

Incorporating Both Genetic and Tobacco Smoking Data to Identify High-Risk Smokers for Lung Cancer Screening

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INTRODUCTION

- Globally, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths.
- Smoking, as the most important risk factor, accounts for more than 80% of the lung cancer cases, and is used in the current screening guidelines to identify high-risk individuals.
- Currently, the U.S. Preventive Services Task Force (USPSTF) recommends that adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke, or have quit within the past 15 years, should receive an annual lung cancer screening using low-dose computed tomography.
- Only about one-third of lung cancer patients meet this criteria and are, thus, eligible for screening.
- USPSTF recently proposed to widen the current lung cancer screening guideline to include less-heavy smokers.
- We sought to incorporate both genetic and tobacco smoking data to identify additional high-risk smokers for screening.

METHODS

- Data from 399,414 participants of European descent in the UK Biobank, a population-based cohort study
- Samples were genotyped by two arrays, the UK BiLEVE Axiom and the UK Biobank Axiom, which shared 95% marker content. Genotyping data were imputed using reference panels of the Haplotype Reference Consortium combined with the UK10K haplotype resource.
- A polygenic risk score (PRS) constructed using 19 risk variants for lung cancer from 14 loci identified by previous genome-wide association studies. [Click to add text](#)
- Cox proportional hazard models used to estimate hazard ratios (HRs) and 5-year absolute risk of lung cancer associated with both tobacco smoking and PRS to identify individuals at a similar or higher risk than those who met the current USPSTF screening guideline.
- Adjusted for covariates: sex, education (college or university degree, some professional qualifications, secondary education, and none of the above), genotype array, and ten principle components for ancestry.

RESULTS

- 1,497 incident lung cancer cases were identified during a median follow-up of 5.7 years,
- An elevated risk of lung cancer was found in all smoking groups compared with never smokers.
- Current smokers with 20-29 pack-years of smoking had a similar risk of lung cancer as smokers who met current screening guidelines. (Table 1)
- The risk of lung cancer was statistically significantly associated with the PRS, following a dose-response pattern regardless of smoking status (trend tests, $p < 0.001$ for each smoking stratum). Interaction tests based on the multiplicative scale were not statistically significant (p for interaction > 0.05).
- Jointly classified by PRS levels and smoking status, the highest risk of lung cancer was observed among current smokers with 20-29 pack-years (HR = 42.1, 95% CI = 25.6-69.0) and those who met the current screening guideline (HR = 28.8, 95% CI = 19.2-43.1) who also had highest genetic risk (Table 2)
- Current smokers with 20-29 pack-years and a high PRS had a higher risk of developing lung cancer than participants who met the current screening guideline.
- Smokers who met the current screening guideline had a 5-year lung cancer risk of 1.2% at age 55, but current smokers who smoked 20-29 pack-years and were at the top 5% of PRS reached the same risk at age 49. (Figure 1)

Table 1. Hazard ratios (95% CI) for lung cancer risk associated with smoking status, UK Biobank, 2006 - 2016.

Smoking status	No. of cases	HR (95% CI)
Never smokers	187	1.00 (reference)
Meeting current screening guidelines*	661	20.3 (17.3-24.0)
Current smokers, ≥ 30 pack-years	378	27.8 (23.2-33.2)
Former smokers, ≥ 30 pack-years, quit in < 15 years	283	15.1 (12.5-18.2)
Other current smokers		
20-29 pack-years	112	20.3 (16.1-25.8)
< 20 pack-years	63	9.53 (7.15-12.7)
Missing pack-year information	75	8.69 (6.63-11.4)
Other former smokers		
≥ 30 pack-years, quit between 15-19 years	42	9.55 (6.81-13.4)
20-29 pack-years, quit in < 15 years	43	7.38 (5.30-10.3)
20-29 pack-years, quit in ≥ 15 years	54	4.32 (3.19-5.87)
Missing pack-years information	126	2.38 (1.89-2.98)
Other	134	2.43 (1.94-3.03)

* Individuals who had a 30 pack-year smoking history and currently smoke or had quit within the past 15 years. HRs were adjusted for sex and education.

Table 2. Estimates of lung cancer risk for groups defined jointly by smoking status and quintiles of polygenic risk score (PRS), UK Biobank, 2006 - 2016.

Smoking status	Q1 (lowest)		Q2		Q3		Q4		Q5 (highest)	
	No. cases	HR	No. cases	HR	No. cases	HR	No. cases	HR	No. cases	HR
Never smokers	28	1.00 (reference)	31	1.10 (0.66, 1.84)	33	1.19 (0.72, 1.96)	38	1.35 (0.83, 2.20)	57	2.01 (1.28, 3.16)
Meeting screening guidelines*	95	19.4 (12.7, 29.7)	124	24.2 (16.0, 36.6)	130	24.7 (16.4, 37.3)	151	27.6 (18.4, 41.4)	161	28.8 (19.2, 43.1)
Current smokers with 20-29 pack-years	18	19.2 (10.6, 34.7)	18	19.6 (10.8, 35.5)	19	21.2 (11.8, 38.0)	21	25.1 (14.2, 44.2)	36	42.1 (25.6, 69.0)
Other current smokers	18	7.25 (4.00, 13.1)	22	9.25 (5.29, 16.2)	34	15.0 (9.07, 24.7)	33	14.7 (8.90, 24.4)	31	15.0 (8.97, 25.0)
Other former smokers	63	3.16 (2.02, 4.93)	71	3.58 (2.31, 5.54)	90	4.55 (2.97, 6.95)	82	4.22 (2.74, 6.48)	93	4.82 (3.16, 7.36)

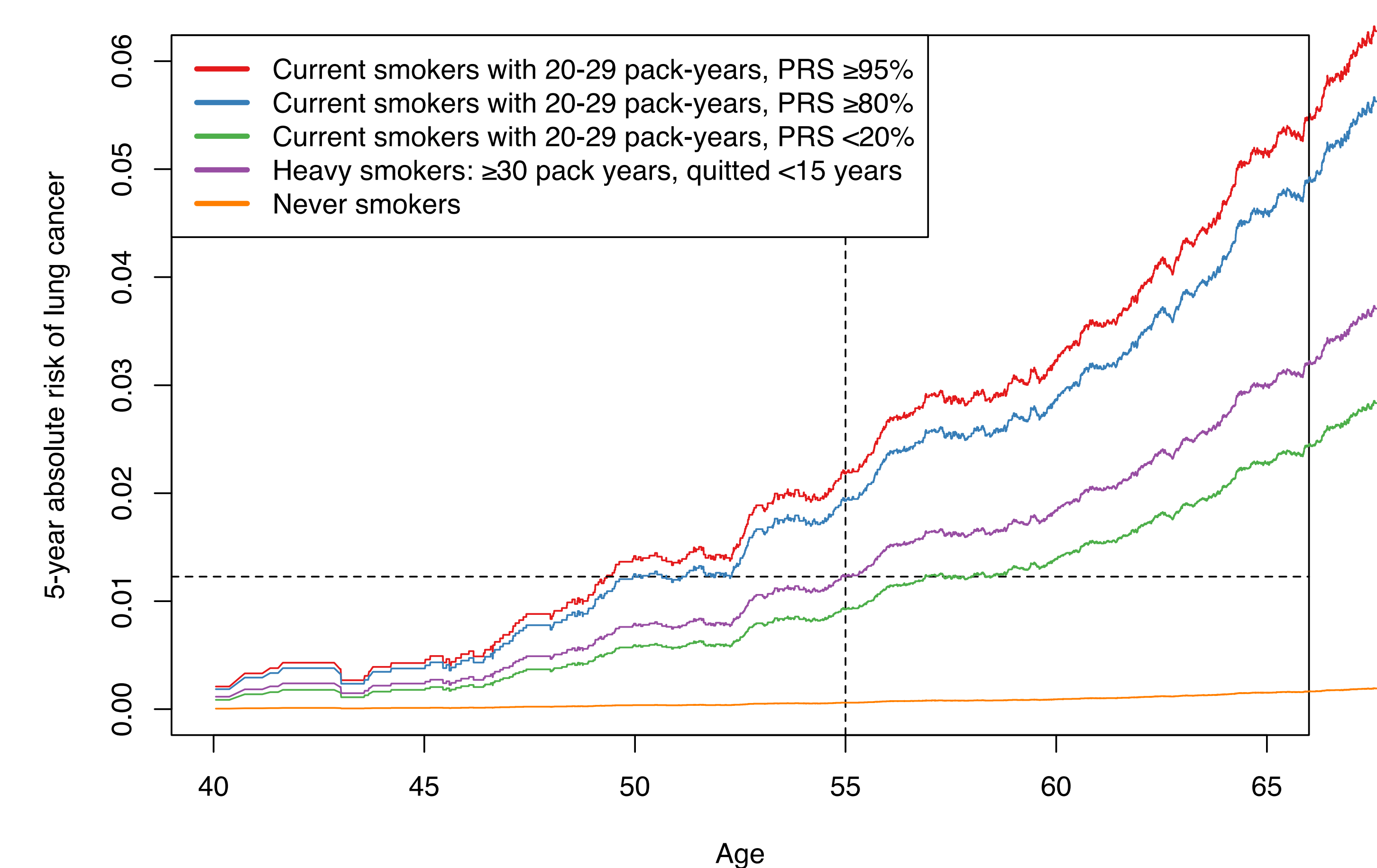


Figure 1. Adjusted 5-year absolute lung cancer risks for never smokers, heavy smokers, current smokers with 20-29 pack-years at a high and low polygenic risk score (PRS). Heavy smokers were defined using the current screening guideline: individuals who had a 30 pack-year smoking history and currently smoke, or had quit within the past 15 years.

CONCLUSION

- Our study supports the modification of lung cancer screening guidelines to include current smokers with 20-29 pack years.
- Findings suggest that heavy smokers at a high genetic risk should receive screening at an earlier age.