**Potential impact of risk-based follow-up for abnormal CT results during lung screening with biennial intervals**

Hilary A. Robbins1, Li C. Cheung2, Anil K. Chaturvedi2, Christine D. Berg2, Hormuzd A. Katki2

1International Agency for Research on Cancer, Lyon, France

2Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA

**Supplementary Results**

*Four properties of NLST LDCT screening after a non-malignant abnormal CT*The LCRAT+CT model accounts for 4 properties of NLST screening that applied among screen-negative individuals.5 We re-examined those properties here for non-malignant abnormal screens. First, the predictiveness of LCRAT+CT after a non-malignant abnormal CT is considerably improved by including individual pre-screening risk (AIC 2293 vs. 2354, p<0.0001). Second, the exponent for pre-screening risk is similar among individuals with a recent abnormal LDCT, even if their prior LDCT result differs (i.e. T0-negative/T1-abnormal [N=1,785] vs. T0-abnormal/T1-abnormal [N=4,694], p=0.62). Therefore, only the most recent (abnormal) LDCT result was considered in our model. Third, the overall risk calculation (exponent for pre-screening risk) is similar across the different NLST screens (i.e. T1 [N=6,483] vs. T2 [N=6,510], p=0.13).

Finally, after accounting for nodule characteristics (described below), we examined whether any pre-screening risk factors had residual effects. We found potential residual effects for decreased risk with a family history of lung cancer (p=0.008) and higher risk among non-Hispanic Blacks (p=0.009). We chose not to include these effects because having lower risk with family history is implausible, estimation among a small group that may be non-representative (race/ethnicity; see **Discussion**), and the expectation of spurious associations identified due to multiple testing.

*Selection of abnormal LDCT features for inclusion in LCRAT+CT risk model*We considered 29 features of an abnormal LDCT, most of which describe nodules, that might affect the calculation for risk of next-screen cancer detection (**Supplementary Table 1**)**.** They were parameterized by considering whether they applied to any nodules present on the LDCT; for example, the variable for “spiculated margins” was equal to 1 if there were any nodules with spiculation, and 0 otherwise.The features affect the exponent for pre-screening risk, and the p-values in **Supplementary Table 1** relate to the null hypothesis that the feature does not affect in the exponent. The following features were selected by at least one approach (i.e., backwards-stepwise selection or the lasso): longest nodule diameter, location in the upper lobe(s), location in the right middle lobe, location in the lingula, mixed attenuation, “other” attenuation, smooth margins, spiculated margins, poorly-defined margins, margins that cannot be determined, and interval nodule growth (**Supplementary Table 1**).

Among these variables, we chose not to include “other” attenuation, as the reasons for its effect are unclear and its unclear definition makes it unlikely to be consistently measurable across settings. We combined right middle lobe and lingula into one effect, and poorly defined margins and margins that cannot be determined into one effect (“indeterminate margins”). We removed smooth margins, which had no effect in addition to the other variables (p=0.73). We then performed four sensitivity analyses. First, the number of nodules on the abnormal CT had no residual effect (p=0.29). Second, the presence of a new nodule (identified at the T1 or T2 screen, and a distinct entity from growing nodules) had no residual effect (p=0.77). Third, we examined a separate effect for diameter to individuals with a ground-glass nodule, stratifying for <20mm vs. ≥20mm as in Lung-RADS v1.0.9, but this worsened the model (AIC 2070 vs. 2085). Finally, even after accounting for the selected nodule features, the model including pre-screening risk was still much better than one without (AIC=2070 vs. 2101).

**Supplementary Table 1: Selection of features identified on a non-malignant abnormal LDCT for inclusion in the LCRAT+CT model for next-screen lung-cancer risk among participants in the National Lung Screening Trial**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Feature (prevalence)** | | **Stepwise** | **Lasso** | **Final model** |
| Presence and size of nodule(s) | Number of nodules (continuous) | --- | --- |  |
| Longest diameter among all nodules  No nodule (1.9%)  4-5 mm (39%)  6-7 mm (30%)  8-10 mm (16%)  11-13 mm (5.7%)  ≥14 mm (7.2%) | p<0.001  Higher risk, 0.20  Reference  Higher risk, 0.07  Higher risk, 0.19  Higher risk, 0.28  Higher risk, 0.22 | p<0.001  Higher risk, 0.16  Reference  Higher risk, 0.06  Higher risk, 0.19  Higher risk, 0.27  Higher risk, 0.21 | p<0.001  Higher risk, 0.20  Reference  Higher risk, 0.06  Higher risk, 0.18  Higher risk, 0.27  Higher risk, 0.22 |
| Benign lung nodule(s) (27%) | --- | --- |  |
| Non-calcified micronodule(s) (opacity <4 mm) (41%) | --- | --- |  |
| Six or more nodules not suspicious for cancer (opacity ≥4 mm) (1.2%) | --- | --- |  |
| Location of nodule(s) | Right or left upper lobe (45%) | Higher risk  0.07, p=0.009 | Higher risk  0.09, p<0.001 | Higher risk  0.07, p=0.01 |
| Right middle lobe (21%) | Lower risk  0.08, p=0.03 | --- | Lower risk  0.09, p=0.009 |
| Lingula (6.3%) | Lower risk  0.08, p=0.17 |  |
| Right or left lower lobe (54%) | --- | --- |  |
| Attenuation of nodule(s) | Soft tissue (80%) | --- | --- |  |
| Ground glass (17%) | --- | --- |  |
| Mixed (5.3%) | Higher risk  0.08, p=0.03 | Higher risk  0.09, p=0.008 | Higher risk  0.07, p=0.04 |
| Other (0.74%) | Higher risk  0.19, p=0.01 | Higher risk  0.16, p=0.01 |  |
| Cannot be determined (5.5%) | --- | --- |  |
| Margins of nodule(s) | Smooth (73%) | --- | Lower risk  0.07, p=0.009 |  |
| Spiculated (9.6%) | Higher risk  0.17, p<0.001 | Higher risk  0.10, p<0.001 | Higher risk  0.16, p<0.001 |
| Poorly defined (24%) | Higher risk  0.07, p=0.02 | --- | Higher risk  0.09, p=0.001 |
| Cannot be determined (4.3%) | Higher risk  0.17, p<0.001 | --- |
| Changes by comparison with prior CT | Any new nodule(s) (14.1%) |  |  |  |
| Interval growth of nodule(s) (6.0%) | Higher risk  0.30, p<0.001 | Higher risk  0.27, p<0.001 | Higher risk  0.26, p<0.001 |
| Suspicious change in attenuation (2.0%) | --- | --- |  |
| Non-nodule features | Non-calcified hilar/mediastinal adenopathy or mass (≥10 mm on short axis) (2.3%) | --- | --- |  |
| Atelectasis, segmental or greater (1.1%) | --- | --- |  |
| Consolidation (0.74%) | --- | --- |  |
| Emphysema (35% | --- | --- |  |
| Reticular/reticulonodular opacities, honeycombing, fibrosis, or scar (24%) | --- | --- |  |
| Other potentially significant abnormality above the diaphragm (6.3%) | --- | --- |  |
| Other potentially significant abnormality below the diaphragm (3.9%) | --- | --- |  |
| Pleural thickening or effusion (6.4%) | --- | --- |  |

The word “nodule” refers to any non-calcified nodule or mass with longest diameter ≥4 mm. All variables are binary (yes/no) unless otherwise indicated (“continuous”). Binary features were parameterized by considering whether any nodule with the feature was present; for example, the variable for “spiculated margins” was equal to 1 if there were any nodules with spiculation, and 0 otherwise. The prevalence of each feature is calculated at the T1 screen, so that each individual contributes only once, and to allow for evaluation of nodule growth. Each variable indicates the amount by which the exponent for pre-screening risk decreases (if higher risk) or increases (if lower risk) if the feature is present. P-values are derived from a model including all the variables selected in the corresponding column. “---” indicates that a variable was not selected.