

**Supplementary Table 1:** Characteristics of the 23 studies comprising the OncoArray Lung dataset

Characteristic and description				Cases		Controls		Total	
				N	(%)	N	(%)	N	(%)
Studies	Norway	Europe: Norway	Population-based CC	314	(43.2)	413	(56.8)	727	(2.5)
	MDACC	North America: USA	Clinic-based CC	952	(50.1)	948	(49.9)	1900	(6.5)
	HLCS	North America: USA	Clinic-based CC	2639	(79.2)	695	(20.8)	3334	(11.3)
	LLP	Europe: UK	Population-based CC	427	(47.9)	464	(52.1)	891	(3.0)
	CARET	North America: USA	Nested CC in RCT	550	(51.4)	520	(48.6)	1070	(3.6)
	NELCS	North America: USA	Population-based CC	172	(50.1)	171	(49.9)	343	(1.2)
	Tampa	North America: USA	Hospital-based CC	88	(40.2)	131	(59.8)	219	(0.7)
	Resoluscent	Europe: UK	Clinic-based CC	576	(66.0)	297	(34.0)	873	(3.0)
	NICCC-LCA	Middle East: Israel	Population-based CC	651	(56.1)	509	(43.9)	1160	(3.9)
	Nijmegen	Europe: Netherlands	Population-based CC	420	(48.7)	443	(51.3)	863	(2.9)
	EAGLE	Europe: Italy	Population-based CC	1801	(50.7)	1750	(49.3)	3551	(12.1)
	CAPUA	Europe: Spain	Hospital-based CC	713	(51.1)	683	(48.9)	1396	(4.7)
	EPIC	Europe: Multi-site	Population nested CC	1192	(49.4)	1219	(50.6)	2411	(8.2)
	MEC	North America: USA	Population nested CC	242	(50.4)	238	(49.6)	480	(1.6)
	PLCO	North America: USA	Nested CC in RCT	1348	(60.3)	886	(39.7)	2234	(7.6)
	IARC-L2	Eastern Europe: Multi-site	Hospital-based CC	1075	(50.2)	1067	(49.8)	2142	(7.3)
	ATBC	Europe: Finland	Nested CC in RCT	1017	(60.4)	666	(39.6)	1683	(5.7)
	KLCRI	North America: USA	Population-based CC	93	(41.5)	131	(58.5)	224	(0.8)
	MDCS	Europe: Sweden	Population nested CC	159	(48.8)	167	(51.2)	326	(1.1)
	BioVU	North America: USA	Clinic-based CC	723	(49.9)	727	(50.1)	1450	(4.9)
	CanScreen	North America: Canada	Population nested CC	213	(32.6)	441	(67.4)	654	(2.2)
	NSHDC	Europe: Sweden	Population nested CC	236	(51.0)	227	(49.0)	463	(1.6)
	GLCS	Europe: Germany	Hospital-based CC	795	(78.3)	220	(21.7)	1015	(3.5)
Histology	Adenocarcinoma			5690	(34.7)	-	-	5690	(19.3)
	Squamous cell carcinoma			4045	(24.7)	-	-	4045	(13.8)
	Large cell carcinoma			504	(3.1)	-	-	504	(1.7)
	Non-small cell carcinoma NOS			1072	(6.5)	-	-	1072	(3.6)
	Small cell carcinoma			1846	(11.3)	-	-	1846	(6.3)
	Other histological types			3239	(19.8)	-	-	3239	(11.0)
Age group	<50 years			1716	(11.1)	1448	(11.6)	3164	(11.3)
	50 to 59 years			3542	(22.9)	3392	(27.2)	6934	(24.8)
	60 to 69 years			5416	(35.0)	4764	(38.2)	10180	(36.4)
	70 to 79 years			4087	(26.4)	2541	(20.4)	6828	(23.7)
	≥80 years			730	(4.7)	318	(2.6)	1048	(3.7)
Sex	Males			10427	(63.6)	8136	(62.5)	18563	(63.1)
	Females			5966	(36.4)	4874	(37.5)	10840	(36.9)
Smoking status	Never smokers			1619	(9.9)	3923	(30.1)	5542	(18.8)
	Ever smokers			14498	(88.4)	8815	(67.7)	23313	(79.3)
	Former smokers			5348	(32.6)	3906	(30.0)	9254	(31.5)
	Current smokers			8543	(52.1)	4149	(31.9)	12692	(43.2)
	Unknown			279	(1.7)	275	(2.1)	554	(1.9)
Total				16396		13013		29409	(100.0)

**Abbreviations:** CC (case-control study); RCT (randomized clinical trial)

**Supplementary Table 2:** Characteristics of the 11 studies included in the pooled OncoArray head and neck cancer dataset

Characteristic and description				Cases		Controls		Total	
				N	(%)	N	(%)	N	(%)
Study	CHANCE	North America: USA	Population-based CC	552	(48.8)	580	(51.2)	1132	(12.0)
	Gencapo	South America: Brazil	Hospital-based CC	344	(49.3)	354	(50.7)	698	(7.4)
	ARCAGE	Europe: Multi-center	Hospital-based CC	733	(50.2)	726	(49.8)	1459	(15.5)
	IARC-CE	Europe: Multi-centre	Hospital-based CC	102	(50.5)	99	(49.5)	201	(2.1)
	EPIC	Europe: Multi-center	Population nested CC	105	(6.3)	1570	(93.7)	1675	(17.8)
	IARC-LA	Brazil, Argentina, Cuba	Hospital-based CC	266	(41.8)	371	(58.2)	637	(6.8)
	IARC-ORC	Multi-site	Hospital-based CC	161	(48.8)	169	(51.2)	330	(3.5)
	Maastricht	Europe: Netherlands	Hospital-based CC	279	(50.5)	274	(49.5)	553	(5.9)
	Pittsburgh	North America: USA	Hospital-based CC	763	(49.5)	777	(50.5)	1540	(16.3)
	Rome	Europe: Italy	Hospital-based CC	87	(48.3)	93	(51.7)	180	(1.9)
UK-5000	Europe: UK	Clinic-based nested CC	1023	(100.0)	0	(0.0)	1023	(10.9)	
Site	Oral cavity			2284	(51.7)	-	-	2284	(24.2)
	Oropharynx			1849	(41.9)	-	-	1849	(19.6)
	Hypopharynx			199	(4.5)	-	-	199	(2.1)
	Overlapping			64	(1.4)	-	-	64	(0.7)
	Other or unknown			19	(0.4)	-	-	19	(0.2)
Age group	<50 years			849	(19.9)	826	(16.9)	1675	(18.3)
	50 to 59 years			1402	(32.8)	1391	(28.4)	2793	(30.5)
	60 to 69 years			1293	(30.3)	1510	(30.9)	2803	(30.6)
	70 to 79 years			637	(14.9)	981	(20.1)	1618	(17.7)
	≥80 years			92	(2.1)	184	(3.8)	276	(3.0)
Sex	Males			3296	(49.2)	3400	(50.8)	6696	(70.8)
	Females			1136	(41.1)	1626	(58.8)	2762	(29.2)
Smoking status	Never smokers			773	(17.5)	1827	(36.4)	2600	(27.6)
	Ever smokers			3108	(70.4)	2865	(57.2)	5973	(63.4)
	Former smokers			1192	(27.0)	1657	(33.1)	2849	(30.2)
	Current smokers			1916	(43.4)	1208	(24.1)	3124	(33.1)
	Unknown			534	(12.1)	321	(6.4)	855	(9.1)
Alcohol consumption	Non drinkers			614	(13.9)	795	(15.9)	1409	(14.9)
	Ever drinkers			3506	(79.4)	3692	(73.6)	7198	(76.3)
	Unknown			295	(6.7)	526	(10.5)	821	(8.7)
Total				4415		5013		9428	(100.0)

**Abbreviations:** CC (case-control study)

**Supplementary Table 3:** Predictors of telomere length in the Toronto (MSH-PMH) and Copenhagen (CGPS) OncoArray studies that comprise the discovery dataset for genetic instruments for telomere length in chromosome 5p15.33

Characteristic	Toronto (MSH-PMH)			Copenhagen (CGPS)			Total		
	$\beta^1$	(SE)	P-value	$\beta^2$	(SE)	P-value	$\beta^3$	(SE)	P-value
Age (years)	-0.004	(0.001)	$3.0 \times 10^{-4}$	-27.36	(2.26)	$6.9 \times 10^{-32}$	-0.020	(0.002)	$2.6 \times 10^{-30}$
Sex									
Women vs. Men	-0.068	(0.023)	$3.0 \times 10^{-3}$	192.36	(59.13)	$1.2 \times 10^{-3}$	0.013	(0.043)	0.76
Smoking status									
Ever vs. Never	-0.017	(0.027)	0.55	-60.14	(58.55)	0.30	-0.039	(0.046)	0.40
Current vs. Never	-0.068	(0.047)	0.15	-	-	-	-0.207	(0.128)	0.11
Cigarette pack-years	-0.001	( $7.3 \times 10^{-4}$ )	0.45	-2.62	(1.64)	0.11	-0.002	(0.001)	0.09
Mean TL (SD)	0.993	(0.373)		3247.50	(999.63)		0.008	(0.997)	
Total (%)	879			1172			2051		

**Abbreviations:** CGPS (Copenhagen General Population Study); MSH-PMH (Mount Sinai Hospital-Princess Margaret Hospital study); SE (Standard error); SD (Standard deviation); TL (telomere length)

- <sup>1</sup> Telomere length measured as a T/S ratio; models adjusted for age and sex
- <sup>2</sup> Telomere length measured in base pairs; models adjusted for age and sex
- <sup>3</sup> Telomere length operationalized as a Z-score, standardized in each study separately to achieve mean=0 and standard deviation=1

**Supplementary Table 4:** Associations of each genetic instrument with smoking status (ever vs. never) and cigarette pack-years among smokers, estimated in the control subjects of the OncoArray lung cancer data set

Instrument	Smoking status (n=13013 controls)			Cigarette pack-years (n=8815 controls)		
	$\beta^1$	(SE)	P-value	$\beta^2$	(SE)	P-value
<i>ACYP2</i> rs10165485	0.02	(0.05)	0.70	0.47	(0.85)	0.58
<i>PXK</i> rs6772228	-0.02	(0.08)	0.75	-0.30	(1.44)	0.84
<i>TERC</i> rs10936599	-0.05	(0.04)	0.14	0.74	(0.67)	0.27
<i>NAF1</i> rs11100479	0.03	(0.04)	0.43	-0.93	(0.69)	0.18
<i>OBFC1</i> rs9420907	-0.01	(0.04)	0.85	-0.60	(0.82)	0.47
<i>ZNF676</i> rs10419926	0.05	(0.03)	0.11	-0.65	(0.61)	0.29
<i>RTEL1</i> rs755017	-0.05	(0.05)	0.31	0.01	(0.94)	0.99
5p15.33	0.00	(0.03)	0.96	-0.51	(0.48)	0.29

<sup>1</sup> Logistic regression model adjusted for age, sex, study, 10 genetic ancestry principal components

<sup>2</sup> Linear regression model adjusted for age, sex, study, 10 genetic ancestry principal components

**Supplementary Table 5:** Decomposition of the total effect of the 5p15.33 genetic instrumental variable (IV) on lung cancer risk, into direct and indirect effects, mediated by telomere length maintenance

TL → Outcome: OR ( $\theta_2$ )	TL×IV $\theta_3$	Main TL Effect: OR ( $\theta_2$ )	OR <sup>TE</sup> (95% CI)	OR <sup>NIE</sup> (95% CI)	OR <sup>NDE</sup> (95% CI)
Lung cancer: Zhang et al. <sup>22</sup>					
1.37 (0.315)	-	-	1.043 (1.012 - 1.075)	1.046 (1.014 - 1.084)	0.997 (0.949-1.042)
1.37 (0.315)	0.10	1.369 (0.314)	1.043 (1.012 - 1.075)	1.061 (1.026 - 1.104)	0.983 (0.934-1.030)
1.37 (0.315)	0.20	1.369 (0.314)	1.043 (1.012 - 1.075)	1.076 (1.037 - 1.125)	0.970 (0.917-1.017)
1.37 (0.315)	0.30	1.370 (0.315)	1.043 (1.012 - 1.075)	1.091 (1.048 - 1.147)	0.956 (0.900-1.004)
Lung adenocarcinoma: Zhang et al. <sup>22</sup>					
2.06 (0.723)	-	-	1.071 (1.029 - 1.115)	1.108 (1.053 - 1.178)	0.967 (0.897- 1.032)
2.06 (0.723)	0.10	2.069 (0.727)	1.071 (1.029 - 1.115)	1.125 (1.068 - 1.195)	0.9523031 (0.884-1.018)
2.06 (0.723)	0.20	2.087 (0.736)	1.071 (1.029 - 1.115)	1.142 (1.076 - 1.228)	0.938 (0.862-1.006)
2.06 (0.723)	0.30	2.121 (0.752)	1.071 (1.029 - 1.115)	1.161 (1.088 - 1.255)	0.922 (0.843-0.993)
Lung cancer: Zhu et al. <sup>11</sup>					
1.28 (0.248)	-	-	1.041 (1.012 - 1.071)	1.013 (1.004 - 1.025)	1.028 (0.998 -1.060)
1.28 (0.248)	0.10	1.281 (0.247)	1.041 (1.012 - 1.071)	1.018 (1.007 - 1.032)	1.023 (0.992 - 1.055)
1.28 (0.248)	0.20	1.282 (0.248)	1.041 (1.012 - 1.071)	1.023 (1.010 - 1.039)	1.017 (0.986 - 1.051)
1.28 (0.248)	0.30	1.288 (0.253)	1.041 (1.012 - 1.071)	1.028 (1.013 - 1.047)	1.012 (0.979 - 1.048)

**Abbreviations:** CI (confidence intervals); IV (instrumental variable); NDE (natural direct effect); NIE (natural indirect effect); OR (odds ratio); SE (standard error); TE (total effect); TL (telomere length)

**Note:** Overlapping subjects between the OncoArray studies and the analysis by Zhang et al. were removed (n=3498, 11.9%) and the total effect (OR<sup>TE</sup>) of the 5p15.33 IV was re-estimated

**Supplementary Table 6:** Decomposition of the total effect of the 5p15.33 lung cancer and lung adenocarcinoma risk loci, into direct and indirect effects and the proportion mediated by leukocyte telomere length

SNP-EA (Gene)	$\Delta TL^1$ (Bojesen et al. <sup>47</sup> )		Lung Cancer Overall <sup>2</sup>					Lung Adenocarcinoma <sup>2</sup>				
	%	<i>P</i>	OR <sup>TE</sup> (95% CI)	<i>P</i> <sub>Lung</sub>	OR <sup>NDE</sup> (95% CI)	OR <sup>NIE</sup> (95% CI)	PM (%)	OR <sup>TE</sup> (95% CI)	<i>P</i> <sub>Adeno</sub>	OR <sup>NDE</sup> (95% CI)	OR <sup>NIE</sup> (95% CI)	PM (%)
rs7705526-A ( <i>TERT</i> )	2.6	2.3×10 <sup>-14</sup>	1.104 (1.061-1.148)	8.0×10 <sup>-7</sup>	1.073 (1.027-1.121)	1.029 (1.010-1.048)	28.7 (10.1-47.6)	1.196 (1.136-1.259)	8.5×10 <sup>-12</sup>	1.121 (1.056-1.189)	1.067 (1.039-1.097)	36.5 (21.3-51.7)
rs2736108-A ( <i>TERT</i> )	1.7	5.8×10 <sup>-7</sup>	1.148 (1.102-1.196)	4.5×10 <sup>-11</sup>	1.126 (1.081-1.176)	1.019 (1.007-1.032)	13.7 (4.8-22.7)	1.209 (1.146-1.275)	2.7×10 <sup>-12</sup>	1.158 (1.097-1.227)	1.044 (1.026-1.064)	22.9 (12.7-35.6)
rs421629-G ( <i>CLPTM1L</i> )	0.5	0.11	1.177 (1.133-1.223)	9.0×10 <sup>-17</sup>	1.171 (1.126-1.217)	1.005 (1.002-1.009)	3.4 (1.2-6.2)	1.175 (1.117-1.236)	3.8×10 <sup>-10</sup>	1.160 (1.102-1.222)	1.013 (1.007-1.018)	7.8 (4.3-13.7)
rs13167280-A ( <i>TERT</i> )	1.9	1.2×10 <sup>-5</sup>	1.126 (1.066-1.189)	2.3×10 <sup>-5</sup>	1.073 (1.014-1.140)	1.049 (1.028-1.070)	40.5 (23.6-57.4)	1.214 (1.131-1.303)	6.9×10 <sup>-8</sup>	1.157 (1.074-1.244)	1.049 (1.028-1.070)	24.8 (13.7-44.5)
rs56345976-G ( <i>TERT</i> )	0.6	0.06	1.119 (1.076-1.162)	9.6×10 <sup>-9</sup>	1.111 (1.069-1.156)	1.007 (1.002-1.011)	5.9 (2.1-9.7)	1.135 (1.080-1.194)	8.0×10 <sup>-7</sup>	1.118 (1.065-1.178)	1.015 (1.009-1.021)	11.9 (6.2 - 21.0)

**Abbreviations:** CI (confidence intervals); EA (effect allele); NDE (natural direct effect); NIE (natural indirect effect); OR (odds ratio); PM (proportion mediated); SE (standard error); TE (total effect); TL (telomere length)

<sup>1</sup> SNP effects are expressed as proportion increase (%) in telomere length, based on fold change reported in Bojesen et al.<sup>47</sup>

<sup>2</sup> Logistic regression models for estimating total effects (OR<sup>TE</sup>) were adjusted for age (years), sex, study, cigarette pack-years, and 10 genetic ancestry PCs

**Note:** Overlapping subjects between the OncoArray studies and the analysis by Zhang et al. were removed (n=3498, 11.9%) and the total effect (OR<sup>TE</sup>) of the 5p15.33 IV was re-estimated