

**Supplementary material: Table 1.** Lung cancer rates and rate ratios (RR) in COSMOS participants according to baseline characteristics

Characteristic	Number	Person-years of follow-up	Lung cancers	Rate per 100 years	RR (95% CI)
<b>All participants</b>	5203	18095	162	0.90	
<b>Sex</b>					
Women	1764	6006	47	0.78	1.00
Men	3439	12089	115	0.95	1.22 (0.87-1.71)
<b>Age</b>					
<55 years	1759	6151	31	0.50	1.00
55-59 years	1725	6084	49	0.81	<b>1.62 (1.03-2.54)</b>
60-64 years	1061	3669	46	1.25	<b>2.50 (1.58-3.95)</b>
≥65 years	658	2191	36	1.64	<b>3.28 (2.02-5.32)</b>
<b>Body mass index (kg/m<sup>2</sup>)</b>					
Underweight (<18.5)	58	196	1	0.51	0.55 (0.08-4.01)
Normal range (18.5-24.99)	2329	8061	74	0.92	1.00
Overweight (25-29.99)	2186	7673	69	0.90	0.98 (0.70-1.36)
Obese (≥30)	606	2113	18	0.85	0.92 (0.55-1.55)
<b>Fruit and vegetable intake</b>					
Less than 3 servings/day	2798	9743	90	0.92	1.00
Three servings/day or more	2279	7938	70	0.88	0.96 (0.70-1.31)
<b>Alcohol consumption</b>					
Never	1463	5010	44	0.88	1.00
Occasionally	2365	8193	70	0.85	0.97 (0.66-1.41)
1-2 glasses/day	1023	3665	34	0.93	1.06 (0.67-1.66)
3-5 glasses/day	156	553	9	1.63	1.85 (0.90-3.81)
More than 5 glasses/day	122	423	3	0.71	0.81 (0.25-2.61)
<b>Smoking status at baseline</b>					
Former smoker	1028	3676	29	0.79	1.00
Current smoker	4175	14419	133	0.92	1.16 (0.78-1.74)
<b>Age started smoking</b>					
<15 years	831	2906	29	1.00	1.00
15-19 years	2913	10194	98	0.96	0.96 (0.63-1.46)
≥20 years	1459	4995	35	0.70	0.70 (0.43-1.15)
<b>Years of cessation</b>					
<5 years	618	2208	17	0.77	1.00
5-10 years	410	1468	12	0.82	1.06 (0.51-2.24)
<b>Smoking duration</b>					
<35 years	865	2970	11	0.37	1.00
35 to 40 years	1623	5713	42	0.74	<b>2.00 (1.03-3.89)</b>
40 to 44 years	1510	5357	54	1.01	<b>2.73 (1.43-5.23)</b>
45 to 49 years	798	2720	24	0.88	<b>2.38 (1.16-4.86)</b>
≥50 years	407	1335	31	2.32	<b>6.27 (3.14-12.5)</b>
<b>Cigarette consumption</b>					
<20/day	911	3143	20	0.64	1.00
20-24/day	2011	7001	54	0.77	1.20 (0.72-2.01)
25-29/day	557	1984	16	0.81	1.27 (0.65-2.45)
30-39/day	973	3401	41	1.21	<b>1.89 (1.11-3.23)</b>
≥40/day	743	2549	31	1.22	<b>1.91 (1.08-3.35)</b>
<b>Pack-years</b>					
20-39 pack-years	1914	6640	35	0.53	1.00
40-59 pack-years	1951	6827	60	0.88	<b>1.66 (1.09-2.52)</b>
≥60 pack-years	1338	4628	67	1.45	<b>2.74 (1.81-4.12)</b>
<b>Passive smoking</b>					
No	476	1657	14	0.84	1.00
Yes	4620	16070	146	0.91	1.08 (0.62-1.88)
<b>Occupational exposure</b>					
Asbestos	247	837	11	1.31	1.47 (0.79-2.73)
Radon	7	28	0	N/A	N/A
Cadmium	22	77	1	1.30	1.43 (0.20-10.3)
Chromium	69	236	1	0.42	0.46 (0.06-3.31)
Beryllium	9	35	0	N/A	N/A
Aluminium	99	337	3	0.89	0.98 (0.31-3.08)
Silica dust	93	345	5	1.45	1.61 (0.66-3.95)
Sulphuric acid	106	371	3	0.81	0.89 (0.28-2.80)
Ether	66	235	0	N/A	N/A
Carbon	56	194	1	0.52	0.57 (0.08-4.10)
<b>Medical history</b>					
Asbestosis	10	36	1	2.78	3.05 (0.42-22.4)
Asthma	231	792	10	1.26	1.42 (0.74-2.70)
Other allergy	974	3458	22	0.64	0.67 (0.42-1.05)
Pulmonitis	671	2328	17	0.73	0.78 (0.47-1.30)
Tuberculosis	114	375	6	1.60	1.78 (0.78-4.05)
Pleuritis	322	1114	10	0.90	1.01 (0.53-1.93)
Pneumothorax	105	379	7	1.85	2.08 (0.97-4.47)

Chronic obstructive pulmonary disease	819	2755	36	1.31	<b>1.60 (1.10-2.33)</b>
Thyroid disease	652	2284	16	0.70	0.80 (0.48-1.35)
Cardiovascular disease	1140	3933	43	1.09	1.27 (0.89-1.80)
Previous cancer	233	809	11	1.36	1.56 (0.84-2.90)
<b>RESPIRATORY SYMPTOMS</b>					
<b>Lung disease limits activity</b>					
No	4663	16285	148	0.91	1.00
Yes	357	1229	9	0.73	0.80 (0.41-1.58)
<b>Wheezing</b>					
No	3795	13313	118	0.89	1.00
Yes	1302	4461	40	0.90	1.01 (0.71-1.45)
<b>Dyspnea</b>					
No	2956	10435	82	0.79	1.00
Yes	1686	5795	64	1.10	<b>1.39 (1.00-1.93)</b>
<b>RESPIRATORY FUNCTION*</b>					
<b>Forced vital capacity (FVC% of predicted)</b>					
≥80%	1782	6251	55	0.88	1.00
50-80%	672	2283	29	1.27	1.44 (0.92-2.27)
<50%	27	85	2	2.35	2.67 (0.64-11.1)
<b>Forced expiratory flow<sub>25-75</sub> (FEF<sub>25-75</sub>% of predicted)</b>					
≥80%	1523	5269	42	0.80	1.00
50-80%	677	2364	28	1.18	1.48 (0.91-2.39)
<50%	281	986	16	1.62	<b>2.03 (1.13-3.62)</b>
<b>Forced expiratory volume in 1 second (FEV1% of predicted)</b>					
≥80%	1810	6306	57	0.90	1.00
50-80%	602	2078	25	1.20	1.33 (0.83-2.14)
<50%	68	231	4	1.73	2.16 (0.78-5.96)
<b>Forced expiratory volume in 1 second (FEV1% of predicted)</b>					
≥90%	1300	4558	30	0.66	1.00
<90%	1180	4056	56	1.38	<b>2.09 (1.34-3.26)</b>
<b>FEV1/FVC</b>					
≥70%	2119	7360	70	0.95	1.00
<70%	355	1231	16	1.30	<b>1.37 (0.79-2.36)</b>

95% confidence intervals (CI) for rate ratios (RR) calculated assuming events followed a Poisson distribution. *P* for trend: age (<0.0001), alcohol consumption (0.50), age started smoking (0.22), smoking duration (<0.01), cigarette consumption (<0.01), pack-years (<0.01), FVC% (0.05); FEF<sub>25-75</sub>% (0.01); FEV1% (0.11).

\* Missing for 2722 participants

**Supplementary material: Table 2.** Risk of being diagnosed with lung cancer in relation to baseline CT findings in COSMOS participants.

Baseline CT finding	Number	Person-years from 2nd CT	Lung cancers <sup>†</sup> identified from 2nd CT	Rate per 100 years	Rate Ratio (95% CI)
<b>All subjects</b>	4596	13035	107	0.82	
<b>Emphysema</b>					
No	2719	7729	41	0.53	1.00
Yes	1843	5208	65	1.25	<b>2.36 (1.59-3.49)</b>
<b>Nodule typology*</b>					
None or calcified	2181	6192	26	0.42	1.00
Solid	1763	5012	42	0.84	<b>2.00 (1.22-3.27)</b>
Partially-solid	494	1385	20	1.44	<b>3.43 (1.91-6.16)</b>
Non-solid	158	446	19	4.26	<b>10.1 (5.57-18.5)</b>
<b>Size of largest non-calcified nodule**</b>					
None	2181	6192	26	0.42	0.65 (0.39-1.07)
<5mm	1949	5538	36	0.65	1.00
5-8mm	327	932	21	2.25	<b>3.46 (2.01-5.96)</b>
>8mm	139	373	24	6.43	<b>9.89 (5.84-16.8)</b>

Rate ratios (RR) starting from the date of 2<sup>nd</sup> CT; 95% confidence intervals (CI) calculated assuming events followed a Poisson distribution.

\* Solid means only solid nodule(s) present; partially solid means at least one partially solid nodule with possibly solid nodule(s), but no non-solid nodule(s); non-solid means at least one non-solid nodule with possibly solid or partially solid nodule(s) present.

\*\**P* for trend <0.01

† includes lung cancers that progressed from pre-existing nodules or appeared as new nodules.

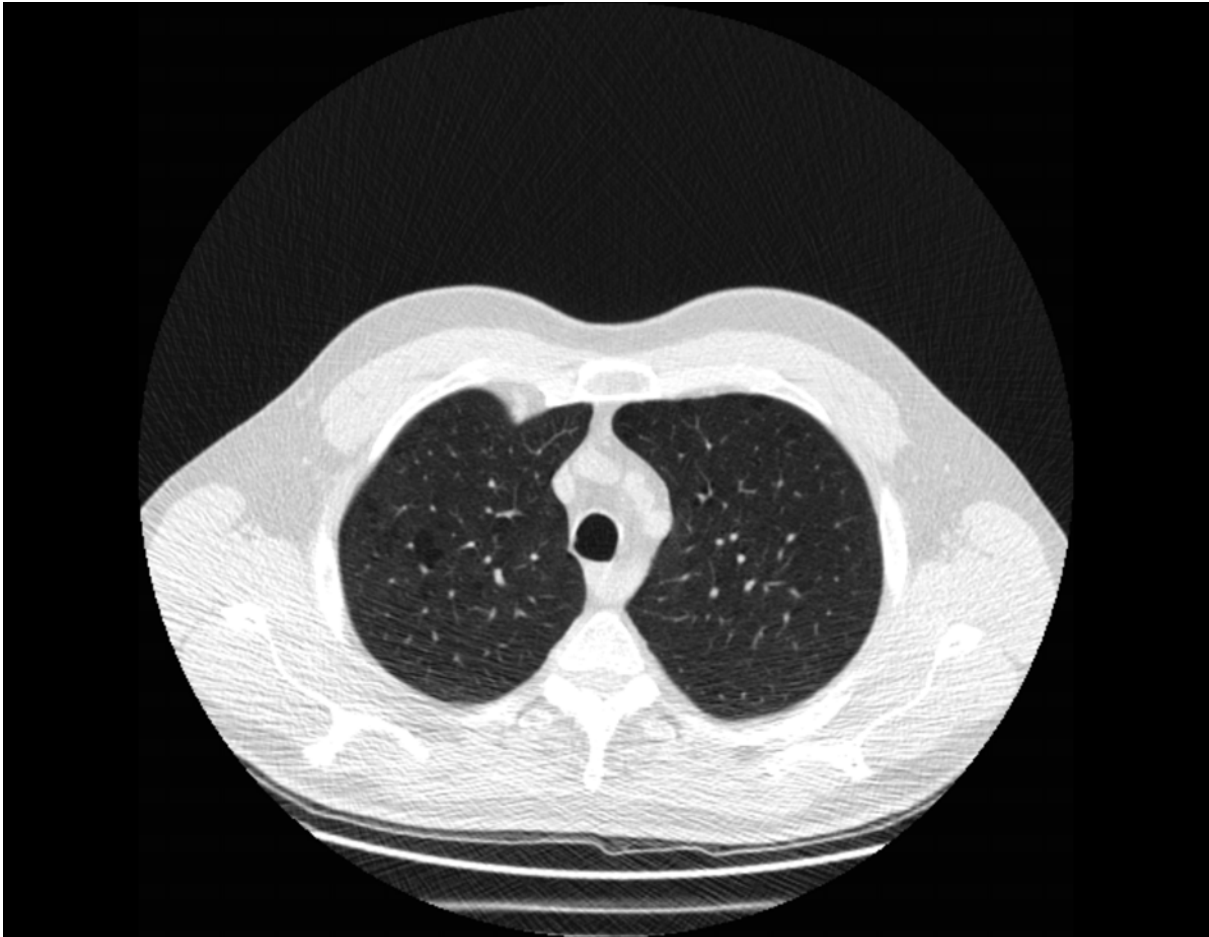
**Supplementary material: Table 3.** Typology of nodules and size of largest non-calcified nodules encountered at baseline CT for patients diagnosed with lung cancer at baseline CT (n=55) or follow-up CTs (n=107)

Baseline CT findings	Participants	Cancers detected at baseline CT	Cancers detected at follow-up CTs
<b>No nodules</b>	2439	-	26
<b>Solid nodule(s)</b> (only solid nodules)			
Largest nodule <5mm	1666	1	19
Largest nodule 5-8mm	259	6	16
Largest nodule >8mm	109	32	7
<b>Partially-solid nodules(s)</b> (at least one partially solid nodule with possibly solid nodule(s), but no non-solid nodule(s))			
Largest nodule <5mm	419	-	12
Largest nodule 5-8mm	72	-	2
Largest nodule >8mm	58	10	6
<b>Non-solid nodule(s)</b> (at least one non-solid nodule with possibly solid or partially solid nodule(s))			
Largest nodule <5mm	118	-	5
Largest nodule 5-8mm	25	-	3
Largest nodule >8mm	38	6	11

**Supplementary material: Table 4.** Numbers of screening and diagnostic procedures carried out, and numbers of lung cancers diagnosed in COSMOS volunteers during the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> screening CT rounds, according to deciles of risk calculated from the risk model.

Deciles of risk*	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Total
No. of participants	459	460	460	459	460	460	459	461	459	459	4596
Person-years of follow-up	1275	1315	1313	1308	1326	1325	1302	1291	1302	1278	13035
No. of screening CTs	1340	1354	1350	1353	1363	1361	1346	1342	1350	1330	13489
No. of recall CTs/PETs	36/3	36/10	48/10	44/13	38/11	69/14	65/9	83/23	86/33	177/66	682/192
No. of benign lesions resected (false positives)	1	3	1	2	1	1	1	2	2	13	27
No. of lung cancers	0	4	4	5	5	3	6	16	19	45	107
Stage I	0	3	3	4	5	2	4	12	14	35	82
Stage II	0	1	0	1	0	0	2	3	3	6	16
Stage III-IV	0	0	1	0	0	1	0	1	2	4	9
Diagnosed at 2 <sup>nd</sup> CT	0	2	1	1	2	0	3	5	8	16	38
Diagnosed at 3 <sup>rd</sup> CT	0	2	2	3	1	1	2	7	5	16	39
Diagnosed at 4 <sup>th</sup> CT	0	0	1	1	2	2	1	4	6	13	30
Annual detection rate	0.00%	0.30%	0.30%	0.38%	0.38%	0.23%	0.46%	1.24%	1.46%	3.52%	0.82%

\* risk score based on model D



**Supplementary material: Figure 1.** Low-dose CT scan of the lung in a patient classified as having emphysema: the subtle areas of low attenuation and loss of parenchimal structures in the upper right lobe are considered the lowest limit to define the presence of emphysema.

## Supplementary material: Risk Calculator

### Original\* and recalibrated Bach models

**Original Bach Model:** One-year probability of being diagnosed with lung cancer =  $1 - S_0^{e(\text{model})}$   
Where,  $S_0 = 0.99629$ ;

**Recalibrated Bach model:** One-year probability of being diagnosed with lung cancer during first CT screening round =  $1 - S_0^{e(\text{model})}$   
Where,  $S_0 = 0.98869$ ;

CPD = cigarettes per day, SMK = duration of smoking, QUIT = duration of quitting, AGE = age, ASB = asbestos exposure, SEX = sex;

Model is represented by the following equation:

$$\begin{aligned} \text{model} = & -9.7960571 \\ & + (0.060818386 * \text{CPD}) - [0.00014652216 * (\text{CPD} - 15)^3] && \text{for all values CPD} > 15 \\ & + [0.00018486938 * (\text{CPD} - 20.185718)^3] && \text{for all values CPD} > 20 \\ & - [0.000038347226 * (\text{CPD} - 40)^3] && \text{for all values CPD} > 40 \\ & + (0.11425297 * \text{SMK}) - [0.000080091477 * (\text{SMK} - 27.6577)^3] && \text{for all values SMK} > 27 \\ & + [0.00017069483 * (\text{SMK} - 40)^3] && \text{for all values SMK} > 40 \\ & - [0.000090603358 * (\text{SMK} - 50.910335)^3] && \text{for all values SMK} > 50 \\ & - (0.085684793 * \text{QUIT}) + [0.0065499693 * \text{QUIT}^3] && \text{for all values} \\ & - [0.0068305845 * (\text{QUIT} - 0.50513347)^3] && \text{for all values QUIT} > 0 \\ & + [0.00028061519 * (\text{QUIT} - 12.295688)^3] && \text{for all values QUIT} > 12 \\ & + (0.070322812 * \text{AGE}) - [0.00009382122 * (\text{AGE} - 53.459001)^3] && \text{for all values AGE} > 53 \\ & + [0.00018282661 * (\text{AGE} - 61.954825)^3] && \text{for all values AGE} > 61 \\ & - [0.000089005389 * (\text{AGE} - 70.910335)^3] && \text{for all values AGE} > 70 \\ & + [0.2153936] && \text{if ASB=yes} \\ & - [0.05827261] && \text{if SEX=female} \end{aligned}$$

**Note:** Include all terms in the equation for which requirements are met. For example, if an individual smokes 25 cigarettes per day, the value for the terms associated with CPD will be  $(0.060818386 * 25) - [0.00014652216 * (25 - 15)^3] + [0.00018486938 * (25 - 20.185718)^3]$ .

**Risk model for screening detected lung cancer at subsequent CT: The one-year probability of a diagnosis of lung cancer at repeated screening CT =  $1 - S_0^{e(\text{model}2)}$**   
Where,  $S_0 = 0.995$ ;

**SQDIAM = Square root of diameter of the largest non-calcified nodule present at first CT**

$$\begin{aligned} \text{model}2 = & -0.5386022 \\ & + (0.5889073 * \text{model}) \\ & + (0.5642264 * \text{SQDIAM}) && \text{for all values, when a non-calcified nodule was present at first CT} \\ & + [0.5625495] && \text{if radiological evidence of emphysema at CT} \\ & - [0.6769903] && \text{if at least one solid but no partially- or non-solid nodule present at first CT} \\ & - [0.2708885] && \text{if at least one partially solid, but no non-solid nodule present at first CT} \\ & + [0.7210263] && \text{if at least one non-solid nodule present at first CT} \end{aligned}$$

\* adapted from Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ, Hsieh LJ, Begg CB. Variations in lung cancer risk among smokers. *J Natl Cancer Inst* 2003;95:470-8.