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Accelerating Longitudinal AI-Derived Lung Cancer Risk Emerges Three Years Before Diagnosis in a Real-World Screening Cohort

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Introduction

- Sybil is an AI model that predicts future lung cancer risk from low-dose chest CT (LDCT) scans.
- Most prior Sybil studies evaluate cross-sectional 1–6-year risk at a single time point rather than how risk changes over repeated screening exams.
- Longitudinal AI-derived risk trajectories may reveal a clinically actionable prediagnostic window for intensified surveillance or early intervention.
- Objective: characterize temporal Sybil risk trajectories and clinically meaningful risk thresholds preceding lung cancer diagnosis.

Methods

- Real-world lung cancer screening cohort with repeated LDCT scans and longitudinal Year 1 Sybil scores.
- Participants were classified into 3 groups: Group 0 = no cancer during follow-up; Group 1 = cancer diagnosed during follow-up after a negative baseline screen; Group 2 = cancer detected at baseline screening.
- Time was centered at final follow-up for Group 0 and at diagnosis for Groups 1 and 2; prior scans were assigned negative time values.
- Mixed-effects models with linear and quadratic time terms estimated longitudinal risk trajectories; Wald tests identified when Group 1 velocity became significantly positive.
- Baseline characteristics and Sybil risk categories were compared with cancer incidence and Lung-RADS.
- Model-derived thresholds of 0.5% and 2.5% in the Sybil Year 1 predicted risk score were used to define clinically interpretable baseline risk groups.

Results

Table 1. Baseline Characteristics by Cancer Category

Characteristic	Overall (N = 3,677)	Group 0 (N = 3,564) No Cancer	Group 1 (N = 41) Cancer Diagnosed Later	Group 2 (N = 72) Cancer Diagnosed at Baseline	p-value
Sybil Year 1 Score					
N non-missing	3538 (96.2%)	3428 (96.2%)	38 (92.7%)	72 (100.0%)	<0.001 [4]
Mean (SD)	0.0143 (0.0547)	0.0096 (0.0290)	0.0105 (0.0225)	0.2271 (0.2475)	
Median	0.0020	0.0020	0.0040	0.1518	
Missing	139 (3.8%)	136 (3.8%)	3 (7.3%)	0 (0.0%)	
BMI closest to baseline scan					
N non-missing	3565 (97.0%)	3452 (96.9%)	41 (100.0%)	72 (100.0%)	0.00201 [2]
Mean (SD)	28.82 (7.17)	28.90 (7.18)	27.04 (5.95)	25.92 (6.65)	
Median	27.95	27.99	26.82	26.11	
Missing	112 (3.0%)	112 (3.1%)	0 (0.0%)	0 (0.0%)	
BMI Category					
Underweight	132 (3.6%)	120 (3.4%)	4 (9.8%)	8 (11.1%)	0.0363 [3]
Healthy Weight	997 (27.1%)	959 (26.9%)	14 (34.1%)	24 (33.3%)	
Overweight	1094 (29.8%)	1066 (29.9%)	8 (19.5%)	20 (27.8%)	
Obesity	1342 (36.5%)	1307 (36.7%)	15 (36.6%)	20 (27.8%)	
Missing	112 (3.0%)	112 (3.1%)	0 (0.0%)	0 (0.0%)	
Family History of Lung Cancer					
No	2368 (64.4%)	2296 (64.4%)	21 (51.2%)	51 (70.8%)	0.00485 [1]
Yes	564 (15.3%)	531 (14.9%)	14 (34.1%)	19 (26.4%)	
Missing	745 (20.3%)	737 (20.7%)	6 (14.6%)	2 (2.8%)	
Lung-RADS Category					
1	784 (21.3%)	776 (21.8%)	8 (19.5%)	0 (0.0%)	<0.001 [3]
2	2035 (55.3%)	2004 (56.2%)	26 (63.4%)	5 (6.9%)	
3	416 (11.3%)	409 (11.5%)	2 (4.9%)	5 (6.9%)	
4	27 (0.7%)	22 (0.6%)	0 (0.0%)	5 (6.9%)	
4A	210 (5.7%)	197 (5.5%)	4 (9.8%)	9 (12.5%)	
4B	93 (2.5%)	61 (1.7%)	1 (2.4%)	31 (43.1%)	
4X	40 (1.1%)	23 (0.6%)	0 (0.0%)	17 (23.6%)	
Missing	46 (1.3%)	46 (1.3%)	0 (0.0%)	0 (0.0%)	

Group 0 = No Cancer Group 1 = Cancer Diagnosed Later Group 2 = Cancer Diagnosed at Baseline
[1] Chi-square test; [2] ANOVA; [3] Fisher exact test; [4] Kruskal-Wallis rank-sum test.

Figure 2. Estimated longitudinal LDCT Sybil trajectories

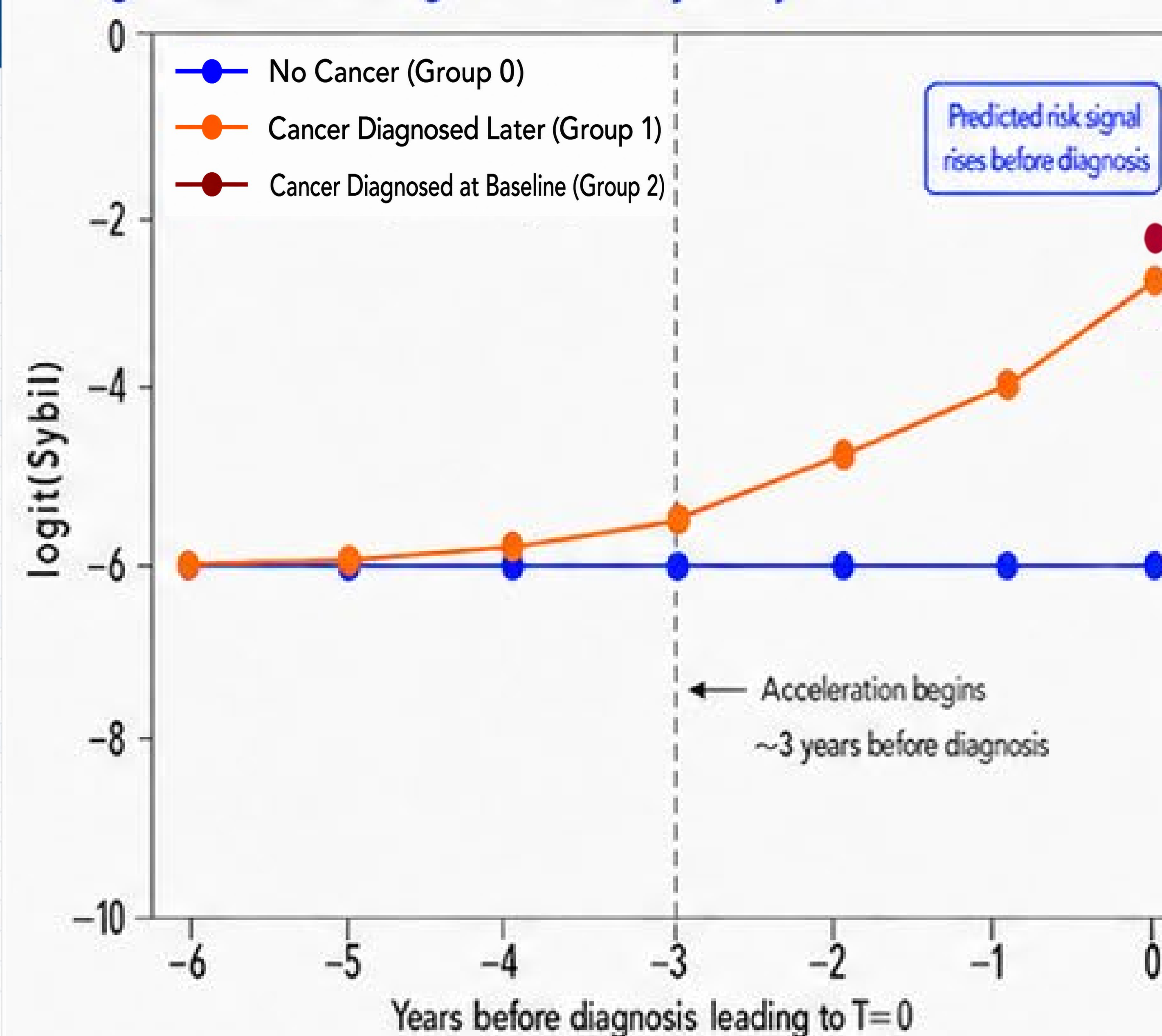


Figure 1. Baseline Year 1 logit(Sybil score) distribution by diagnosis group

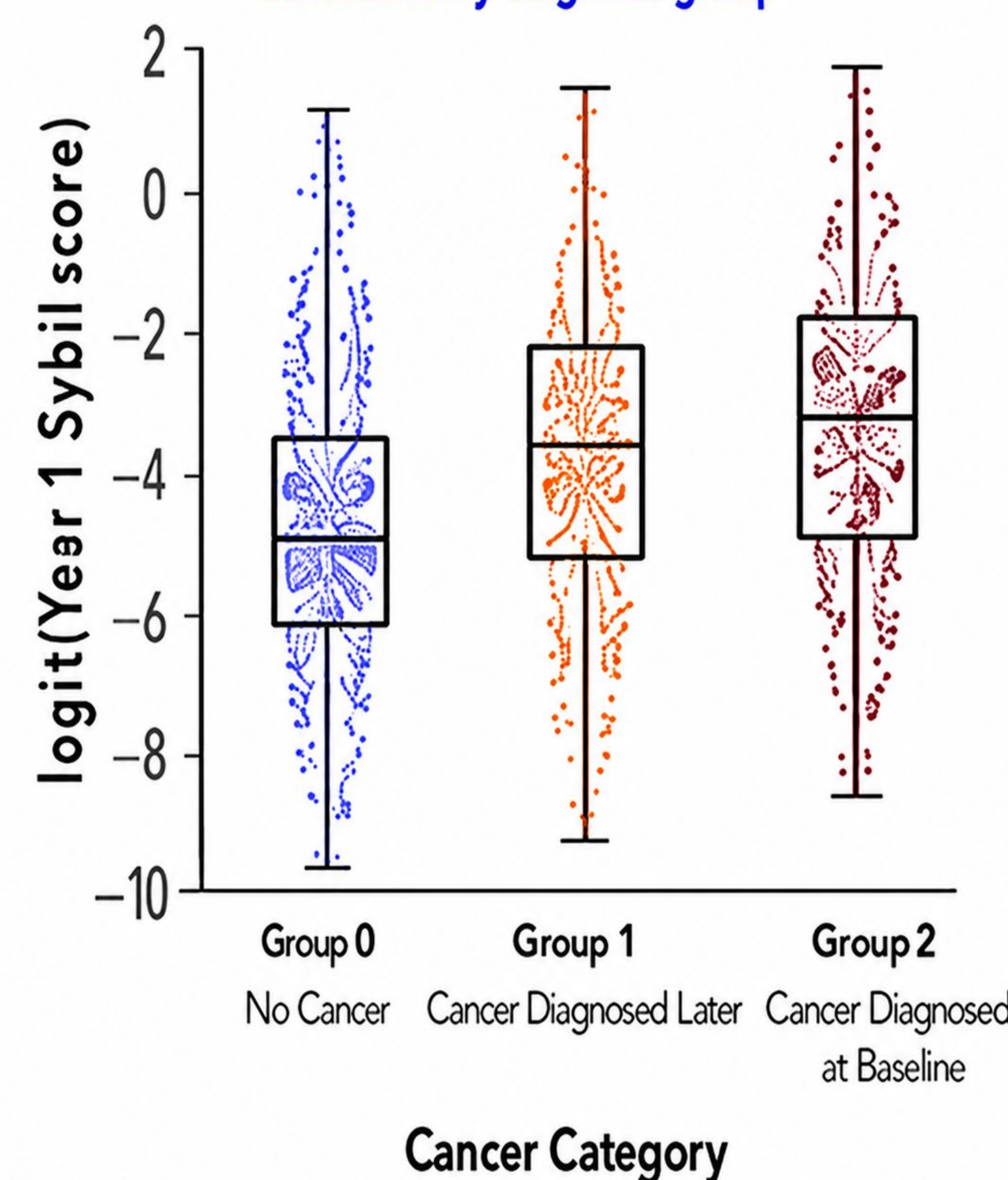


Table 2. Baseline Year 1 Sybil risk categories by relative risk and baseline Lung-RADS

Sybil Year-1 Predicted Risk	N	Cancer n (%)	RR (95% CI)	Baseline Lung-RADS distribution, n (%)				
				1	2	3	4	Missing
Level 1 (<0.005)	2,522	37 (1.5%)	1.00 (Reference)	591 (23.4%)	1,517 (60.2%)	259 (10.3%)	115 (4.6%)	40 (1.6%)
Level 2 (0.005–0.025)	742	17 (2.3%)	1.56 (0.88–2.76)	145 (19.5%)	360 (48.5%)	109 (14.7%)	108 (14.6%)	20 (2.7%)
Level 3 (>0.025)	274	56 (20.4%)	13.93 (9.37–20.70)	24 (8.8%)	80 (29.2%)	28 (10.2%)	133 (48.5%)	9 (3.3%)
Total	3,538	110 (3.1%)	—	760 (21.5%)	1,957 (55.3%)	396 (11.2%)	356 (10.1%)	69 (2.0%)

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Conclusion

- Cancer-free individuals demonstrate stable Sybil trajectories over time, whereas incident cancers show accelerating risk beginning approximately 3 years before diagnosis.
- Longitudinal change in Sybil—not just a single cross-sectional score—reveals a clinically actionable prediagnostic signal.
- Data-derived risk thresholds (0.5% and 2.5%) stratify clinically meaningful risk, with Level 3 showing markedly elevated cancer risk.
- Sybil risk categories may identify elevated risk even when baseline Lung-RADS appears low.
- These findings support AI-guided precision screening strategies and provide a rationale for prospective trials integrating Sybil trajectories with biomarker-based early detection.

Clinical Implications: Visual Overview



Level 1 (<0.005)	Continue routine annual screening	
Level 2 (0.005–0.025)	Consider shortened-interval surveillance / closer follow up	
Level 3 (>0.025)	Expedited workup, biomarker integration, precision screening / prevention trials	

★ Many higher-risk patients still had low Lung-RADS (1–2): 68% of Level 2 and 38% of Level 3.

Figure Legends

Figure 1. Box-and-whisker plot of baseline Year 1 logit(Sybil score) by diagnosis group

Figure 2. Longer centered panel showing estimated longitudinal LDCT Sybil trajectories for the three groups. Group 1 demonstrates acceleration in risk ~3 years before diagnosis, whereas Group 0 remains stable and Group 2 begins at high risk near time T=0.