

# Extrapulmonary Cancer Risk After Lung Cancer Screening With Low-Dose CT

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# Background

- Low-dose CT (LDCT) screening reduces lung cancer mortality.<sup>1</sup> Radiation-associated malignancy remains a concern after repeated LDCT exposure.<sup>2</sup>
- Existing risk estimates are based largely on projection models<sup>3,4</sup> and younger CT-exposed populations.<sup>5,6</sup>
- Direct epidemiologic evidence in screening-eligible adults is limited.

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2. United States Preventive Services Task Force. JAMA. 2021;325(10):962-970.

3. Brenner DJ. Radiology. 2004;231(2):440-445.

4. Bach PB, et al. JAMA. 2012;307(22):2418-2429.

5. Pearce MS, et al. The Lancet. 2012;380(9840):499-505.

6. Bosch de Basea M, et al. Nat Med. 2023;29(12):3111-3119.

# Objective

- To evaluate whether three annual rounds of LDCT lung cancer screening are associated with an increased risk of incident leukemia, thyroid cancer, and other extrapulmonary cancers compared with chest radiography (CXR) screening.

# Study design

- Secondary analysis of the National Lung Screening Trial
  - Adults aged 55–74 years
  - At least 30 pack-years; current smokers or quit within the previous 15 years
  - Randomized 1:1 to to three screening rounds of LDCT or CXR
  - Enrolled between 2002 and 2004
- Cancer diagnoses tracked from the initial examination through the end of 2014
  - active follow-up until 2009 & additional passive follow-up using state cancer registries and the National Death Index.

# Cancer identification and Radiation dose

- Identification of incident cancers
  - Leukemia
  - Thyroid cancer
  - All other extra-pulmonary cancers
- Doses were estimated with the NCI dosimetry system using CT parameters, scan range, and participant characteristics.
  - Effective dose
  - Organ dose: Active marrow dose, Thyroid dose

# Latency Period, Outcomes and Statistical analysis

- Latency period after the initial LDCT exposure
  - 2 years (leukemia), 5 years (thyroid cancer), 10 years (other cancers)
  - Lung cancer was excluded because screening directly affects observed incidence.
- Cause-specific hazard models; death treated as censoring
  - Adjusted for sex, race, age, smoking status, and pack-year smoking burden
- Fine–Gray models and alternative latency periods used for sensitivity analyses.

# Participants

|                   |        |
|-------------------|--------|
| NLST participants | 53,452 |
|-------------------|--------|

|          |       |
|----------|-------|
| Excluded | 1,025 |
|----------|-------|

(222 ineligible; 744 no screening or unknown first screening date; 59 unavailable data)

|                     |                                               |
|---------------------|-----------------------------------------------|
| <b>Final cohort</b> | <b>52,427</b> (mean age, 61 years; male, 59%) |
|---------------------|-----------------------------------------------|

|            |        |
|------------|--------|
| - LDCT arm | 26,320 |
|------------|--------|

|           |        |
|-----------|--------|
| - CXR arm | 26,107 |
|-----------|--------|

# Baseline characteristics of participants

| Variable                                             | LDCT arm<br>(n = 26,320) | Chest radiography arm<br>(n = 26,107) | Standardized mean<br>difference |
|------------------------------------------------------|--------------------------|---------------------------------------|---------------------------------|
| Sex <sup>a</sup>                                     |                          |                                       | 0.001                           |
| Male                                                 | 15,552 (59.1%)           | 15,435 (59.1%)                        |                                 |
| Female                                               | 10,768 (40.9%)           | 10,672 (40.9%)                        |                                 |
| Age, years <sup>b</sup>                              | 61 (5)                   | 61 (5)                                | 0.001                           |
| Race <sup>a</sup>                                    |                          |                                       | 0.009                           |
| White                                                | 24,004 (91.2%)           | 23,809 (91.2%)                        |                                 |
| Black                                                | 1,168 (4.4%)             | 1,147 (4.4%)                          |                                 |
| Asian                                                | 547 (2.1%)               | 526 (2.0%)                            |                                 |
| Other                                                | 601 (2.3%)               | 625 (2.4%)                            |                                 |
| Smoking status <sup>a</sup>                          |                          |                                       | <0.001                          |
| Current smoker                                       | 13,563 (51.5%)           | 13,454 (51.5%)                        |                                 |
| Former smoker                                        | 12,757 (48.5%)           | 12,653 (48.5%)                        |                                 |
| Pack-year smoking burden <sup>b</sup>                | 56 (24)                  | 56 (24)                               | 0.003                           |
| Duration of smoking cessation, years <sup>b, c</sup> | 7.8 (4.5)                | 7.8 (4.5)                             | 0.001                           |
| Height, cm <sup>b</sup>                              | 172 (10)                 | 172 (10)                              | 0.001                           |
| Weight, kg <sup>b</sup>                              | 83 (18)                  | 83 (18)                               | 0.002                           |
| History of thyroid cancer <sup>a</sup>               | 34 (0.1%)                | 47 (0.2%)                             | 0.013                           |
| History of other extrapulmonary cancers <sup>a</sup> | 1,031 (3.9%)             | 1,129 (4.3%)                          | 0.021                           |

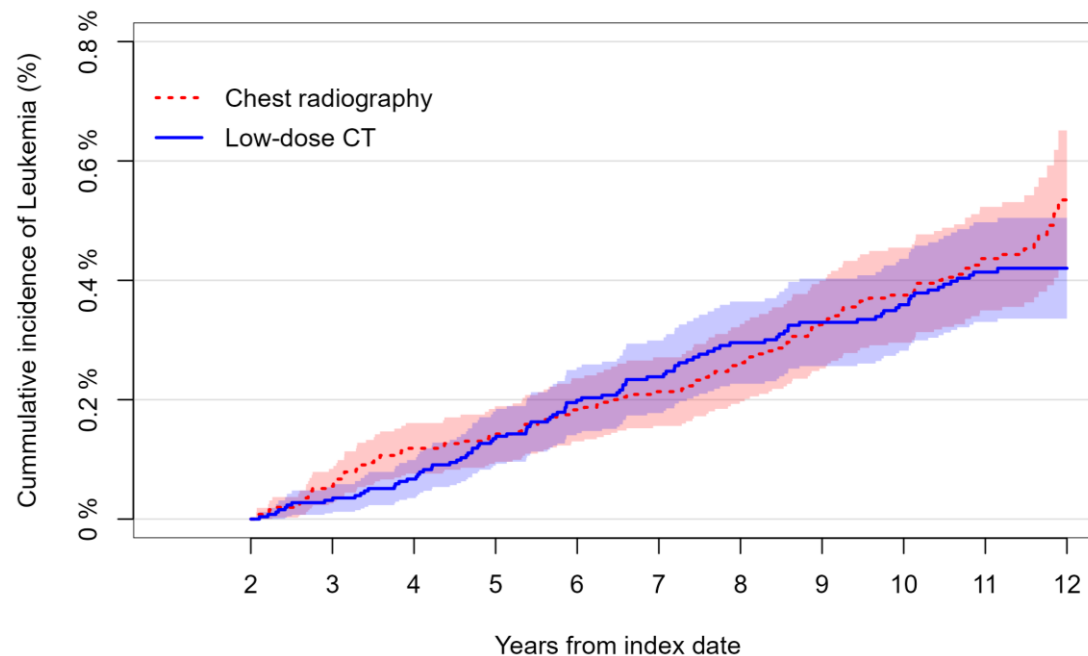
aNumbers indicate numbers of participants with percentages in parentheses; bNumbers indicate mean values with standard deviations in parentheses; cNumbers were obtained from former smokers only.

# Radiation dose estimation and exposure

- 23,478 of 26,320 LDCT participants (89.2%) completed all 3 screening scans.
- Mean effective dose per LDCT scan:  $2.5 \pm 2.8$  mSv
- Mean cumulative effective dose:  $6.9 \pm 5.6$  mSv
- Mean cumulative active bone marrow dose:  $4.2 \pm 3.4$  mGy
- Mean cumulative thyroid gland dose:  $9.0 \pm 8.5$  mGy

# Incident leukemia after LDCT screening

- 96 events in the LDCT arm and 105 events in the CXR arm
- Incidence: 4.67 vs 5.15 per 10,000 person-years



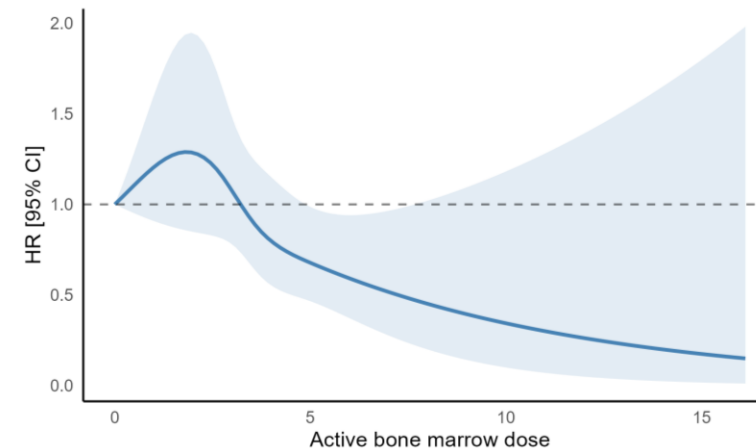
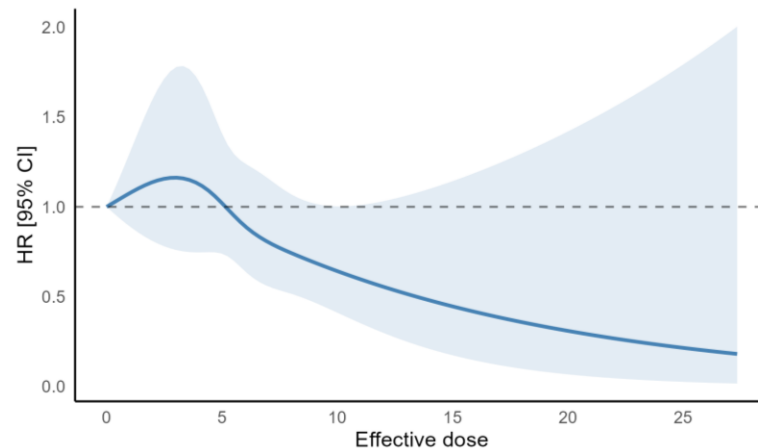
Chest radiography 25484 25090 24702 24212 23446 20364 19180 18650 18107 15252 2276  
Low-dose CT 25577 25176 24831 24394 23621 20517 19355 18877 18313 15435 2222

- HR for screening LDCT arm, 0.91 (95% CI, 0.69–1.20)

# Incident leukemia after LDCT screening

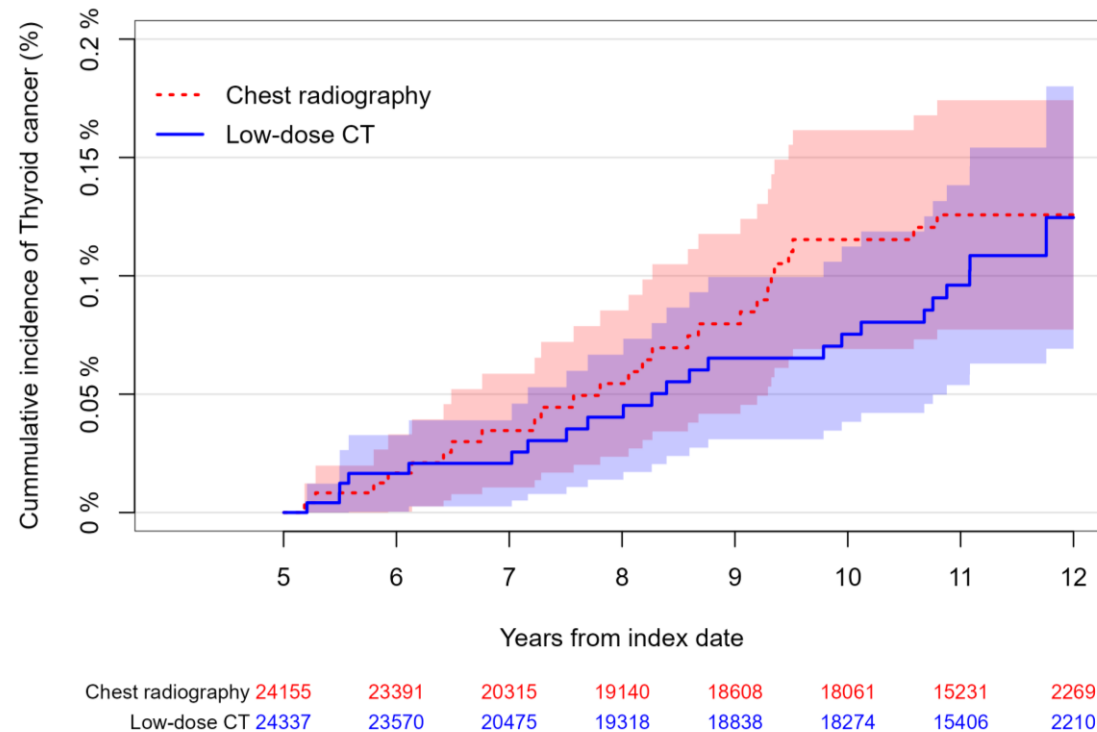
| Exposures                                                                                      | Hazard ratios for leukemia |
|------------------------------------------------------------------------------------------------|----------------------------|
| Number of screening LDCT exams (reference: screening with chest radiography)                   |                            |
| 1                                                                                              | 0.72 (0.36–1.43)           |
| 2                                                                                              | 0.59 (0.29–1.21)           |
| 3                                                                                              | 1.04 (0.76–1.43)           |
| Cumulative effective dose of LDCT exams (reference: screening with chest radiography)          |                            |
| First quartile (<4.8 mSv)                                                                      | 1.13 (0.74–1.71)           |
| Second quartile (4.8–6.0 mSv)                                                                  | 0.90 (0.57–1.41)           |
| Third quartile (6.0–7.7 mSv)                                                                   | 0.81 (0.50–1.31)           |
| Fourth quartile ( $\geq 7.7$ mSv)                                                              | 0.69 (0.41–1.15)           |
| Cumulative active bone marrow dose of LDCT exams (reference: screening with chest radiography) |                            |
| First quartile (<2.8 mGy)                                                                      | 1.16 (0.77–1.75)           |
| Second quartile (2.8–3.7 mGy)                                                                  | 0.97 (0.62–1.49)           |
| Third quartile (3.7–4.7 mGy)                                                                   | 0.89 (0.57–1.42)           |
| Fourth quartile ( $\geq 4.7$ mGy)                                                              | 0.47 (0.25–0.88)           |

Models were adjusted for sex, race, age, smoking status, and pack-year smoking burden



# Incident thyroid cancer after LDCT screening

- 23 events in the LDCT arm and 26 events in the CXR arm
- Incidence: 1.77 vs 2.02 per 10,000 person-years

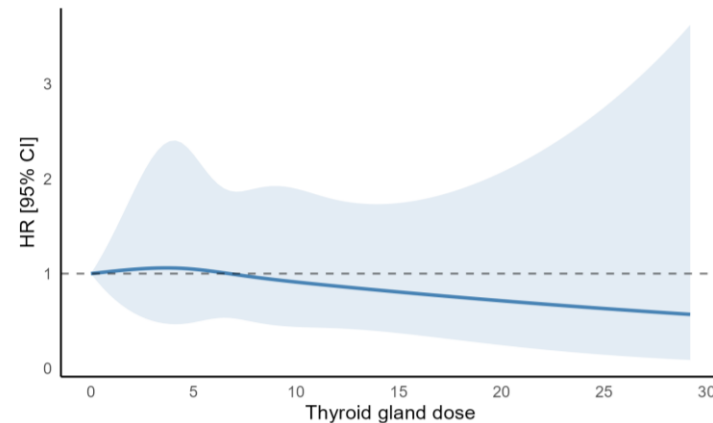
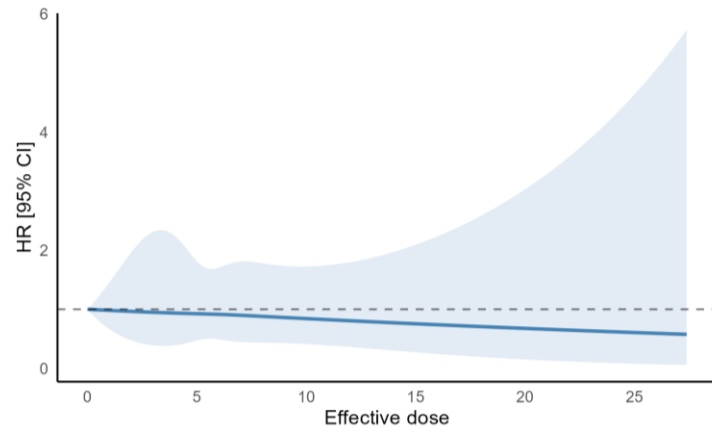


- HR for screening LDCT arm, 0.88 (95% CI, 0.50–1.54)

# Incident thyroid cancer after LDCT screening

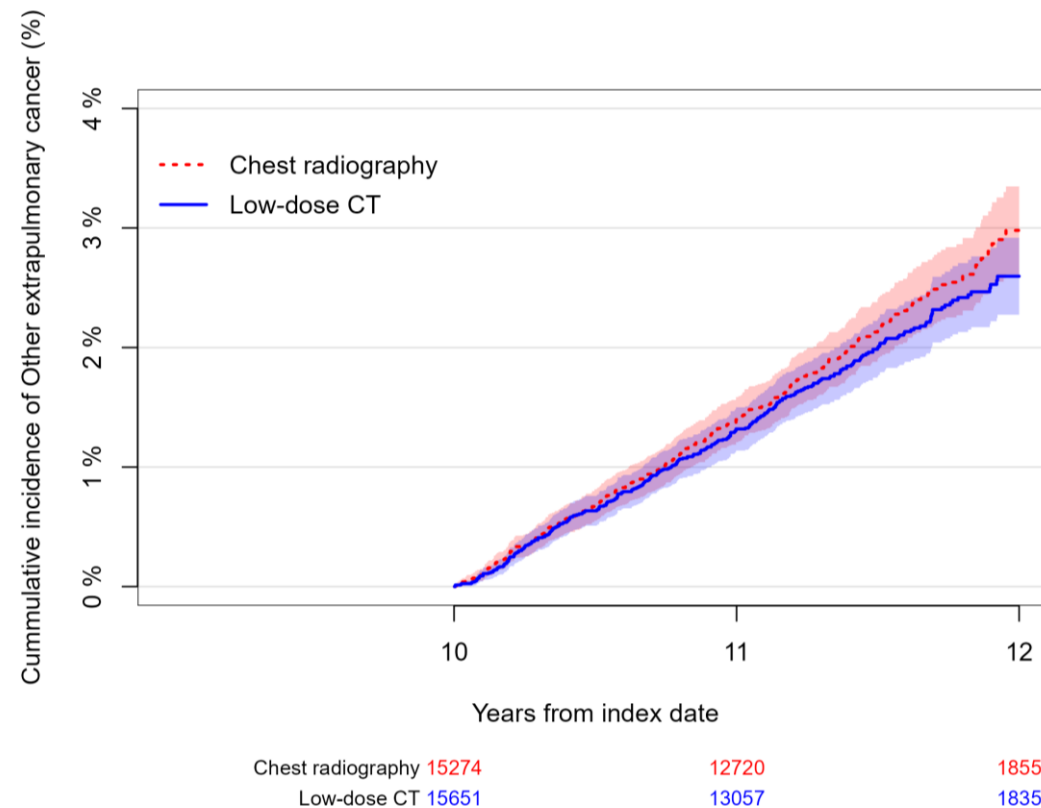
| Exposures                                                                                 | Hazard ratios for thyroid cancer |
|-------------------------------------------------------------------------------------------|----------------------------------|
| Screening with LDCT (reference: screening with chest radiography)                         | 0.88 (0.50–1.54)                 |
| Number of screening LDCT exams (reference: screening with chest radiography)              |                                  |
| 1                                                                                         | 1.13 (0.36–3.57)                 |
| 2                                                                                         | 0.93 (0.25–3.46)                 |
| 3                                                                                         | 0.83 (0.43–1.62)                 |
| Cumulative effective dose of LDCT exams (reference: screening with chest radiography)     |                                  |
| First quartile (<4.8 mSv)                                                                 | 0.65 (0.23–1.86)                 |
| Second quartile (4.8–6.0 mSv)                                                             | 1.26 (0.57–2.79)                 |
| Third quartile (6.0–7.7 mSv)                                                              | 0.82 (0.31–2.12)                 |
| Fourth quartile (≥7.7 mSv)                                                                | 0.83 (0.32–2.15)                 |
| Cumulative thyroid gland dose of LDCT exams (reference: screening with chest radiography) |                                  |
| First quartile (<5.0 mGy)                                                                 | 0.62 (0.21–1.82)                 |
| Second quartile (5.0–7.5 mGy)                                                             | 1.14 (0.49–2.62)                 |
| Third quartile (7.5–10.8 mGy)                                                             | 1.16 (0.50–2.67)                 |
| Fourth quartile (≥10.8 mGy)                                                               | 0.66 (0.23–1.90)                 |

Models were adjusted for sex, race, age, smoking status, and pack-year smoking burden



# Incident other extrapulmonary cancers after LDCT

- 309 events in the LDCT arm and 336 events in the CXR arm
- Incidence: 135.39 vs 150.85 per 10,000 person-years

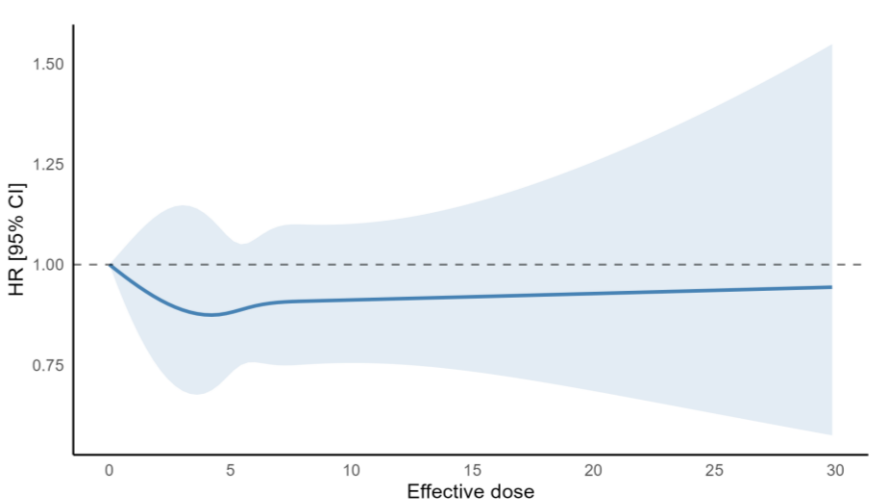


- HR for screening LDCT arm, 0.90 (95% CI, 0.77–1.05)

# Incident other extrapulmonary cancers after LDCT

| Exposures                                                                             | Hazard ratios for other extrapulmonary cancers |
|---------------------------------------------------------------------------------------|------------------------------------------------|
| Screening with LDCT (reference: screening with chest radiography)                     | 0.90 (0.77–1.05)                               |
| Number of screening LDCT exams (reference: screening with chest radiography)          |                                                |
| 1                                                                                     | 0.90 (0.75–1.08)                               |
| 2                                                                                     | 0.93 (0.73–1.20)                               |
| 3                                                                                     | 0.37 (0.09–1.48)                               |
| Cumulative effective dose of LDCT exams (reference: screening with chest radiography) |                                                |
| First quartile (<4.8 mSv)                                                             | 0.93 (0.72–1.20)                               |
| Second quartile (4.8–6.0 mSv)                                                         | 0.75 (0.57–0.98)                               |
| Third quartile (6.0–7.7 mSv)                                                          | 0.97 (0.76–1.24)                               |
| Fourth quartile (≥7.7 mSv)                                                            | 0.95 (0.75–1.22)                               |

Models were adjusted for sex, race, age, smoking status, and pack-year smoking burden



# Conclusion

- Three annual rounds of LDCT were not associated with a measurable increase in extrapulmonary cancer risk.
- No consistent positive dose-response relationship was observed across effective or organ-specific dose metrics.
- Modest increases in rare or long-latency cancers cannot be excluded.
- These findings apply to older heavy smokers undergoing a limited number of screening rounds.
- **Radiation-associated cancer concerns should not deter eligible high-risk individuals from lung cancer screening.**

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