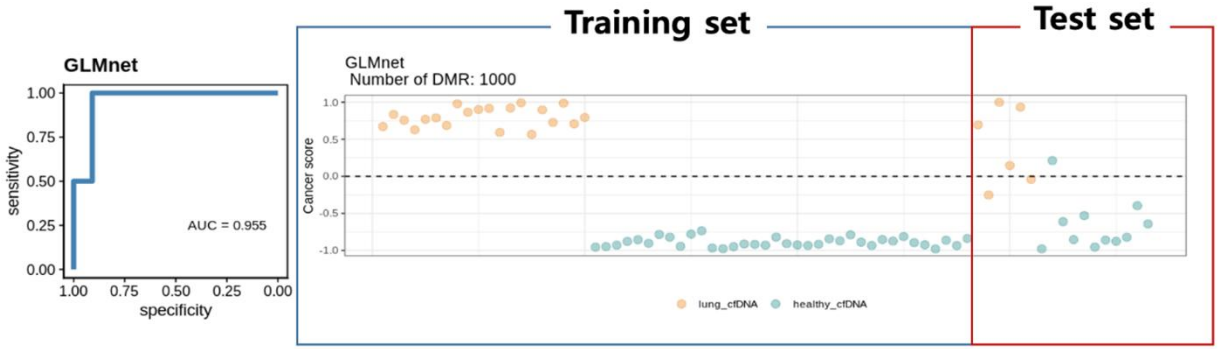
Clin Cancer Res. 2017 Nov 15;23(22):7141-7152.

Biomarker for lung cancer detection: methylation of ctDNA

- Whole genome methylation sequencing

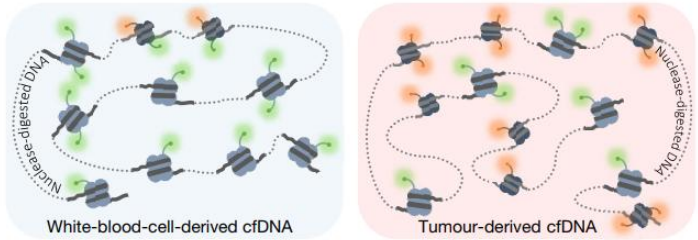


Lung cancer N= 26, Control N= 47
Prediction model using cancer methylated signature



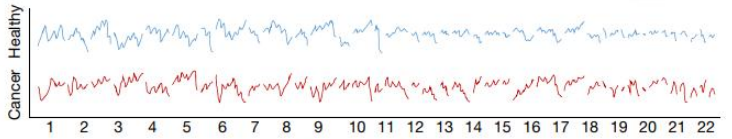
Biomarker for lung cancer detection: DNA fragmentomics

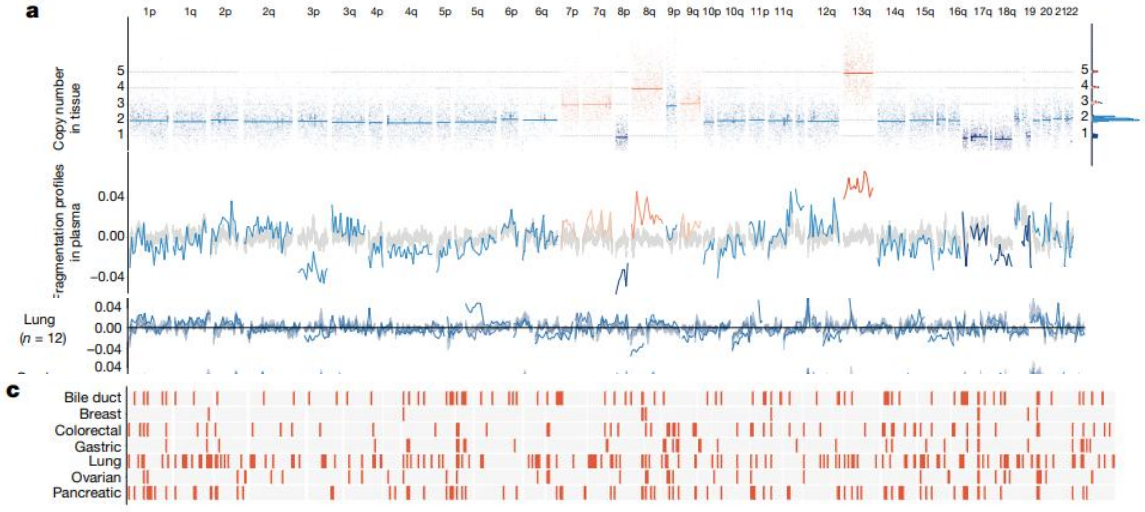
- Fragmentation pattern of ctDNA

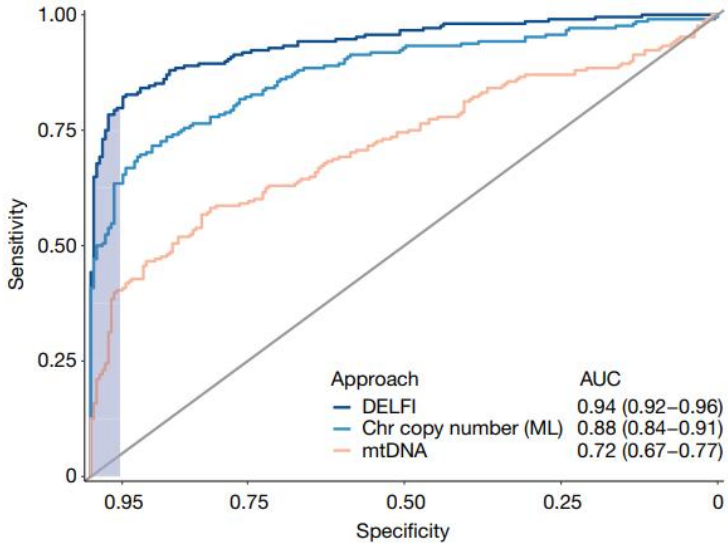


Genome-wide cell-free DNA fragmentation in patients with cancer

Stephen Cristiano[1,2,15], Alessandro Leal[1,15], Jillian Phallen[1,15], Jacob Fiksel[1,2,15], Vilmos Adleff[1], Daniel C. Bruhm[1],





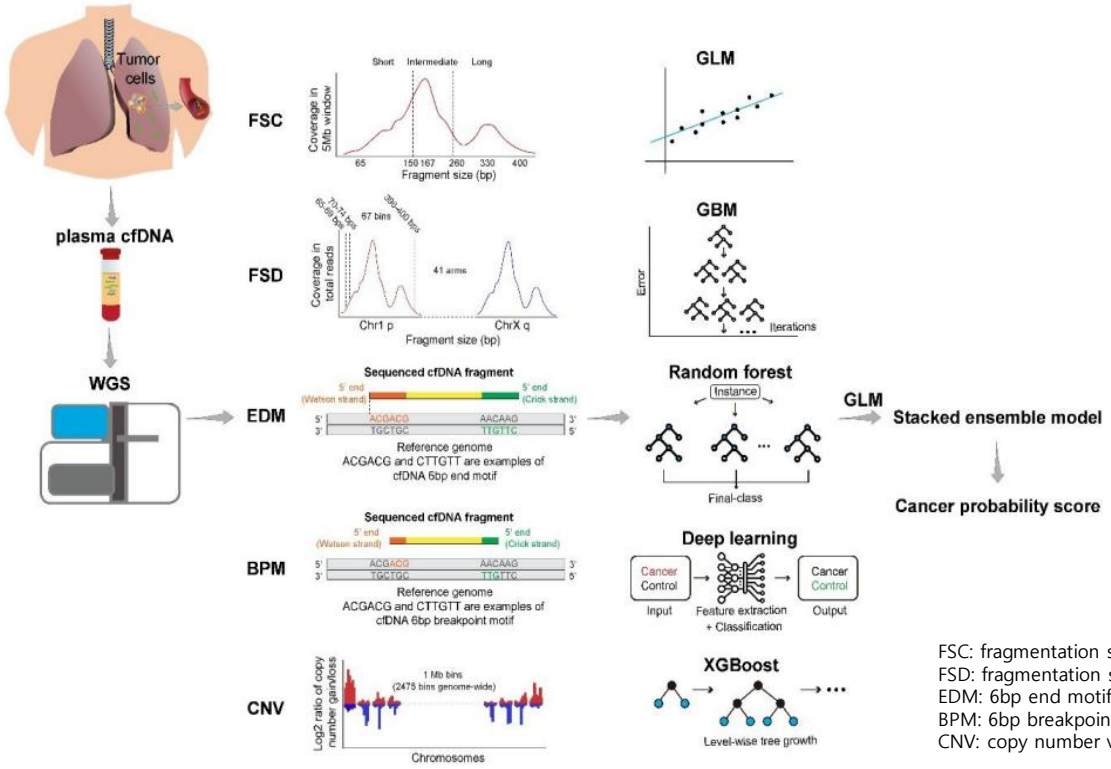


Nature. 2019;570:385-389.

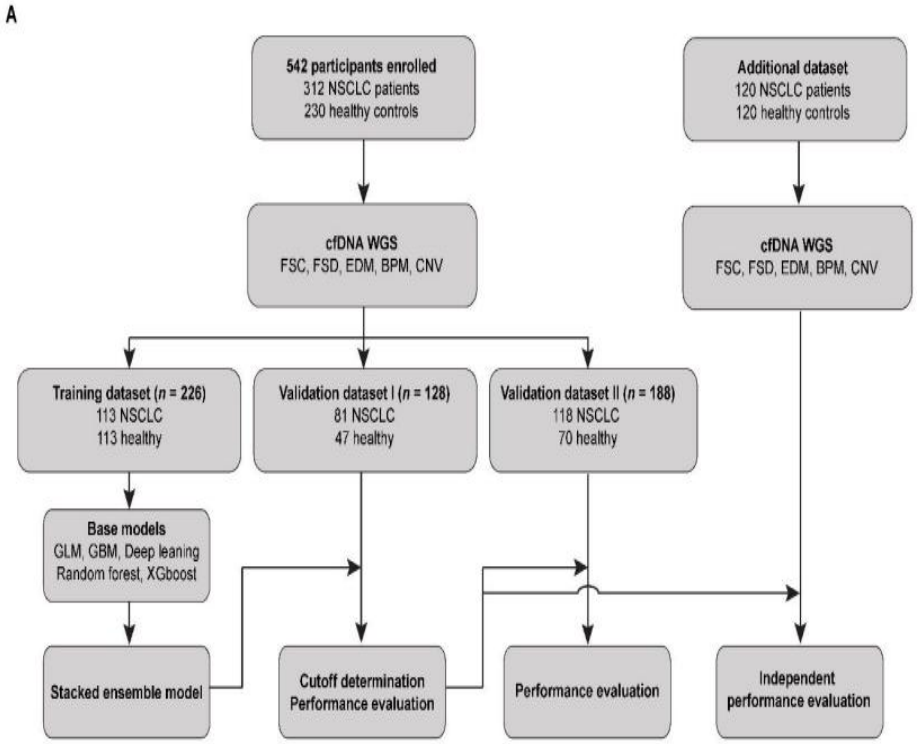
Biomarker for lung cancer detection: DNA fragmentomics

Multi-Dimensional Cell-free DNA Fragmentomic Assay for Detection of Early-Stage Lung Cancer

Siwei Wang , Fanchen Meng , Ming Li , Hua Bao , Xin Chen , Meng Zhu , Rui Liu , Xiuxiu Xu , Shanshan Yang , Xue Wu , Yang Shao , Show All...



FSC: fragmentation size cc
FSD: fragmentation size di
EDM: 6bp end motif
BPM: 6bp breakpoint moti.
CNV: copy number variation



Am J Respir Crit Care Med. 2022 Nov 8.

Biomarker for lung cancer detection: DNA fragmentomics

Multi-Dimensional Cell-free DNA Fragmentomic Assay for Detection of Early-Stage Lung Cancer

Siwei Wang , Fanchen Meng , Ming Li , Hua Bao , Xin Chen , Meng Zhu , Rui Liu , Xiuxiu Xu , Shanshan Yang , Xue Wu , Yang Shao , Show All...

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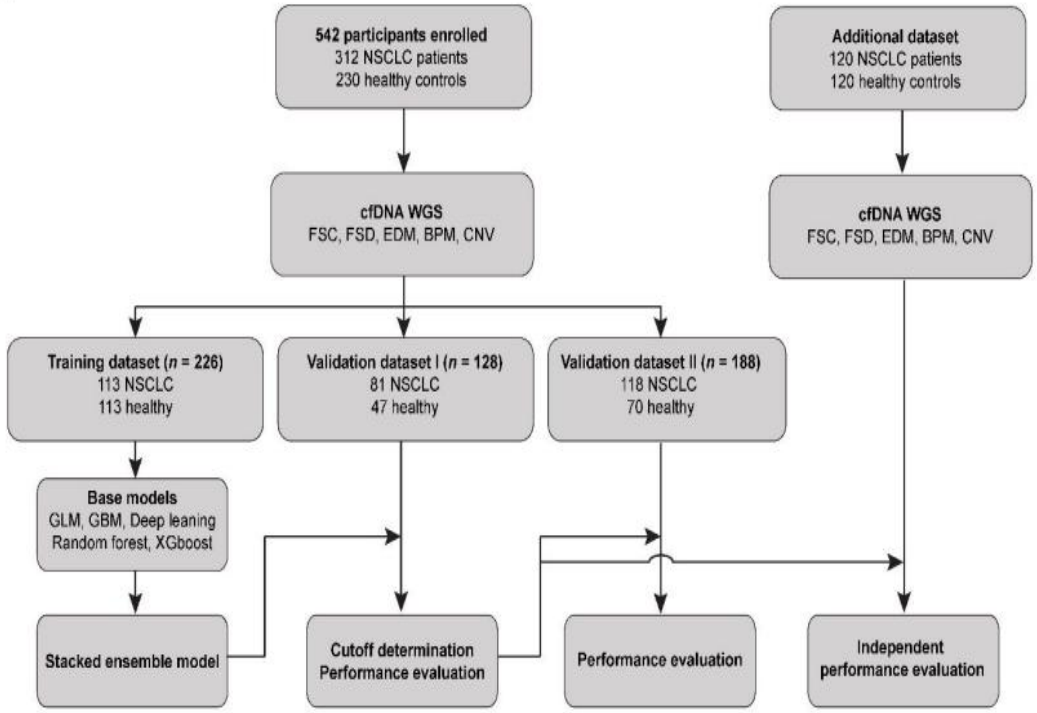

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Biomarker for lung cancer detection: DNA fragmentomics

Multi-Dimensional Cell-free DNA Fragmentomic Assay for Detection of Early-Stage Lung Cancer

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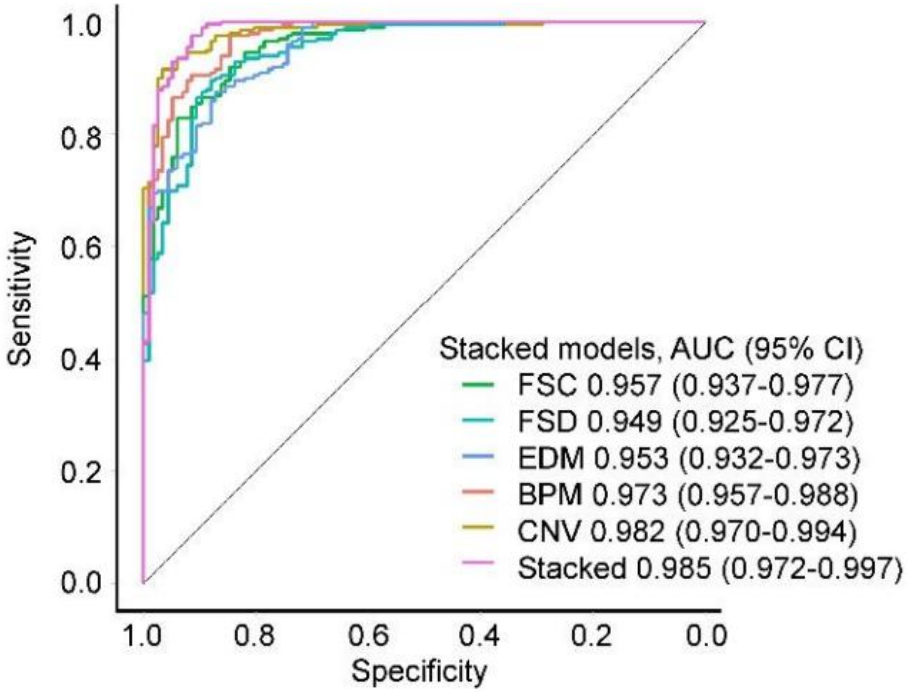
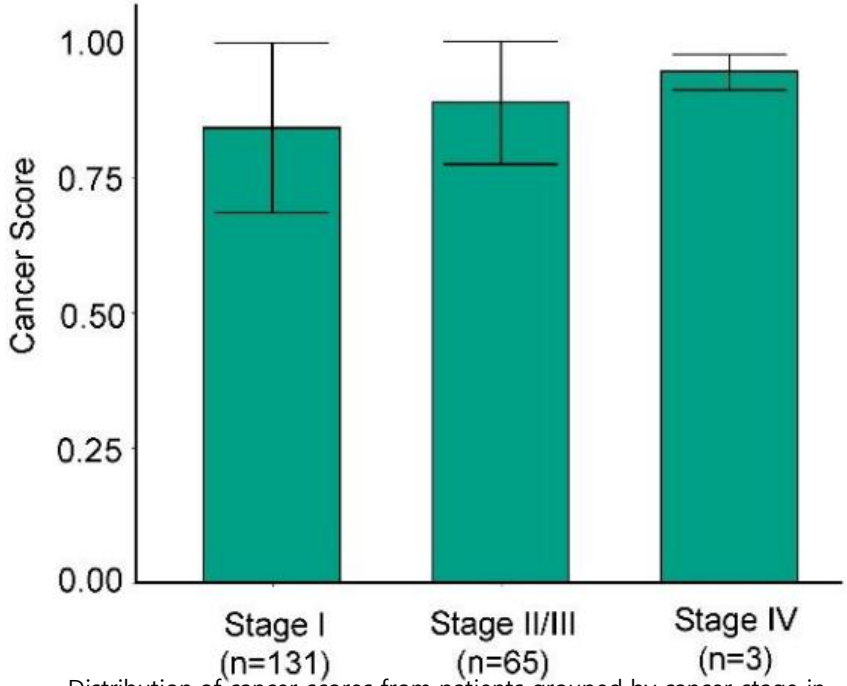


ROC curve evaluating the performance of different stacking models in distinguishing early lung cancer patients from healthy subjects in the combined validation cohorts



Distribution of cancer scores from patients grouped by cancer stage in the validation cohorts

Am J Respir Crit Care Med. 2022 Nov 8.

Biomarker for lung cancer detection: DNA fragmentomics

Multi-Dimensional Cell-free DNA Fragmentomic Assay for Detection of Early-Stage Lung Cancer

Siwei Wang , Fanchen Meng , Ming Li , Hua Bao , Xin Chen , Meng Zhu , Rui Liu , Xiuxiu Xu , Shanshan Yang , Xue Wu , Yang Shao , Show All...

Cohort		Validation I		Validation II		Combined validation	
		Sensitivity (95% CI)	TP/ Total	Sensitivity (95% CI)	TP/ Total	Sensitivity (95% CI)	TP/ Total
Histology	ADC	90.9% (81.3%-96.6%)	60/66	84.7% (77.0%-90.7%)	100/118	87.0% (81.2%-91.5%)	160/184
	SCC	93.3% (68.1%-99.8%)	14/15	N/A	N/A	93.3% (68.1%-99.8%)	14/15
Stage	I	91.3% (79.2%-97.6%)	42/46	78.8% (68.6%-86.9%)	67/85	83.2% (75.7%-89.2%)	109/131
	II/III	90.6% (75.0%-98.0%)	29/32	100.0% (89.4%-100.0%)	33/33	95.4% (87.1%-99.0%)	62/65
	IV	100.0% (29.2%-100.0%)	3/3	N/A	N/A	100.0% (29.2%-100.0%)	3/3
Tumor size	< 1 cm	81.2% (54.4%-96.0%)	13/16	100.0% (39.8%-100.0%)	4/4	85.0% (62.1%-96.8%)	17/20
	≥ 1 cm	93.9% (85.0%-98.3%)	61/65	84.2% (76.2%-90.4%)	96/114	87.7% (82.0%-92.1%)	157/179

Table 2. The diagnostic sensitivities of the predictive model in different lung cancer patient subgroups of the Validation I and II cohorts and their combination.

- ✓ Early screening tool?
- ✓ Discriminate benign from malignancy?

Am J Respir Crit Care Med. 2022 Nov 8.

Biomarker for lung cancer detection: CANDLE study

연구 계획서

(국문) 말초혈액 순환 DNA (circulating cell-free DNA, cfDNA)의

암 시그니처 앙상블(cancer signature ensemble, CSE)을 이용한

CT에서 발견된 폐결절의 암 감별

(영문) Discrimination of malignancy in CT detected lung nodules

by Cancer Signature Ensemble (CSE) of peripheral blood cfDNA

CANDLE 1 project

(**CAN**cer signature ensemble for **D**iscrimination of malignancy in CT detected **L**ung nodul**E**s)

Protocol version: CANDLE 1 1.0

연구 의뢰기관: 국립 암센터 2022년 암정복추진연구개발사업

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Biomarker for lung cancer detection: CANDLE study

- CANDLE study

- 연구목적
  - 흉부 CT에서 발견된 폐 결절 환자에서, 결절의 악성 가능성을 평가하는 지표로서 말초혈액 순환 DNA의 암 시그니처 앙상블을(CSE) 기계학습을(machine learning) 통하여 개발하고, 실제 임상에 적용하여 유용성을 확인함.

- 선정기준
  - 가. ECOG performance status 0 또는 1
  - 나. 연령: 만 50~80세
  - 다. 흡연력: 20갑년 이상의 현재 흡연자 또는 금연기간 15년 이내인 과거 흡연자
  - 라. 아래 A 또는 B 또는 C 조항에 해당하는 사람
    - A. 흉부 CT에서 발견된 폐 결절이 Lung-RADS category 4B 또는 4X이면서, TNM 병기(8판) clinical stage IA 폐암 의증 으로 병리학적 진단이 예정된 사람
    - B. TNM 병기(8판) clinical stage III~IV 폐암 의증 환자로서 조직학적 진단이 예정된 사람
    - C. 폐 결절의 초기 평가 당시 Lung-RADS category 4B 또는 4X이면서, 만일 악성이라면 TNM 병기(8판) clinical stage IA 상태였으나,
      - 가) 다른 검사로 이미 양성결절로 판정 되고 제거되지 않고, 6개월 이상기간 동안 변화가 없는 경우
      - 나) 조직검사 없이 2개월 이상 경과 관찰하여 항암치료 없이 크기가 줄어드는 고형결절
      - 다) 2년 이상 크기의 변화가 없는 고형결절은 조직검사 없이 양성 결절 소지자로 추정하고 등록 가능함.

Biomarker for lung cancer detection: CANDLE study

- CANDLE study

- 연구방법

  - Cancer Signature Ensemble (CSE)은 말초혈액 cfDNA의
    1) whole genome methylation signature
    2) fragmentation pattern (fragmentomics)
    3) copy number variation (CNV)으로 구성된 통합 생체 표지자(biomarker)로 정의함

  - Detection study
    Training set: 조기 폐암(case 역할, 80명), 진행성 폐암(positive control 역할, 20명), 양성 폐결절(negative control 역할, 50명)
    Stochastic gradient boosting model을 적용한 기계학습을(machine learning) 통해
    CSE가 악성과 양성 폐결절을 감별할 수 있도록 5등급의 범주화 지표로 개발

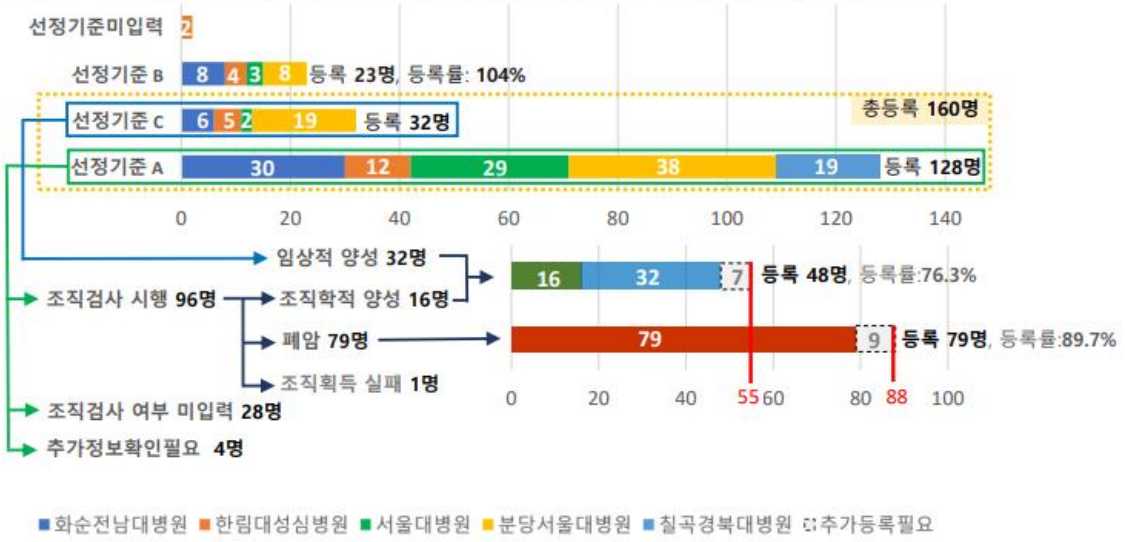
  - Validation study
    개발된 CSE가 같은 조건의 validation set에서 일치된 결과를 보이는지 확인함

Biomarker for lung cancer detection: methylation of ctDNA

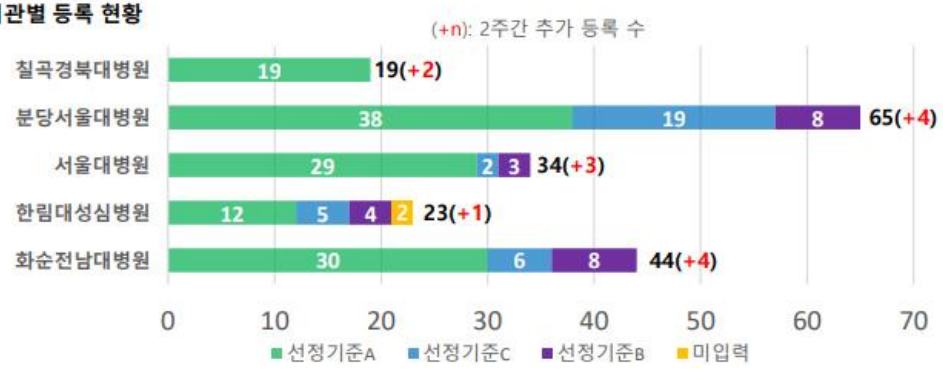
- CANDLE study

▪ **등록현황**

목표 대상자 수 Training set 165명; Stage I 143명 (**조기폐암 88명, 양성폐결절 55명**), **Stage III-IV 22명**

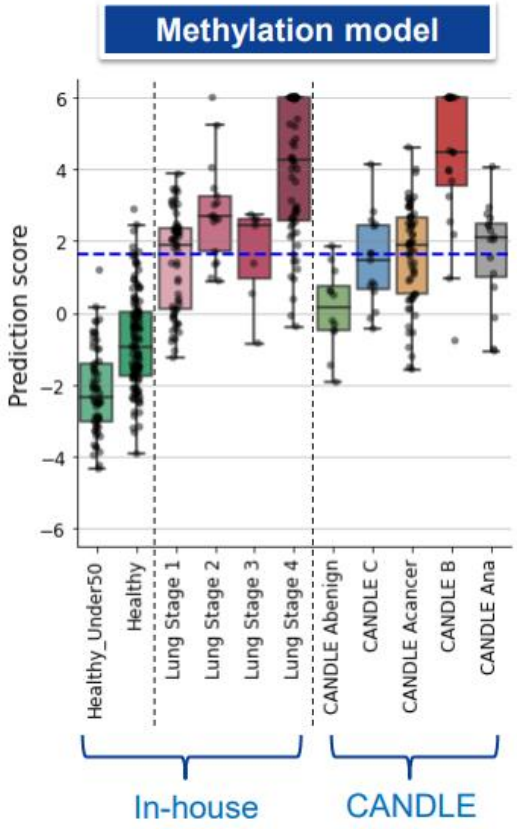


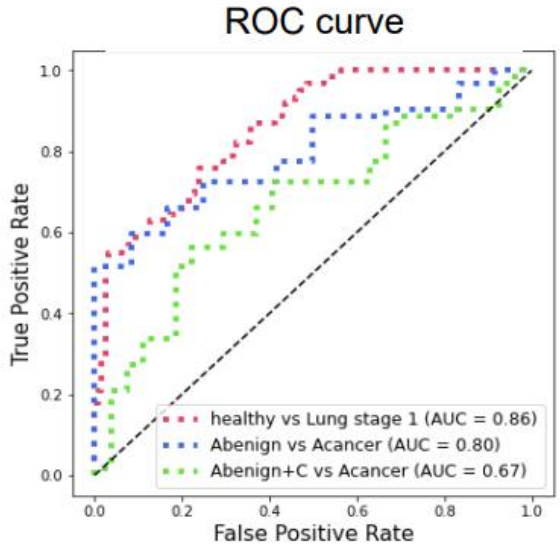
▪ **각 기관별 등록 현황**



Biomarker for lung cancer detection: methylation of ctDNA

Applying AlphaLiquid® Screening to CANDLE cohort





(0) Healthy vs. Lung stage 1 (AUC=0.86)

	Healthy	Lung stage 1
Benign	6	34
Cancer	120	28

* **Specificity** : 95.2% / **Sensitivity** : 54.8%

(1) A-benign vs. A-cancer **(AUC=0.80)**

	A-benign	A-cancer
Benign	11	26
Cancer	1	36

* **Specificity** : 83.33% / **Sensitivity** : 58.06%

(2) A-benign+C vs. A-cancer **(AUC=0.67)**

	A-benign	C	A-cancer
Benign	11	8	26
Cancer	1	7	36

* **Specificity** : 70.37% / **Sensitivity** : 58.06%

- Decent separation between A-benign and A-cancer using AL Screening
- C class scored somewhat higher than A-benign, leading lowered performance

Summary

- Stage shift by early detection could improve lung cancer survival
- Risk factors more than smoking and age:
  - Air pollution, Genetic information (single nucleotide polymorphism, clonal hematopoiesis)
- Categorical vs Quantified risk model
- Lung cancer screening in never smoker
  - Familial history
- Biomarker of lung cancer
  - Circulating proteins for additional screening tool
  - Liquid biopsy (ex. ctDNA) for discrimination of malignantcy and detection of lung cancer