A comparative modeling analysis of risk-based lung cancer screening strategies

Online supplementary material

Supplementary Methods

Description of the Bach model

The Bach model was developed in the Carotene and Retinol Efficacy Trial (CARET) using 36,286 individuals (1,070 lung cancer cases) [1]. The Bach model consists of two components, i.e. a model for lung cancer diagnosis and a model for death in the absence of lung cancer diagnosis, estimated through Cox proportional hazards regression, and together predict lung cancer incidence for a one-year timeframe (as a binary outcome event). Applying the models iteratively allows for predictions over longer timeframes. The model predictors include: age, gender, asbestos exposure, smoking intensity (cigarettes per day), smoking duration, and quit-time in former smokers. The component for estimating the one-year probability of death in the absence of lung cancer diagnosis is:

$$1 - S_0^{e(model)}$$

With $S_0 = 0.9917663$ and $model$ being represented by the following equation, where CPD = cigarettes per day, SMK = duration of smoking, QUIT = duration of quitting, AGE = age, ASB = asbestos exposure, and GENDER = gender;

$$
\begin{aligned}
&-7.2036219 + (0.015490665 * \text{CPD}) - (0.00001737645 * (\text{CPD} - 15)^3) && \text{for all values CPD>15}\\
&\quad + (0.000021924149 * (\text{CPD} - 20.185718)^3) && \text{for all values CPD>20}\\
&\quad - (0.0000045476985 * (\text{CPD} - 40)^3) && \text{for all values CPD>40}\\
&+ (0.020041889 * \text{SMK} + (0.0000065443781 * (\text{SMK} - 27.6577)^3) && \text{for all values SMK>27}\\
&\quad - (0.000013947696 * (\text{SMK} - 40)^3) && \text{for all values SMK>40}\\
&\quad + (0.0000074033175 * (\text{SMK} - 50.910335)^3) && \text{for all values SMK>50}\\
&- (0.023358962 * \text{QUIT} + ((0.0019208669 * \text{QUIT})^3) && \text{for all values}\\
&\quad - (0.0020031611 * (\text{QUIT} - 0.50513347)^3) && \text{for all values QUIT>0}\\
&\quad + (0.000082294194 * (\text{QUIT} - 12.295688)^3) && \text{for all values QUIT>12}\\
&+ (0.099168033 * \text{AGE} + (0.0000062174577 * (\text{AGE} - 53.459001)^3) && \text{for all values AGE>53}\\
&\quad - (0.000012115774 * (\text{AGE} - 61.954825)^3) && \text{for all values AGE>61}\\
&\quad + (0.0000058983164 * (\text{AGE} - 70.910335)^3) && \text{for all values AGE>70}
\end{aligned}
$$

$+ (0.06084611)$ if ASB = yes

$- (0.49042298)$ if GENDER=female

The component for estimating the one-year probability diagnosis of lung cancer is:

$$1 - S_0^{e(model)}$$

With $S_0 = 0.99629$ and $model$ being represented by the following equation, where CPD = cigarettes per day, SMK = duration of smoking, QUIT = duration of quitting, AGE = age, ASB = asbestos exposure, and GENDER = gender;

$$-9.7960571 + (0.060818386 * \text{CPD}) - (0.00014652216 * (\text{CPD} - 15)^3) \quad \text{for all values CPD>15}$$
$$+(0.00018486938 * (\text{CPD} - 20.185718)^3) \quad \text{for all values CPD>20}$$
$$-(0.000038347226 * (\text{CPD} - 40)^3) \quad \text{for all values CPD>40}$$

$$+(0.11425297 * \text{SMK} + (0.000080091477 * (\text{SMK} - 27.6577)^3) \quad \text{for all values SMK>27}$$
$$-(0.00017069483 * (\text{SMK} - 40)^3) \quad \text{for all values SMK>40}$$
$$+(0.000090603358 * (\text{SMK} - 50.910335)^3) \quad \text{for all values SMK>50}$$

$$-(0.085684793 * \text{QUIT} + ((0.0065499693 * \text{QUIT})^3) \quad \text{for all values}$$
$$-(0.0068305845 * (\text{QUIT} - 0.50513347)^3) \quad \text{for all values QUIT>0}$$
$$+(0.00028061519 * (\text{QUIT} - 12.295688)^3) \quad \text{for all values QUIT>12}$$

$$+(0.070322812 * \text{AGE} + (0.00009382122 * (\text{AGE} - 53.459001)^3) \quad \text{for all values AGE>53}$$
$$-(0.00018282661 * (\text{AGE} - 61.954825)^3) \quad \text{for all values AGE>61}$$
$$+(0.000089005389 * (\text{AGE} - 70.910335)^3) \quad \text{for all values AGE>70}$$

$+ (0.2153936)$ if ASB = yes

$- (0.0582726)$ if GENDER=female

The model has been externally validated by the authors in 6,239 smokers (with 333 lung cancer cases) from the placebo-arm of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study [2].

For the analyses in this study, it was assumed that only information on age and smoking history was known. Therefore, it was assumed that no asbestos exposure occurred.

Description of the PLCOm2012 model

The PLCOm2012 model was developed in the control-arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), using 36,286 individuals (630 lung cancer cases) [3]. The model was estimated through multivariate logistic regression and predicts lung cancer incidence for a six-year timeframe. It was initially validated in 37,332 individuals (678 lung cancer cases) of the PLCO intervention-arm (in which chest radiography screening occurred).

The model predictors include seven non-smoking variables: age, race/ethnicity, education (an estimator of socioeconomic circumstance), body mass index, personal history of cancer, family history of lung cancer, and chronic obstructive pulmonary disease. The model includes four smoking variables: smoking status (former vs. current), smoking intensity (cigarettes per day), smoking duration, and quit-time in former smokers. Using multivariable fractional polynomials, smoking intensity was shown to have a nonlinear relationship with lung cancer, and this nonlinear effect is incorporated into PLCOm2012. The risk-factors incorporated in the model are listed in **Supplementary Table 1**, along with their log odds ratios and corresponding model coefficients.

The initial predictive performance evaluation of the PLCOm2012 in the PLCO intervention-arm demonstrated high discrimination (AUC = 0.80) and calibration (predicted probabilities / observed = 0.95). The model has also been externally validated by the authors in 51,033 (1,826 cases) participants of the National Lung Screening Trial [3].

The truncated version of the PLCOm2012 model uses the same parameter estimates as the original PLCOm2012 model. However, it is assumed that only information on age and smoking history is known. For the analyses in this study, it was assumed that the participant was white, had a body mass index of 27 (centre value), some college education (centre value), no chronic obstructive pulmonary disease, no personal history of cancer, and no family history of lung cancer.

The full version of the PLCOm2012 model has been compared to the truncated PLCOm2012 model within four different cohorts (PLCO control arm, PLCO chest radiography screening arm, NLST CT screening arm and the NLST chest radiography screening arm) in a previous investigation [4]. The AUCs for 6-year lung cancer incidence were similar between the full and truncated versions of the PLCOm2012 models, as shown in **Supplementary Table 2**. **Supplementary Figure 1** shows the calibration plots for the full model and the truncated model. Both models slightly underestimate the risk for persons with an observed risk between 2.5-5.0%. However, as **Supplementary Figure 3** and **Supplementary Table 7** show, 50% of all individuals in the PLCO control arm have a risk of less than 0.93% and 75% of individuals have a truncated PLCOm2012 model risk of less than 2.23%. Therefore, both the full and truncated model are generally well-calibrated.

Description of the constrained Lung Cancer Death Risk Assessment Tool (LCDRAT) model

The LCDRAT model was developed in 39,180 ever-smokers of the control-arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) [5]. It estimates lung cancer mortality over a 1-10 year timeframe through Cox proportional hazards regression, accounting for competing causes of death. The cumulative 5-year risk of lung cancer death is:

$$R = \int_0^5 \lambda_1(u; x_1) \exp\left\{-\int_0^u \left(\lambda_1(v; x_1) + \lambda_2(v; x_2)\right) dv\right\} du$$

Where $\lambda_2(t)$ is the cause-specific hazard models for all other (i.e. non-lung-cancer) causes of death and $\lambda_1(t)$ is the cause-specific hazard of lung cancer death. The model is available in the R package "lcmodels", accessible at: https://dceg.cancer.gov/tools/risk-assessment/lcmodels.

The model predictors include seven non-smoking variables: age, gender, race/ethnicity, education (an estimator of socioeconomic circumstance), body mass index, family history of lung cancer, and emphysema. The model includes four smoking variables: pack-years smoked, smoking intensity (dichotomized at >1 pack per day), smoking duration, and quit-years in former smokers. The risk-factors incorporated in the model are listed in **Supplementary Table 3** (adapted from [5]), along with their hazard ratios..

The full LCDRAT model has been validated by the authors in the chest radiography group of the PLCO, the National Lung Screening Trial (NLST), the NIH-AARP cohort, and the American Cancer Society CPS-II cohort [6]. In addition, external validation in National Health Interview Survey (NHIS: 1997-2001) ever-smokers ages 50-80 years showed good calibration (predicted probabilities / observed: 0.94) and discrimination (AUC: 0.78) [5].

For the analyses in this study, a truncated version of the LCDRAT model was used, which was provided by Dr. Cheung and Dr. Katki. The truncated LCDRAT model was refitted using only age, gender and smoking variables, for both the submodel for lung cancer death and for competing mortality; the corresponding hazard ratios are shown in **Supplementary Table 3**. The constrained model can be obtained for research purposes through contacting the developers (https://dceg.cancer.gov/tools/risk-assessment/lcmodels).

The developers investigated the differences in individual predictions between the full and constrained LCDRAT models (**Supplementary Table 4**). They found that they were similar for Caucasian individuals with no emphysema or family of lung cancer. As expected, they found substantial differences for other races and ethnicities and individuals with emphysema or family history of lung cancer, as shown in **Supplementary Table 4**.

In addition, differences in calibration and discrimination were examined in ever-smokers aged 50-80 in 1997-2001 National Health Interview Survey data, with mortality follow-up through 2006 (**Supplementary Table 5**). The constrained LCDRAT was well-calibrated for all US ever-smokers ages 50-80 (E/O=0.89, 95%CI: 0.80-1.00). As expected, the AUC was reduced between the full and constrained LCDRAT (AUC of 0.78 vs 0.77).

Application of risk prediction models for life-time risk

The Smoking History Generator (SHG) was used to simulate the smoking histories and other-cause mortality (corrected for smoking behaviour) probabilities for a U.S. cohort of men and women born in 1950 [7]. The simulated smoking history of each individual consist of: whether the person ever initiates smoking, the age of smoking initiation, the average number of cigarettes per day (CPD) smoked at each age (averaged over the person's smoking-years up to that age), and the age of cessation.

The Bach, PLCOm2012 and LCDRAT models were consequently applied to these generated histories to estimate the risk at each age of life between ages 45 and 80. For example, consider a woman who started smoking at age 14 and quit at age 56. At ages 15-18 she smoked 10 cigarettes per day, and from ages 19-55 20 cigarettes per day. **Supplementary Table 6** notes this person's smoking characteristics at ages 50, 55, 60 and 65 as they are applied in the Bach, PLCOm2012 and LCDRAT models.

Due to variations in a person's smoking history over the person's life-time, the accumulation of risk may vary widely between individuals. The variation in the estimated accumulated risk is shown for five different male individuals for the Bach, PLCOm2012 and LCDRAT models in **Supplementary Figure 2.**

Estimated risk-distributions in ever-smokers of the PLCO control-arm

Supplementary Figure 3 shows the distribution of estimated six-year lung cancer incidence for the Bach and PLCOm2012 models, as well as the six-year lung cancer mortality risks for the LCDRAT model for ever-smokers in the PLCO control-arm. The median estimated incidence risk was 1.04% for the Bach model (interquartile range: 0.34-2.62%), 0.93% for PLCOm2102 (interquartile range: 0.36-2.23%), while the median estimated lung cancer mortality risk was 0.64% for the LCDRAT model (interquartile range: 0.24-1.59%). While both the Bach and PLCOm2012 models had a net benefit over the USPSTF-criteria for risk scores in the second risk quartiles, <10% of lung cancer incidence occurred in these quartiles (**Supplementary Table 7**) [4]. The number of individuals needed to screen to detect one lung cancer was substantially higher for these risk quartiles (Bach: 170, PLCOm2012: 186) compared to the highest risk quartiles (Bach: 22, PLCOm2012: 21), in which 65-68% of cancers occurred. Similar results were found for the LCDRAT model for lung cancer mortality, in which 7.44% of all lung cancer deaths occurred in the second quintile (requiring screening 286 individuals to detect one lung cancer that leads to mortality), compared to 65.11% in the highest quintile requiring screening 33 individuals to detect one lung cancer that leads to mortality) (**Supplementary Table 7**) Therefore, low risk-thresholds may yield positive net benefits, but would inefficiently select individuals for screening.

Indeed, higher risk-thresholds required screening fewer individuals to detect one lung cancer (or lung cancer leading to lung cancer death for LCDRAT) than lower risk-thresholds (**Supplementary Table 7**). However, while screening individuals in the third risk quartile was less efficient (Bach: 58, PLCOm2012: 64, LCDRAT: 83) than screening individuals in the highest risk quartile, approximately 22-25% of lung cancer (deaths) still occurred in the third risk quartiles.

CISNET natural-history model characteristics

Each CISNET natural-history model generates two life-histories for each individual: one in which screening does not occur, and one in which screening occurs under the evaluated screening strategy. These two life-histories are compared to each other to evaluate the effects of screening. For example, a cancer is defined as overdiagnosed if it is detected through screening in the screening scenario, but would not have been clinically detected before death from other causes occurs in the no-screen scenario. **Supplementary Table 8** provides an overview of the characteristics of the CISNET natural-history models participating in these analyses. **Supplementary Figure 6** compares modeled age-specific lung cancer incidence rates for the 1950 birth-cohort in the absence of screening from each natural-history model to observed SEER-18 (Surveillance, Epidemiology, and End Results Program) data from 2000-2016 [8]. While SEER-18 is not completely representative of the U.S. population, it provides a point of reference for the models.

The Erasmus and University of Michigan models assume CT screening sensitivity differs by stage and histology, as described in ten Haaf et al [9]. The MGH model assumes a sensitivity of 63% for 1-4mm peripheral nodules, a sensitivity of 77% for 4-8mm peripheral nodules, and sensitivity of 100% for peripheral nodules >8mm, as reported in the model's online profile (accessible at: https://cisnet.flexkb.net/mp/pub/CISNET_ModelProfile_LUNG_MGHITA_001_01132012_83639.pdf). Sensitivities for central lesions of the same diameter are assumed to be 25% lower than those for peripheral lesions. The Stanford model assumes CT sensitivity by nodule size and gender, applying CT detection thresholds of 2.5 mm (women) and 2.75 mm (men), which each tumor having a screen-detection threshold that follows a Weibull distribution [10].

Supplementary References

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Supplementary Tables

Supplementary Table 1: Risk-factors considered in the PLCOm2012 model

Risk-factor	Log odds ratio	Model coefficient
Age, per one-year increase (centred on age 62)	1.081	0.0778868
Race or ethnic group (self-reported)		
White (non-Hispanic)	1.00 (reference)	0.000 (reference)
Black (non-Hispanic)	1.484	0.3944778
Hispanic	0.475	−0.7434744
Asian	0.627	−0.466585
Native Hawaiian or Pacific Islander	1.00	0.000
American Indian or Alaskan Native	2.793	1.027152
Education, per increase of 1 level. Education was centred on level 4*	0.922	−0.0812744
Body-mass index, per 1-unit increase (centred on 27)	0.973	−0.0274194
Chronic obstructive pulmonary disease		
No	1.00 (reference)	0.000 (reference)
Yes	1.427	0.3553063
Personal history of cancer		
No	1.00 (reference)	0.000 (reference)
Yes	1.582	0.4589971
Family history of lung cancer		
No	1.00 (reference)	0.000 (reference)
Yes	1.799	0.587185
Smoking status		
Former	1.00 (reference)	0.000 (reference)
Current	1.297	0.2597431
Smoking intensity†	‡	−1.822606
Duration of smoking, per 1-year increase (centred on 27 years)	1.032	0.0317321
Smoking quit time, per 1-year increase (centred on 10 years)	0.970	−0.0308572
Model constant		−4.532506

* Education was measured in six ordinal levels: less than high-school graduate (level one), high-school graduate (level two), some training after high school (level three), some college (level four), college graduate (level five), and postgraduate or professional degree (level six).

† For smoking intensity, the contribution of the variable to the model should be calculated by dividing the number of cigarettes per day by 10, exponentiating by the power −1, centring by subtracting 0.4021541613, and multiplying this number by the beta coefficient of the variable.

‡ This variable is nonlinear so no single odds ratio represents the entire association

Supplementary Table 2: Comparative discrimination capability between the full and truncated PLCOm2012 models*

Investigated cohort	Full PLCOm2012 model AUC†	Truncated PLCOm2012 model AUC
PLCO Control arm	0.7959	0.7804
PLCO chest radiography screening arm	0.7926	0.7804
NLST CT screening arm	0.6949	0.6884
NLST chest radiography screening arm	0.7098	0.6929

* Adapted from: [4]

† AUC: area under the receiver operating characteristic curve

Supplementary Table 3: Risk-factors considered in the full and constrained LCDRAT models

Risk-factor	Hazard ratio (95% confidence interval)*			
	Full version		Truncated version	
	Lung Cancer Death	Competing Mortality	Lung Cancer Death	Competing Mortality
Age				
Log term	431.81 (185.06-1007.58)	-	565.15	-
Squared	-	1.001 (1.001-1.001)	-	1.001
Female sex (binary)	0.84 (0.74-0.95)	0.57 (0.53-0.60)	0.89	0.60
Race (categorical)				
White, non-Hispanic	1.00 (reference)	1.00 (reference)	-	-
Black, non-Hispanic	1.48 (1.18-1.87)	1.47 (1.33-1.62)	-	-
Hispanic	0.69 (0.40-1.19)	1.00 (0.83-1.21)	-	-
Asian or other	0.66 (0.45-0.96)	0.85 (0.74-0.97)	-	-
Education[†](trend)	0.91 (0.87-0.94)	0.96 (0.94-0.97)	-	-
BMI ≤ 18.5[‡]				
Binary	1.43 (0.90-2.27)	2.01 (1.63-2.47)	-	-
Log term	0.45 (0.30-0.68)	-	-	-
Squared§	-	1.004 (1.003-1.004)	-	-
Pack-years (Categorical)				
0-29.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
30-39.9	1.74 (1.35-2.24)	1.08 (0.99-1.19)	1.72	1.06
40-49.9	2.11 (1.68-2.66)	1.13 (1.03-1.24)	2.11	1.12
>50	2.45 (1.68-3.21)	1.21 (1.08-1.35)	2.51	1.22
Quit years (Log term[‖])	0.69 (0.64-0.74)	0.83 (0.80-0.86)	0.66	0.83
Years smoked				
Log term	1.395 (1.099-1.771)	-	1.45	-
Linear	-	1.002 (0.998-1.006)	-	1.005
>1 pack per day (Binary)	1.27 (1.05-1.54)	1.13 (1.04-1.22)	0.89	1.14
Emphysema (Binary)	1.74 (1.45-2.09)	1.92 (1.75-2.10)	-	-
Lung cancer family history[¶] (Trend[#])	1.53 (1.30-1.79)	-	-	-

* Cells with hyphens indicate that the risk factor, or parameterization of the risk factor, was not included. An increase of 1 year higher age results in the hazards increasing by hazard ratio of $\exp\{\ln(\text{age}+1)-\ln(\text{age})\}$. If all other factors are the same, a 61-year-old has $\exp\{\ln(431.812)\times[\ln(61)-\ln(60)]\} = 1.11$ times greater hazards of lung cancer death than a 60-year-old. For competing mortality models, an increase of 1 year higher age results in hazards increasing by hazard ratio $\exp\{(\text{age}+1)2-\text{age}2\}$. If all other factors are the same, a 61-year-old has $\exp\{\ln(1.001)\times[612-602]\} = 1.13$ times greater hazards of death from other causes than a 60-year-old.
† Less than grade 12 = 1, high-school graduate = 2, post high school but no college = 3, some college = 4, bachelor's degree = 5, graduate school = 6.
‡, Calculated as weight in kilograms divided by height in meters squared.
§,This is the square of BMI centered at 25. BMI is modeled as a binary category for being underweight (BMI≤18.5) and continuously for BMI greater than 18.5.
|| This is natural logarithm of the sum of 1 and quit-years. All log terms are natural logarithms.
¶, Number of First-degree relatives (siblings, parents, children) with personal history of lung cancer
#, Definition: No first-degree relatives with lung cancer = 0, 1 first-degree relative with lung cancer = 1, 2 or more first-degree relatives with lung cancer = 2.

Supplementary Table 4: Differences in 5-year predicted lung cancer death risk between the full and constrained LCDRAT models*

Age	Gender	Years. smoked	Years quit	CPD	Race/ Ethnicity	Emphysema?	Parents with lung cancer	BMI	Education.	5-year full LCDRAT, %	5-year constrained LCDRAT, %
66	Male	43	N/A	36	White	No	None	23	Post high school, no college	4.3	4.4
58	Female	37	N/A	36	Black	Yes	2	28	Bachelor's degree	6.7	1.7
75	Male	45	9	40	Hispanic	Yes	None	26	Associates. Degree	3.5	3.7
72	Female	42	6	24	Hispanic	No	2	27	Bachelor's degree	3.4	3.1
56	Male	29	6	40	Other	Yes	None	24	Bachelor's degree	0.6	0.6

* CPD = cigarettes smoked per day; BMI = Body Mass Index; LCDRAT=Lung Cancer Death Risk Assessment Tool; N/A = not applicable.

Supplementary Table 5: Population-wise calibration and discrimination in U.S. ever-smokers (using data on participants aged 50-80 in 1997-2001 from National Health Interview Survey) between the full and constrained LCDRAT models.

Population	Number Observed	Full LCDRAT					Constrained LCDRAT				
		Number Expected	E/O*	95% CI	AUC†	95% CI	Number Expected	E/O*	95% CI	AUC†	95% CI
All ever-smokers	452,937	424,778	0.94	(0.84,1.05)	0.78	(0.76,0.80)	404,128	0.89	(0.80,1.00)	0.77	(0.75,0.80)
USPSTF-eligible ever-smokers	266,455	271,709	1.02	(0.88,1.18)	0.69	(0.63,0.66)	257,686	0.97	(0.84,1.12)	0.69	(0.65,0.73)
USPSTF-ineligible ever-smokers	186,482	153,166	0.82	(0.69,0.98)	0.75	(0.71,0.79)	146,536	0.79	(0.66,0.94)	0.74	(0.70,0.78)

* "E/O" is the ratio of the number of expected lung cancer deaths ("number expected") to the number of observed lung cancer deaths ("number observed").
†AUC" is the area under the receiver operating characteristic curve.

Supplementary Table 6: Example of smoking characteristics over an individual's life-time as applied in the Bach, PLCOm2012 and LCDRAT models

Age	Smoking status	Smoking duration in years (at the start of the age)	Average number of cigarettes smoked (over smoking duration)	Years since smoking cessation
50	Current smoker	35	18.89	0 (current smoker)
55	Current smoker	40	19.02	0 (current smoker)
60	Former smoker	41	19.02	5
65	Former smoker	41	19.02	9

Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool

Supplementary Table 7: Occurrence of lung cancer in the PLCO control-arm by risk-prediction model and risk quartile

Risk-prediction Model	Risk quartile	1st	2nd	3rd	4th
Bach model, 6-year risk for lung cancer incidence	Corresponding risk thresholds	Risk < 0.34%	Risk ≥ 0.34% to 1.04%	Risk ≥ 1.04% to 2.62%	Risk ≥ 2.62%
	Proportion of lung cancers	2.54%	8.32%	24.54%	64.60%
	Number of individuals needed to screen to detect one lung cancer	557	170	58	22
PLCOm2012 model, 6-year risk for lung cancer incidence	Corresponding risk thresholds	Risk 0.36< %	Risk ≥ 0.36% to 0.93%	Risk ≥ 0.93% to 2.23%	Risk ≥ 2.23%
	Proportion of lung cancers	1.97%	7.62%	22.00%	68.41%
	Number of individuals needed to screen to detect one lung cancer	716	186	64	21
LCDRAT model, 6-year risk for lung cancer mortality	Corresponding risk thresholds	Risk 0.24< %	Risk ≥ 0.24% to 0.64%	Risk ≥ 0.64% to 1.59%	Risk ≥ 1.59%
	Proportion of lung cancer deaths	1.91%	7.45%	25.53%	65.11%
	Number of individuals needed to screen to detect one lung cancer that leads to mortality	1,113	286	83	33

Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool, PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Supplementary Table 8: Overview of the natural-history models used in the comparative modelling analysis

	Erasmus model (MISCAN-Lung)	**MGH-HMS model (Lung Cancer Policy Model)**	**Stanford model (Lung Cancer Outcomes Simulator)**	**University of Michigan model**
Main model reference(s)	[9]	[11, 12]	[10, 13]	[14]
Data sources used for calibration	NHS/HPFS, SEER, NLST, PLCO	SEER, NLST, PLCO	NHS/HPFS, SEER, NLST, PLCO	NHS/HPFS, NLST, PLCO, U.S. lung cancer mortality data
Dose-response model	Two-stage clonal expansion model	Probabilistic by histology	Two-stage clonal expansion model	Two-stage clonal expansion model
Modelled lung cancer histologies	Adenocarcinoma/large cell/BAC, squamous , other non-small cell, small cell	Adenocarcinoma, adenocarcinoma in situ, large cell, squamous, small cell, and other	Adenocarcinoma, large cell, squamous, small cell, BAC	Adenocarcinoma, squamous, small cell, other
Modelled lung cancer stages	IA, IB, II, IIIA, IIIB, IV	IA1, IA2, IB, II, IIIA, IIIB, IV	Early (I-II), advanced (III-IV)	IA1, IA2, IB, II, IIIA, IIIB, IV
Stage progression	Markov state-transition by histology	Based on tumour volume and metastatic burden	Based on tumour volume and metastatic burden	Backward model based on histology and stage at lung cancer incidence
Lung cancer survival	By sex, histology and stage; based on SEER 18 2004–2010	Calibrated to SEER 18 2004–2013	Based on SEER 17 1988–2003	By sex, histology, stage and age at diagnosis; based on SEER 18 2005–2012
Screening sensitivity model	By stage and histology	By size (mm) and location in lung (central/peripheral)	By size (mm) and histology	By stage and histology
Screening effectiveness	Cure model	Earlier stage detection from the natural-history model	Not stage-shift model	Cure model and earlier stage detection
Positive nodule (non-lung cancer) follow-up algorithm	Implicit; based on NLST	Explicitly modelled using Fleischner and Lung-RADS guidelines; lung cancers diagnosed on follow-up are categorized as "non-screened-detected"	Explicit based on Lung-RADS	Implicit based on NLST

Abbreviations: BAC: bronchioloalveolar carcinoma; Lung-RADS: Lung Imaging Reporting and Data System; MGH-HMS: Massachusetts General Hospital–Harvard Medical School; MISCAN: Microsimulation Screening Analysis; NHS/HPFS: Nurses' Health Study/Health Professionals' Follow-up Study; NLST: National Lung Screening Trial; PLCO: Prostate, Lung, Colorectal, and Ovarian; SEER: Surveillance, Epidemiology, and End Results.

Supplementary Table 9: Benefits and harms of the USPSTF-criteria and selected Bach model screening strategies (screening ages 55-80) compared to no screening* (Erasmus model)

Strategy description	Corresponding risk-threshold, %	Percentage ever screened, %	Number of CT screens per 100,000	Lung cancer deaths prevented per 100,000	Lung cancer mortality reduction, %	Lifeyears gained per 100,000	Lifeyears gained per lung cancer death prevented	Number of overdiagnosed lung cancers per 100,000	Percentage of screen detected cases that is overdiagnosed, %	Average number of screens per lung cancer death avoided	Average number of screens per lifeyear gained	Average number of screens per person screened	Average age at first screening, y
USPSTF-criteria	USPSTF-criteria	20.6	333,369	865	16.9	11,281	13.0	156	8.1	385	30	16	55.8
Similar proportion of individuals selected as the USPSTF-criteria in the PLCO control-arm	1.59	33.6	533,542	1,161	22.7	14,386	12.4	219	8.4	460	37	16	61.1
Similar sensitivity as the USPSTF-criteria in the PLCO control-arm	1.91	31.2	471,544	1,121	21.9	13,727	12.2	216	8.6	421	34	15	61.9
Similar CT screens required as the USPSTF-criteria	2.80	25.4	332,450	976	19.1	11,492	11.8	201	8.9	341	29	13	64.1
Similar lung cancer deaths averted as the USPSTF-criteria	3.40	22.1	261,076	891	17.4	10,146	11.4	190	9.2	293	26	12	65.4
Similar life-years gained as the USPSTF-criteria	2.80	25.4	332,450	976	19.1	11,492	11.8	201	8.9	341	29	13	64.1

***** Results are per 100,000 individuals alive at age 45. Lung cancer incidence in the no-screening strategy was 6,606 per 100,000 persons; lung cancer mortality was 5,112 per 100,000 persons.

Abbreviations: USPSTF: United States Preventive Services Task Force

Supplementary Table 10: Benefits and harms of the USPSTF-criteria and selected Bach model screening strategies (screening ages 55-80) compared to no screening* (MGH model)

Strategy description	Corresponding risk-threshold, %	Percentage ever screened, %	Number of CT screens per 100,000	Lung cancer deaths prevented per 100,000	Lung cancer mortality reduction, %	Lifeyears gained per 100,000	Lifeyears gained per lung cancer death prevented	Number of overdiagnosed lung cancers per 100,000	Percentage of screen detected cases that is overdiagnosed, %	Average number of screens per lung cancer death avoided	Average number of screens per lifeyear gained	Average number of screens per person screened	Average age at first screening, y
USPSTF-criteria	USPSTF-criteria	18.7	337,726	337	6.7	4,665	13.9	49	10.4	1,003	72	18	55.8
Similar proportion of individuals selected as the USPSTF-criteria in the PLCO control-arm	1.59	30.2	530,311	502	10.0	6,432	12.8	77	10.5	1,057	82	18	61.1
Similar sensitivity as the USPSTF-criteria in the PLCO control-arm	1.91	28.0	469,611	463	9.2	5,830	12.6	72	10.4	1,014	81	17	61.9
Similar CT screens required as the USPSTF-criteria	2.80	22.8	333,458	364	7.3	4,384	12.0	60	10.1	915	76	15	64.1
Similar lung cancer deaths averted as the USPSTF-criteria	3.40	19.8	263,459	303	6.1	3,529	11.6	52	9.7	869	75	13	65.5
Similar life-years gained as the USPSTF-criteria	2.80	22.8	333,458	364	7.3	4,384	12.0	60	10.1	915	76	15	64.1

***** Results are per 100,000 individuals alive at age 45. Lung cancer incidence in the no-screening strategy was 6,518 per 100,000 persons; lung cancer mortality was 5,010 per 100,000 persons.

Abbreviations: MGH: Massachusetts General Hospital USPSTF: United States Preventive Services Task Force

Supplementary Table 11: Benefits and harms of the USPSTF-criteria and selected Bach model screening strategies (screening ages 55-80) compared to no screening* (Stanford model)

Strategy description	Corresponding risk-threshold, %	Percentage ever screened, %	Number of CT screens per 100,000	Lung cancer deaths prevented per 100,000	Lung cancer mortality reduction, %	Lifeyears gained per 100,000	Lifeyears gained per lung cancer death prevented	Number of overdiagnosed lung cancers per 100,000	Percentage of screen detected cases that is overdiagnosed, %	Average number of screens per lung cancer death avoided	Average number of screens per lifeyear gained	Average number of screens per person screened	Average age at first screening, y
USPSTF-criteria	USPSTF-criteria	19.0	301,659	470	8.6	6,494	13.8	109	5.6	642	46	16	56.0
Similar proportion of individuals selected as the USPSTF-criteria in the PLCO control-arm	1.59	30.5	483,152	671	12.3	8,762	13.1	164	5.9	718	55	16	61.8
Similar sensitivity as the USPSTF-criteria in the PLCO control-arm	1.91	28.3	426,885	642	11.8	8,280	12.9	159	6.0	663	51	15	62.7
Similar CT screens required as the USPSTF-criteria	2.80	23.0	300,767	553	10.1	6,849	12.4	145	6.2	541	44	13	65.0
Similar lung cancer deaths averted as the USPSTF-criteria	3.40	20.0	236,096	496	9.1	5,960	12.0	136	6.5	472	39	12	66.4
Similar life-years gained as the USPSTF-criteria	2.80	23.0	300,767	553	10.1	6,849	12.4	145	6.2	541	44	13	65.0

***** Results are per 100,000 individuals alive at age 45. Lung cancer incidence in the no-screening strategy was 6,889 per 100,000 persons; lung cancer mortality was 5,445 per 100,000 persons.

Abbreviations: USPSTF: United States Preventive Services Task Force

Supplementary Table 12: Benefits and harms of the USPSTF-criteria and selected Bach model screening strategies (screening ages 55-80) compared to no screening* (Michigan model)

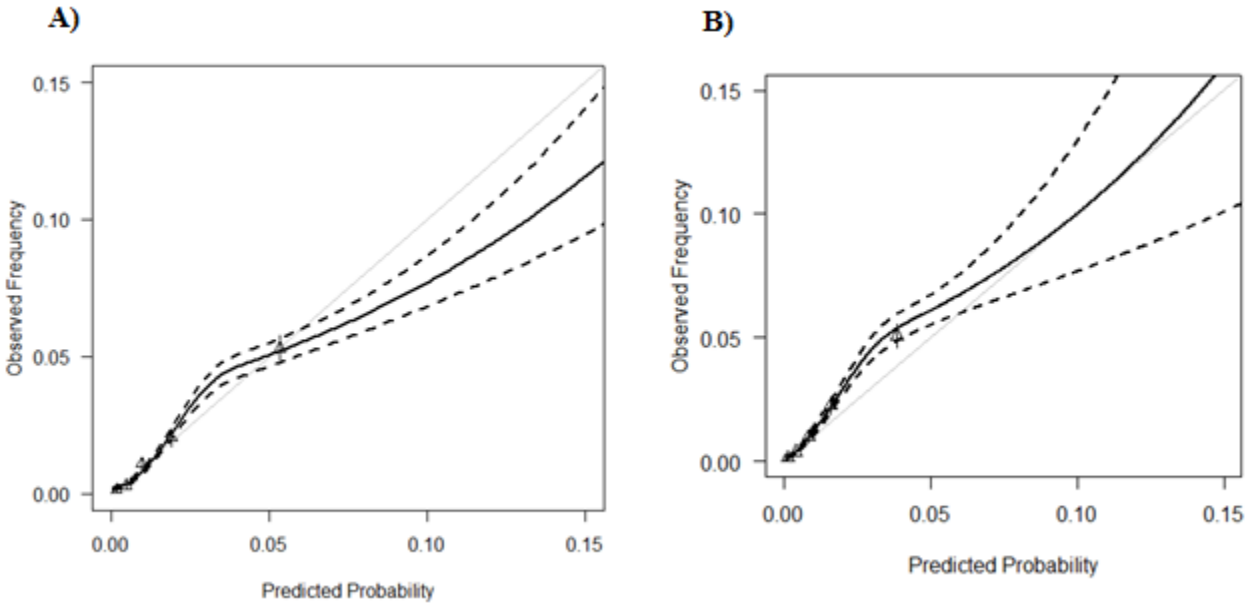
Strategy description	Corresponding risk-threshold, %	Percentage ever screened, %	Number of CT screens per 100,000	Lung cancer deaths prevented per 100,000	Lung cancer mortality reduction, %	Lifeyears gained per 100,000	Lifeyears gained per lung cancer death prevented	Number of overdiagnosed lung cancers per 100,000	Percentage of screen detected cases that is overdiagnosed, %	Average number of screens per lung cancer death avoided	Average number of screens per lifeyear gained	Average number of screens per person screened (	Average age at first screening, y
USPSTF-criteria	USPSTF-criteria	21.2	333,676	779	11.0	11,922	15.3	147	5.3	428	28	16	55.8
Similar proportion of individuals selected as the USPSTF-criteria in the PLCO control-arm	1.59	33.7	525,128	1,050	14.8	15,198	14.5	211	5.6	500	35	16	61.1
Similar sensitivity as the USPSTF-criteria in the PLCO control-arm	1.91	31.2	463,608	1,004	14.1%	14,293	14.2	208	5.7	462	32	15	61.8
Similar CT screens required as the USPSTF-criteria	2.80	25.5	325,875	879	12.4	11,914	13.6	191	6.0	371	27	13	64.0
Similar lung cancer deaths averted as the USPSTF-criteria	3.40	22.1	255,358	793	11.1	10,330	13.0	178	6.1	322	25	12	65.4
Similar life-years gained as the USPSTF-criteria	2.80	25.5	325,875	879	12.4	11,914	13.6	191	6.0	371	27	13	64.0

***** Results are per 100,000 individuals alive at age 45. Lung cancer incidence in the no-screening strategy was 8,450 per 100,000 persons; lung cancer mortality was 7,114 per 100,000 persons.

Abbreviations: USPSTF: United States Preventive Services Task Force

Supplementary Figures

Supplementary Figure 1: Calibration plot of the full (A) and truncated (B) PLCOm2012 model in the PLCO control arm (6-year lung cancer incidence).



Abbreviations: PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Supplementary Figure 2: Variation in life-time risk for the Bach model (A), PLCOm2012 model (B) and LCDRAT model (C) (six-year risks at each age by model)

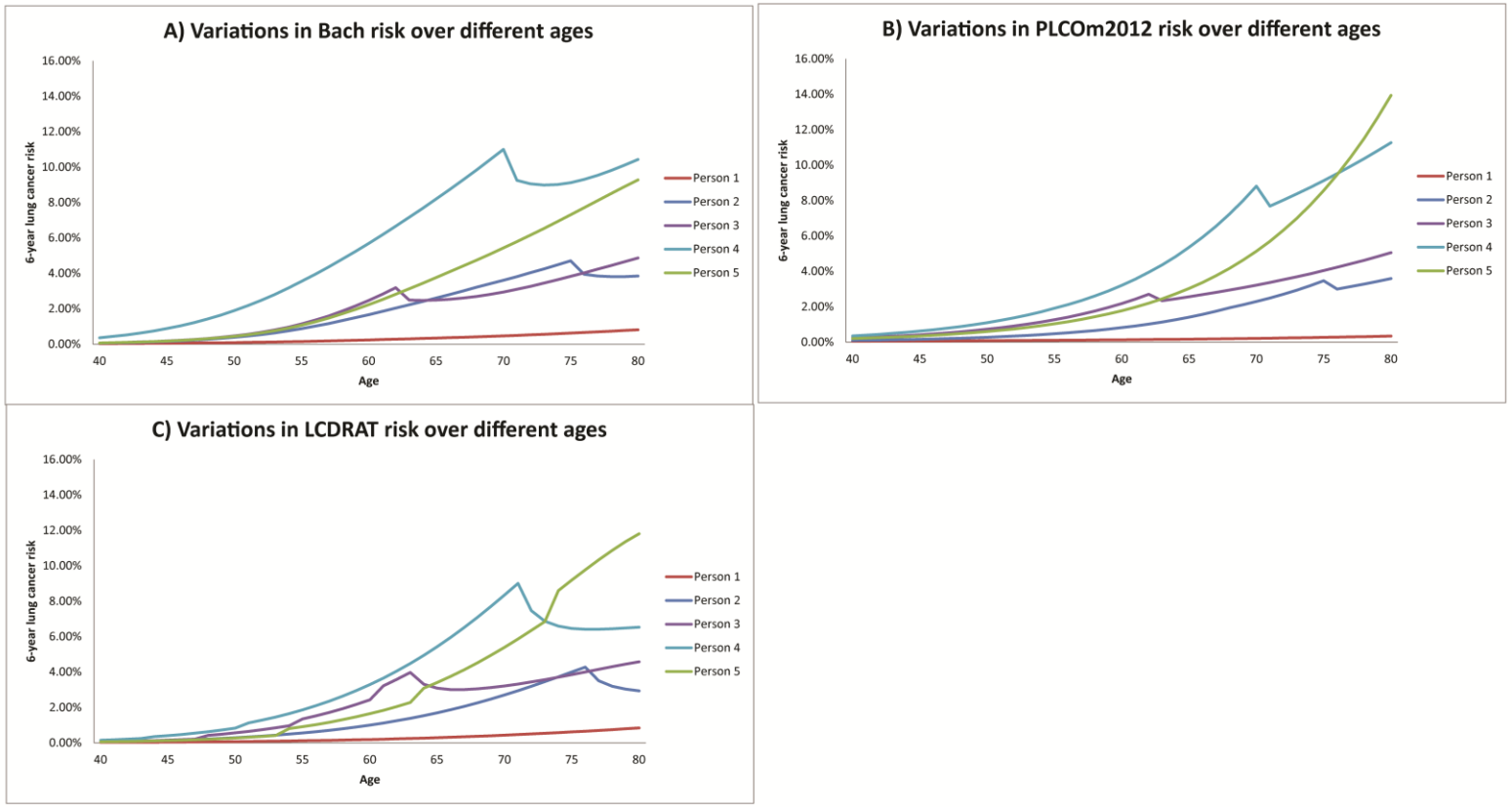


Figure notes:

Person 1: Male, smoked from ages 14 to 31. Smoked on average 10 cigarettes per day from ages 14 to 31.

Person 2: Male, smoked from ages 20 to 75. Smoked on average 10 cigarettes per day from ages 20 to 68, and 3 cigarettes per day from ages 69 to 75.

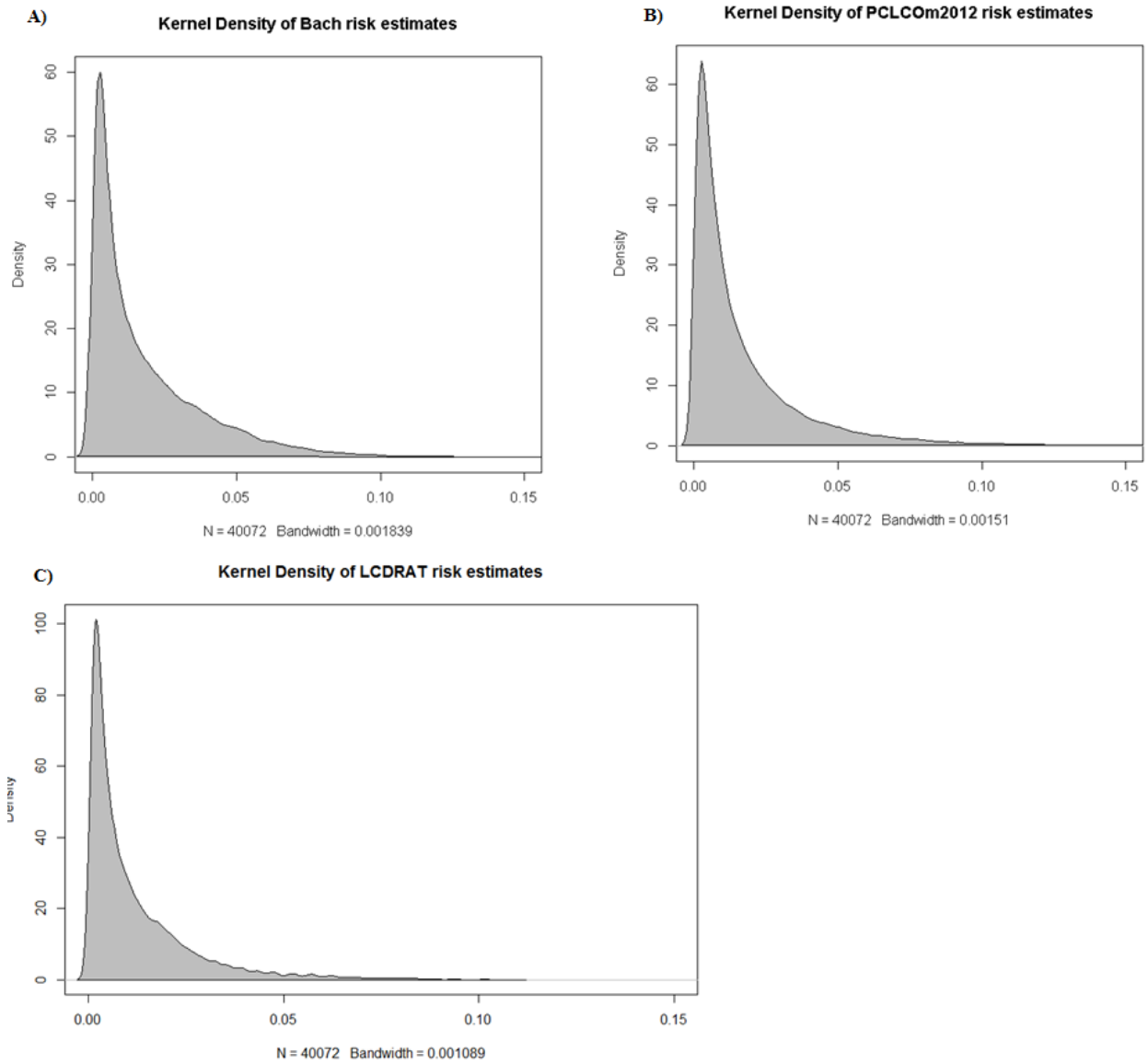
Person 3: Male, smoked from ages 26 to 62. Smoked on average 20 cigarettes per day from ages 26 to 29, and 30 cigarettes per day from ages 31 to 62.

Person 4: Male, smoked from ages 11 to 70. Smoked on average 20 cigarettes per day from ages 11 to 28, 30 cigarettes per day from ages 29 to 55, and 20 cigarettes per day from ages 56 to 70.

Person 5: Male, started smoking at age 24 and still smokes at age 80. Smoked on average 20 cigarettes per day from ages 24 to 80.

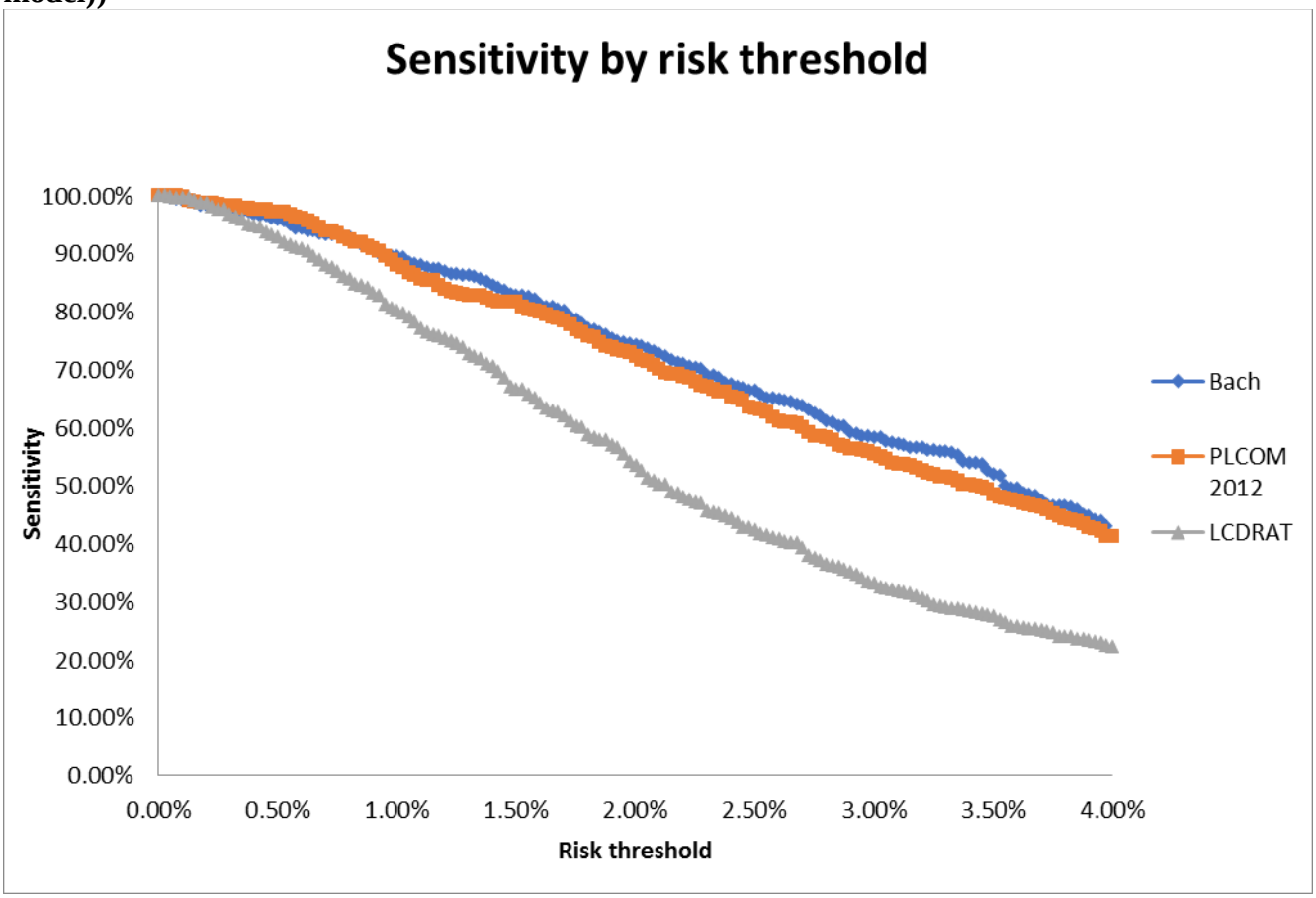
Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool

Supplementary Figure 3: Distribution of estimated risk in the PLCO control-arm for the Bach model (A), PLCOm2012 model (B) and LCDRAT model (C) (six-year risks at each age by model)



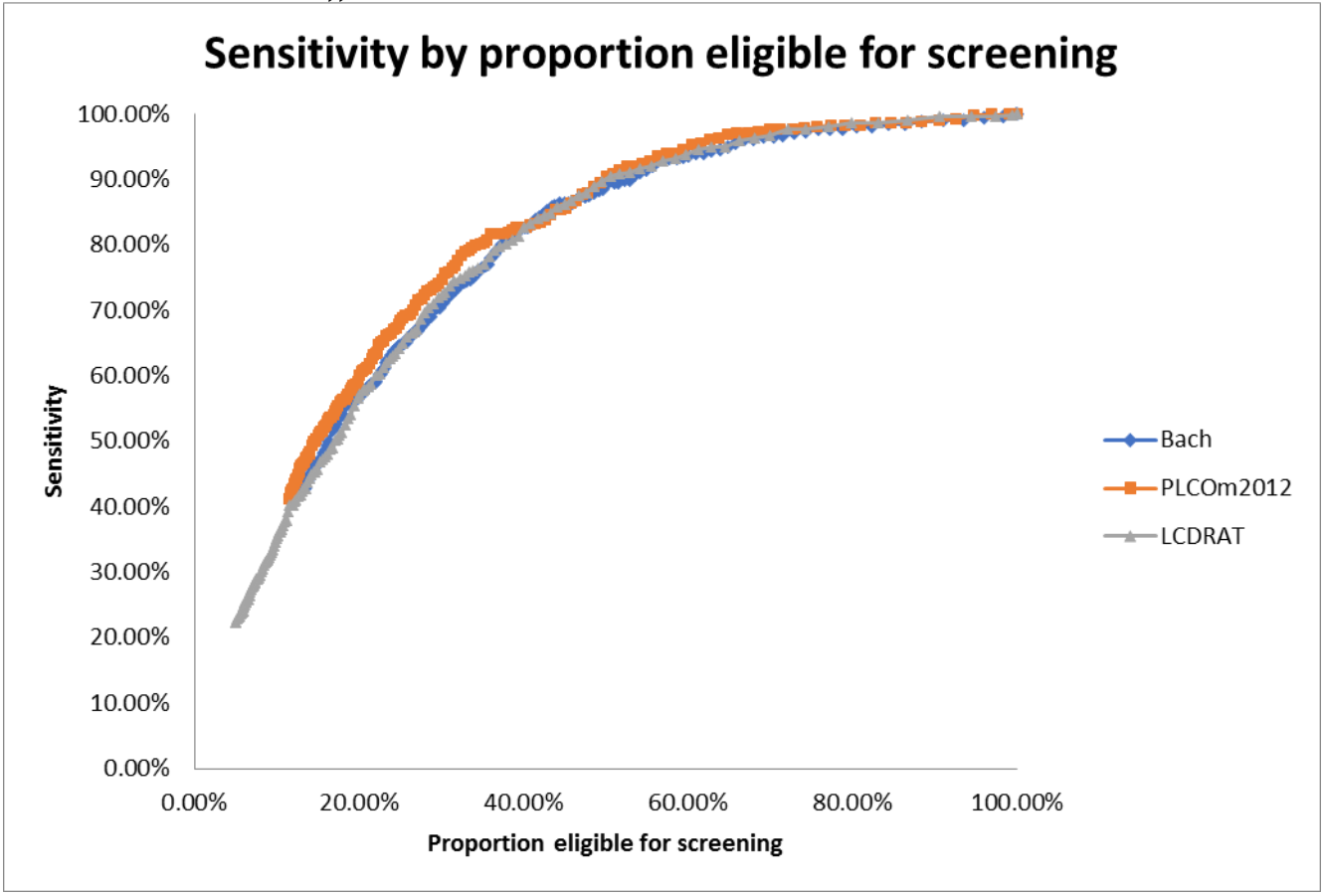
Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool, PLCO: Prostate Lung, Colorectal and Ovarian Cancer Screening Trial

Supplementary Figure 4: Sensitivity (lung cancer incidence) in the PLCO control-arm by risk-threshold (six-year risk for lung cancer incidence (lung cancer mortality for the LCDRAT model))



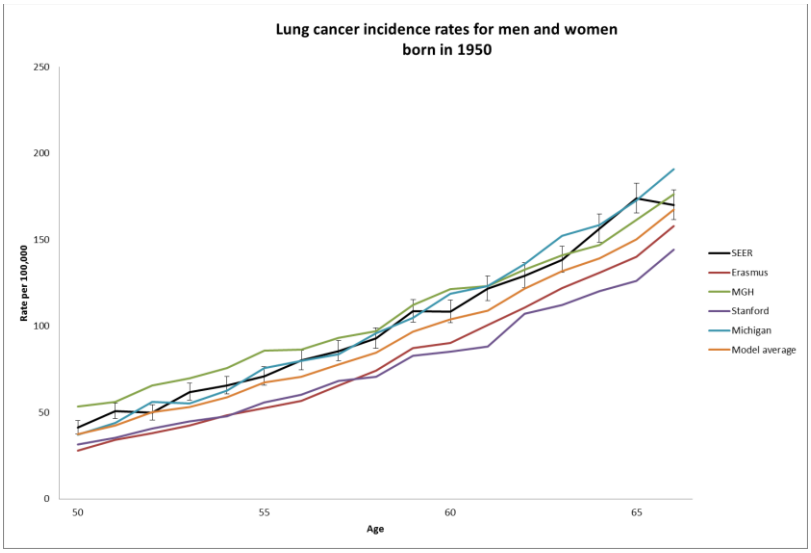
Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool, PLCO: Prostate Lung, Colorectal and Ovarian Cancer Screening Trial

Supplementary Figure 5: Sensitivity (lung cancer incidence) in the PLCO control-arm by proportion eligible for screening (six-year risk for lung cancer incidence (lung cancer mortality for the LCDRAT model))



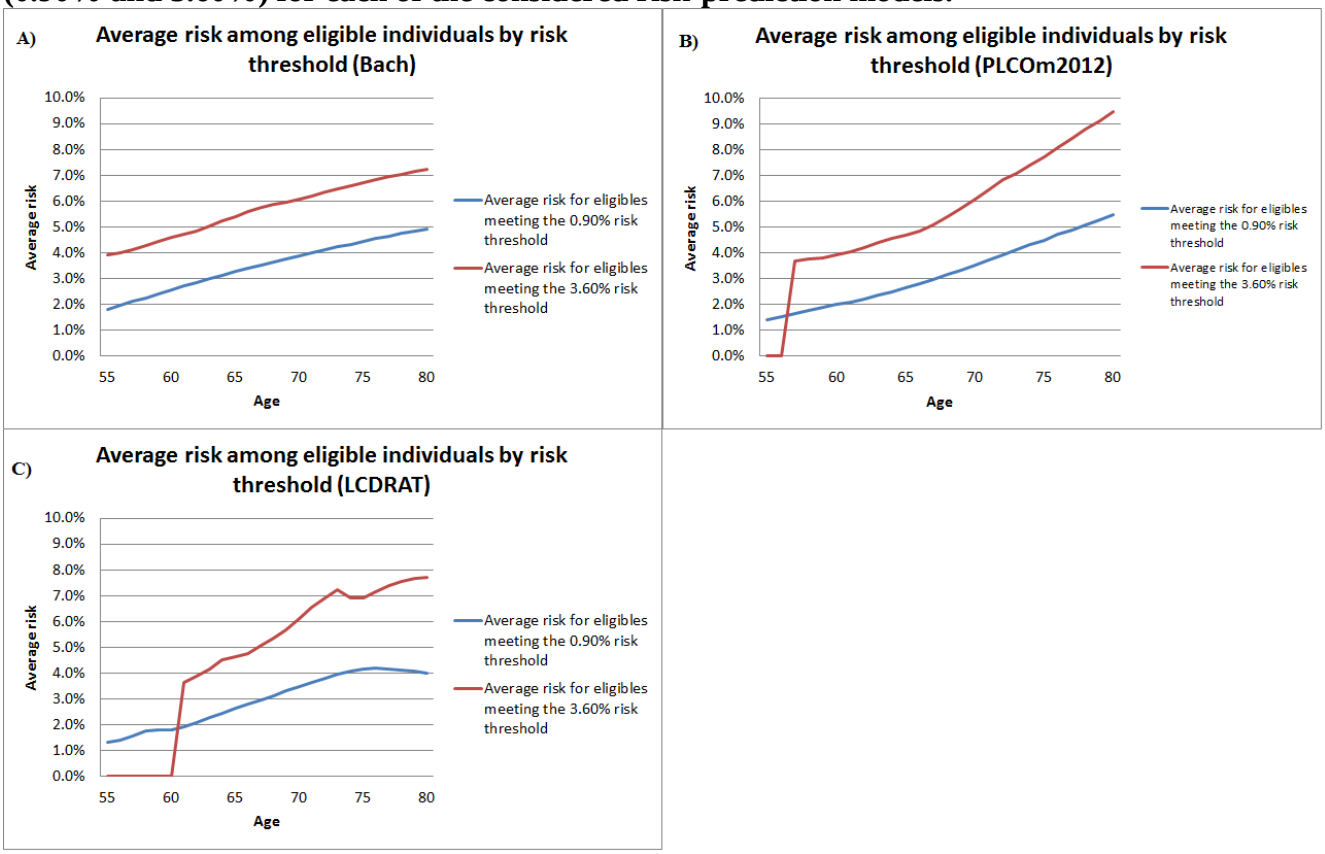
Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool, PLCO: Prostate Lung, Colorectal and Ovarian Cancer Screening Trial

Supplementary Figure 6: Observed and model-specific lung cancer incidence rates by age for the 1950 birth-cohort



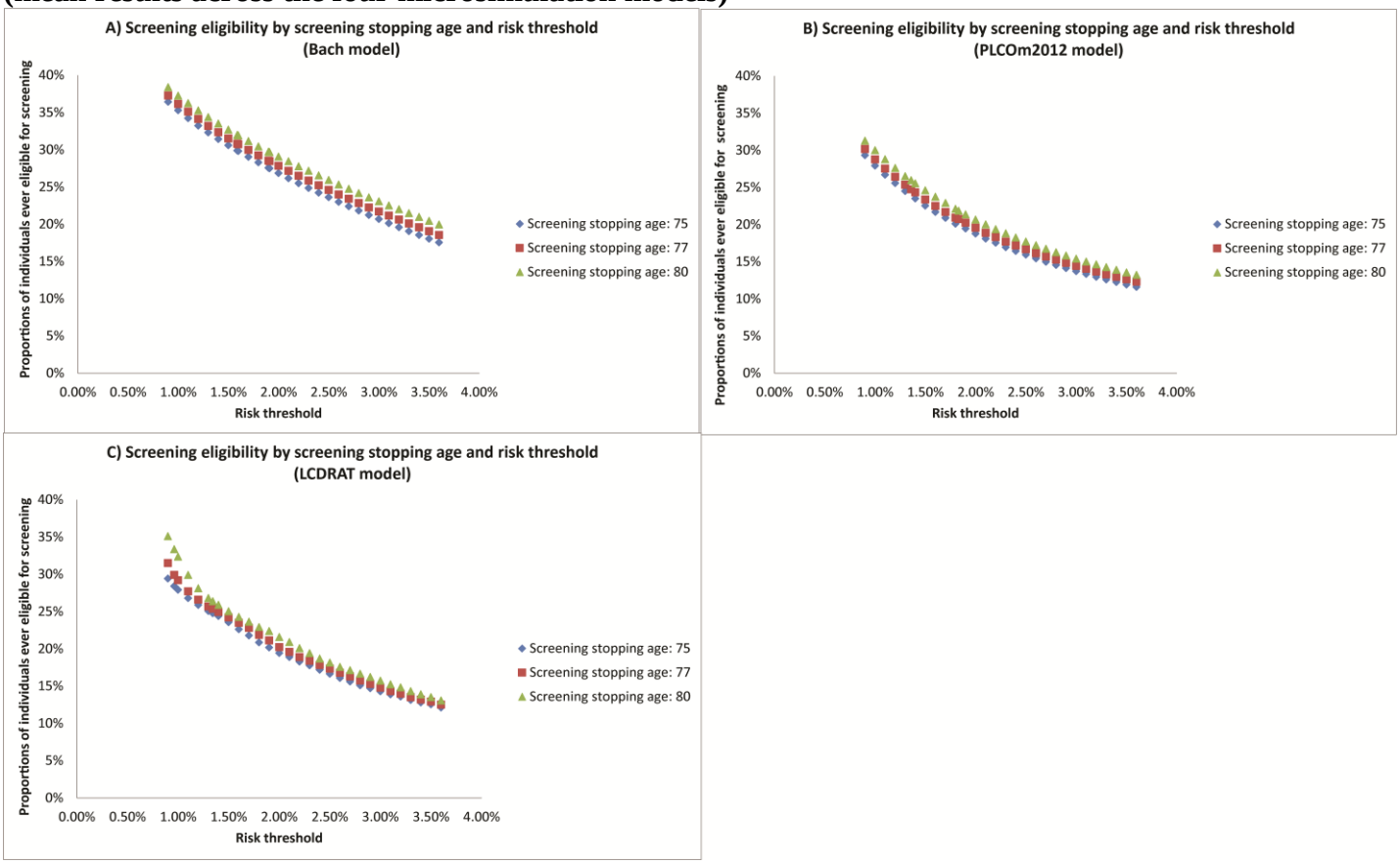
Abbreviations: MGH: Massachusets General Hospital, SEER: Surveillance, Epidemiology, and End Results.

Supplementary Figure 7: Average risk over time for individuals exceeding fixed risk thresholds (0.90% and 3.60%) for each of the considered risk-prediction models.



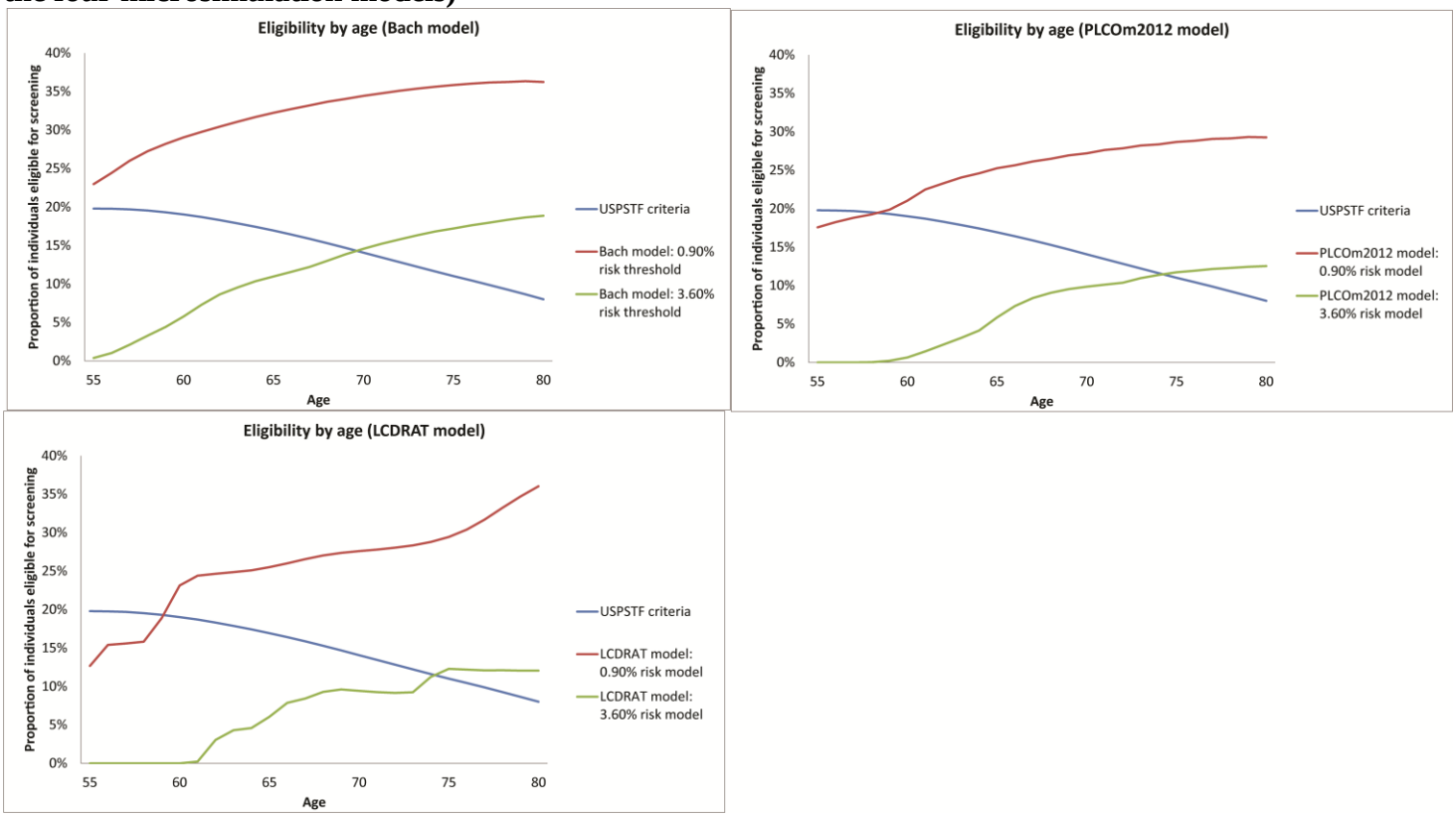
Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool

Supplementary Figure 8: Screening eligibility by screening stopping age and risk-threshold (mean results across the four microsimulation models)



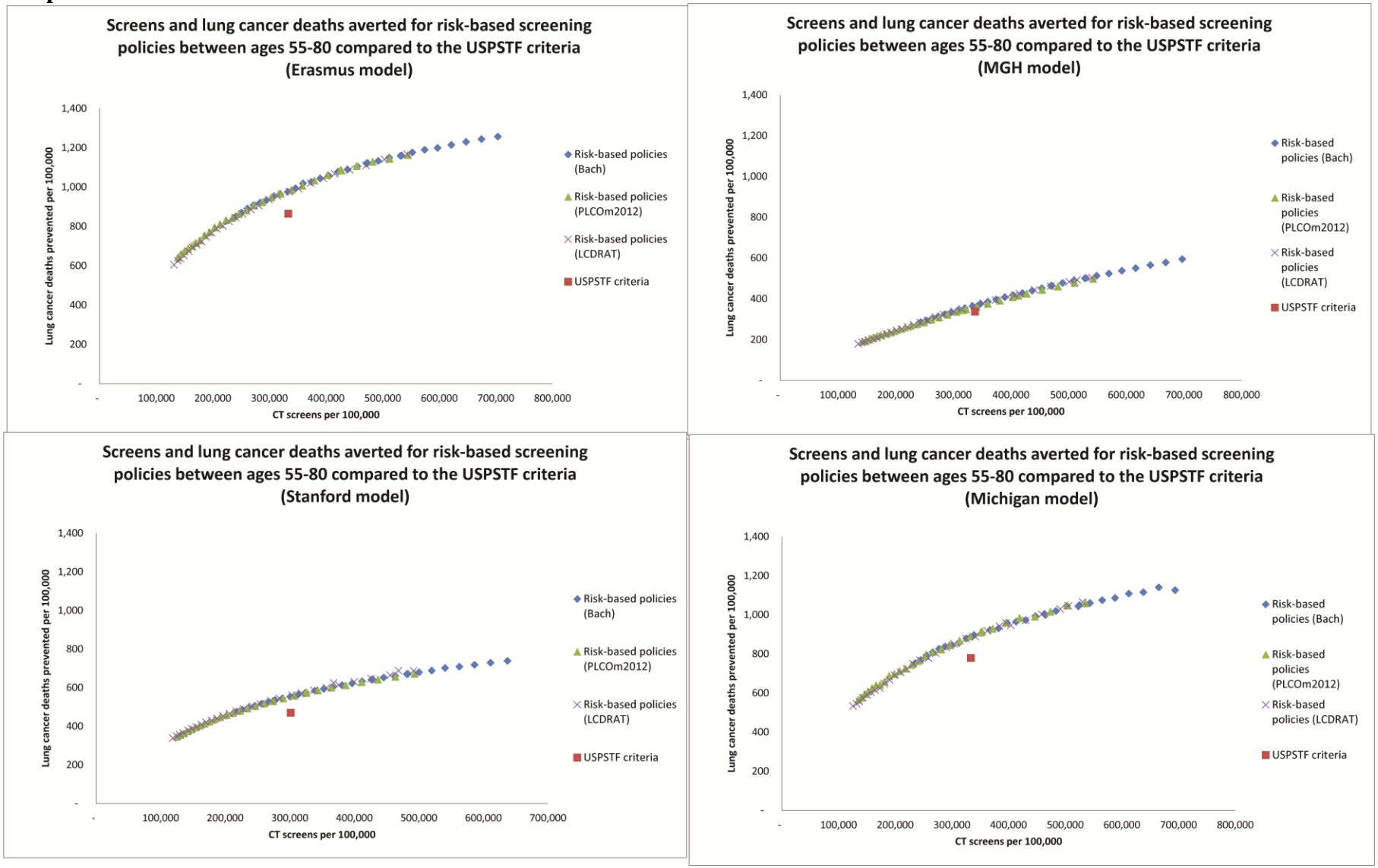
Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool

Supplementary Figure 9: Screening eligibility at each age by risk-threshold (mean results across the four microsimulation models)



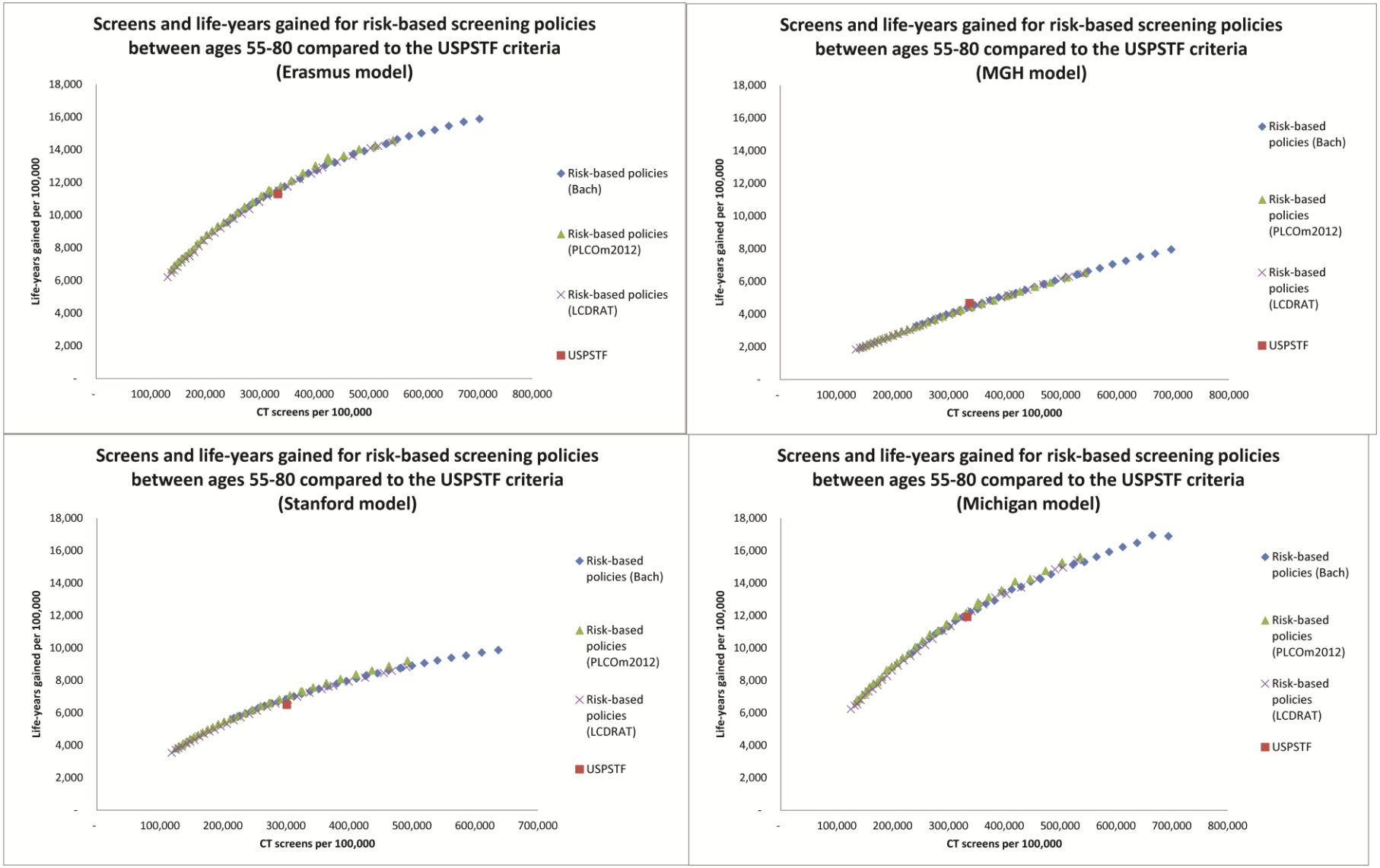
Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool, USPSTF: United States Preventive Services Task Force

Supplementary Figure 10: Screens and lung cancer deaths averted for risk-based screening strategies screening between ages 55-80 compared to the USPSTF-criteria for all microsimulation models



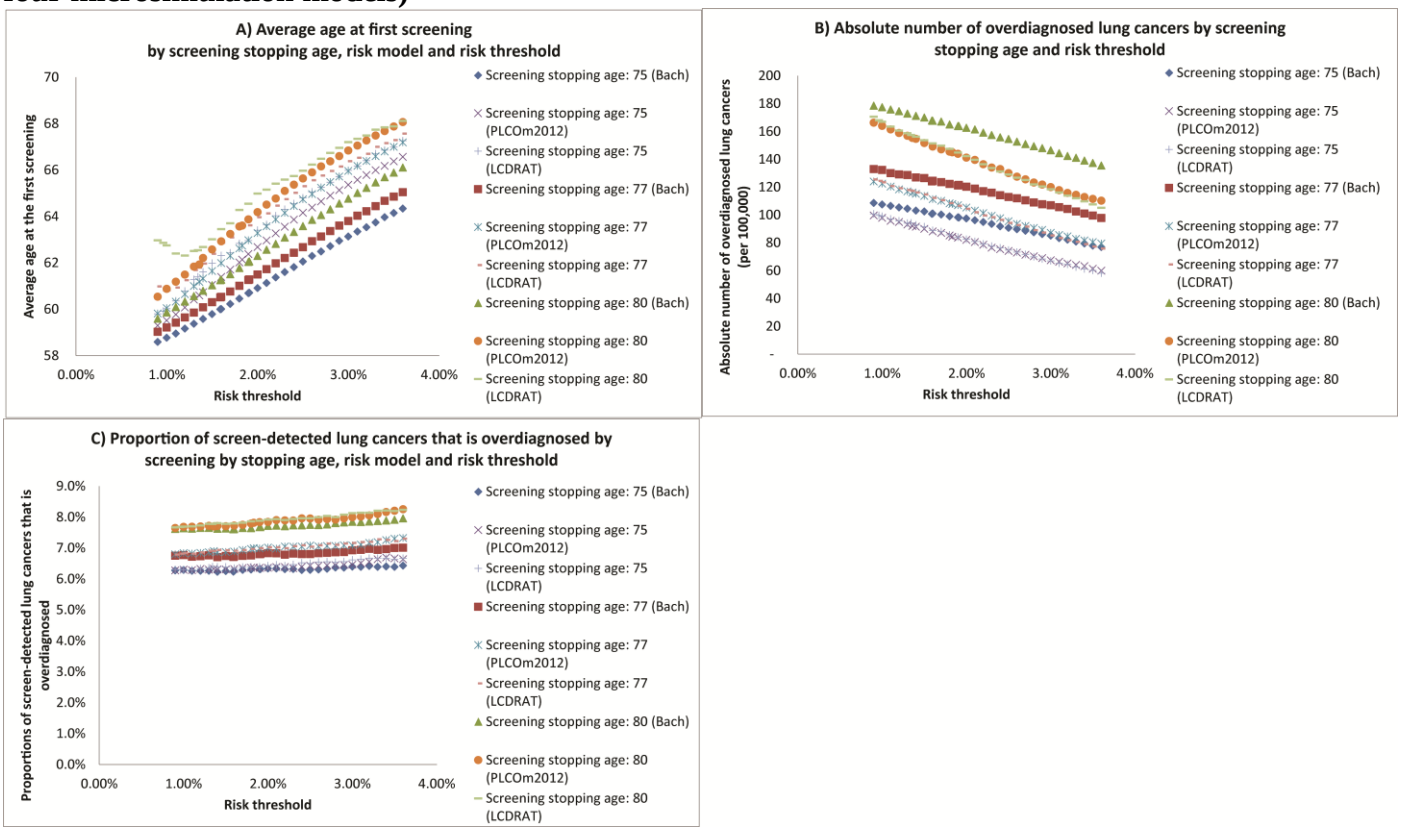
Abbreviations: MGH: Massachusetts General Hospital USPSTF: United States Preventive Services Task Force

Supplementary Figure 11: Screens and life-years gained for risk-based screening strategies screening between ages 55-80 compared to the USPSTF-criteria for all microsimulation models



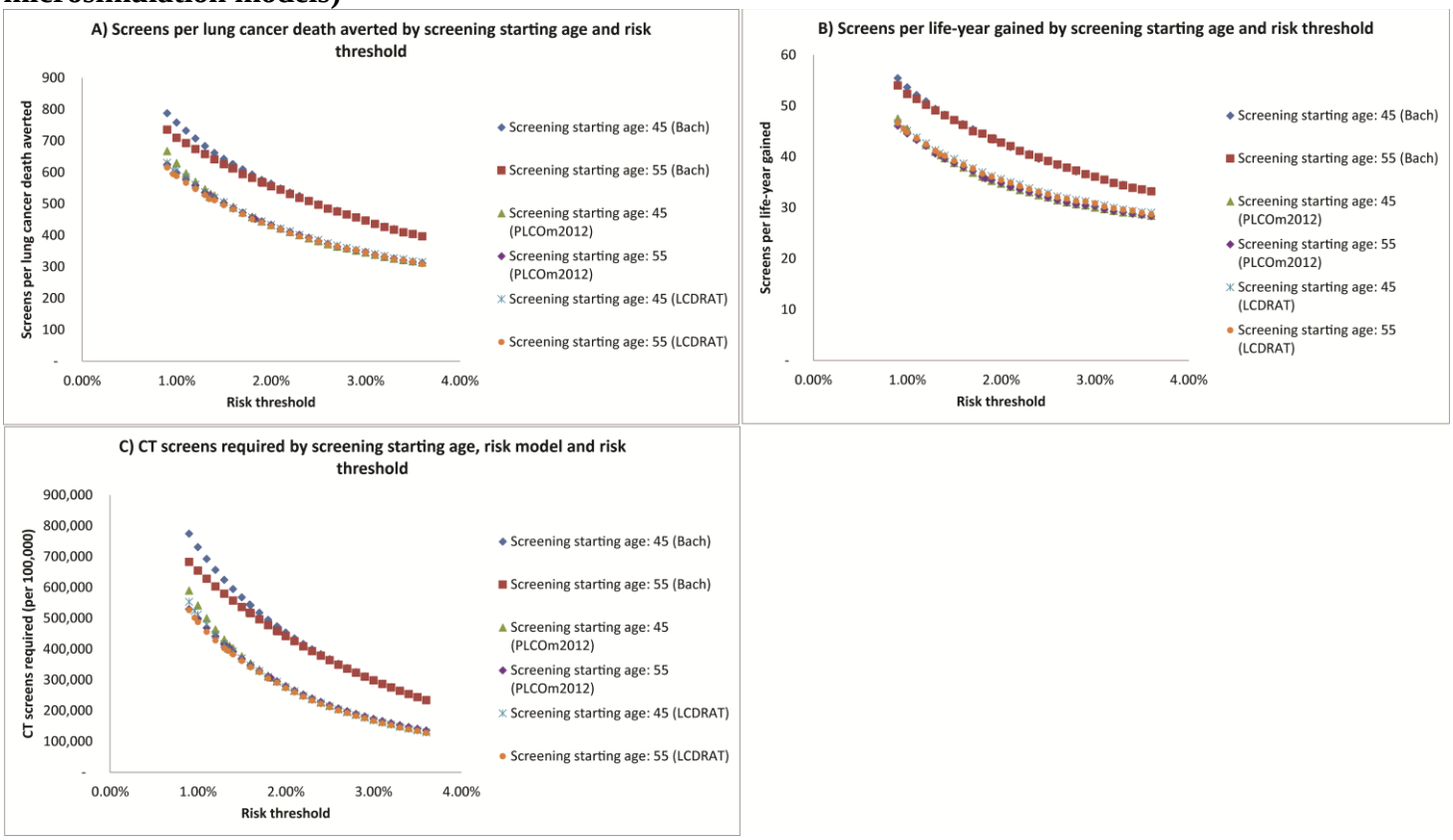
Abbreviations: MGH: Massachusetts General Hospital USPSTF: United States Preventive Services Task Force

Supplementary Figure 12: Average age at first screening (A), proportion of screen-detected lung cancers that is overdiagnosed (B) and absolute number of overdiagnosed lung cancers (per 100,000) (C) by screening stopping age, risk model and risk threshold (mean results across the four microsimulation models)



Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool

Supplementary Figure 13: Absolute number of lung cancer deaths prevented (per 100,000) (A), absolute number of life-years gained (per 100,000) (B) and CT screens required (per 100,000) (C) by screening starting age, risk model and risk threshold (mean results across the four microsimulation models)



Abbreviations: LCDRAT: Lung Cancer Death Risk Assessment Tool