10633

Overall and Non-Lung Cancer Incidence in the National Lung Screening Trial (NLST) as Indicators of Potential for Multi-Cancer Screening

ASCO 2023
June 2–6, 2023
Chicago, IL, USA

Ellen T. Chang,[1] Sam M. Janes,[2] Allan Hackshaw,[2] Christina A. Clarke,[1] Diana S. M. Buist,[1] Earl A. Hubbell[1]
[1]GRAIL, LLC, Menlo Park, California, USA; [2]University College London, London, United Kingdom

INTRODUCTION

- Single-cancer screening strategies address only one component of the overall population cancer burden
  - For example, lung cancer, the leading cause of cancer mortality worldwide and in the United States, comprises approximately one fifth of cancer deaths[1,2]
- Public health actions that simultaneously address multiple cancers have the potential to yield a far broader impact than those that target one cancer at a time
- The burden of cancers missed by single-cancer screening strategies can be characterized by evaluating the incidence of all cancers in a designated screening population
- Few cancer screening trials, however, have reported the incidence of cancer types not targeted by the screening intervention (i.e., "untargeted" cancers)

OBJECTIVE

- To understand the overall cancer burden in a single-cancer screening population, we evaluated the incidence of all newly diagnosed invasive cancers, especially non-lung, following study entry in the NLST (ClinicalTrials.gov number NCT00047385)[3]

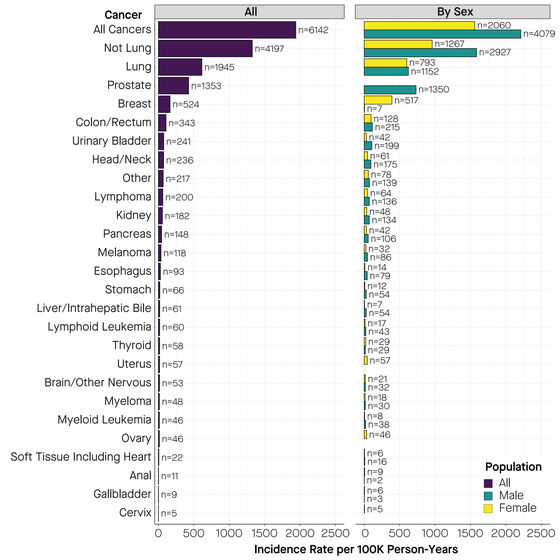
METHODS

- The NLST was a randomized controlled trial of lung cancer screening with low-dose computed tomography or chest radiography[3]
- From 33 participating medical institutions across the US between August 2002 and April 2004, the trial enrolled 53 454 adults who were aged 55–74 years at randomization, had no history of cancer in the last 5 years, and had at least a 30-pack-year history of cigarette smoking, and, if former smokers, had quit within the previous 15 years
- Participants were actively followed for cancer incidence through December 31, 2009 via annual or semiannual participant-completed questionnaires, death certificates obtained through linkage with the National Death Index, and, rarely, direct notification by a participant's relative; all positive notifications were confirmed by medical record abstraction
- Data on all incident cancers diagnosed during study follow-up (up to four cancers per person) were coded using International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes for topography, morphology, behavior, and grade, as well as SEER site categorizations derived from the ICD-O-3 codes
  - Data were cleaned to remove bad data and ineligible participants
- The present analysis includes first invasive primary cancers (ICD-O-3 behavior code 3/malignant) diagnosed after study randomization
  - Non-lung cancer incidence was similar between the two trial arms, which were therefore combined for analysis
  - Incidence rates were calculated using person-time from randomization until cancer diagnosis, loss to follow-up (<4%), or the end of 2009, whichever occurred first
- For comparisons between the NLST study population and the US general population, we used crude cancer incidence rates in 2002–2009 among US adults aged 55–79 years in 22 SEER geographic regions, accessed using SEER*Stat software[8]
- This analysis is limited by the initial ascertainment of incident cancers based largely on self-report, although positive notifications were validated based on medical records; thus, cancer incidence may have been underestimated
  - If participants were more likely to report a diagnosis of lung cancer than non-lung cancer, then the true proportion of non-lung cancers in the NLST may have been even greater

THE INCIDENCE OF NON-LUNG CANCER IS MORE THAN DOUBLE THAT OF LUNG CANCER, EVEN IN A HIGH-RISK SMOKER POPULATION

- Among 53 229 subjects (median follow-up 6.5 years), the incidence of any first primary cancer during active follow-up after randomization was 1941 per 100 000 person-years, of which 1327 per 100 000 (68%) was non-lung cancer (**Figure 1**)
  - After lung cancer, the most common cancers were other leading cancer types in the general US population (i.e., prostate, breast, and colon/rectum[2]), as well as other smoking-related cancers
  - No recommended population-based screening modalities exist for 54% of observed cancer cases (3332 of 6142, excluding lung, female breast, colon/rectum, and uterine cervix[4])
  - "Rare" cancers (defined by the National Cancer Institute as those affecting <40 000 persons per year in the US[5]) accounted for 15% of observed cancer cases (912 of 6142, including myeloma, stomach, brain/other nervous system, esophagus, acute myeloid leukemia, and less common types)

Figure 1. Incidence rates of first primary invasive cancers after randomization in the NLST study population by cancer type and sex. Case counts are indicated next to rates.



- The non-lung cancer incidence rate exceeded that for lung cancer in all 5-year age categories, especially at younger ages (**Figure 2A**)
- Non-lung cancer incidence also exceeded lung cancer incidence in all quintiles of smoking pack-years, especially with fewer pack-years (**Figure 2B**)

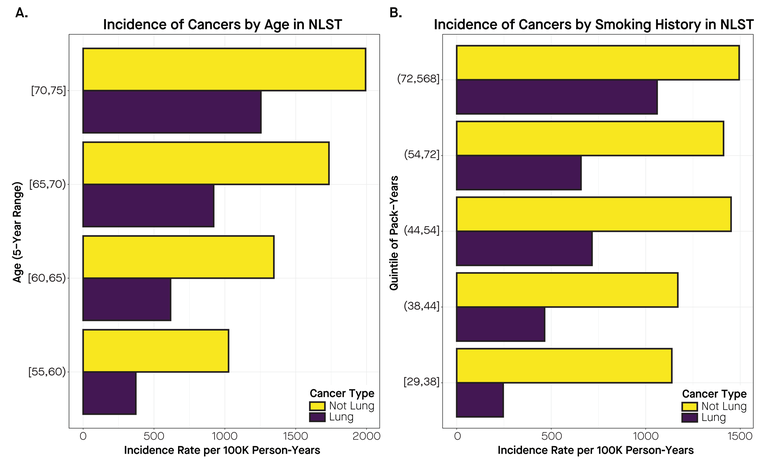


Figure 2. Incidence rates of first primary invasive lung and non-lung cancers after randomization in the NLST study population, stratified by risk factors. A) Stratified by 5-year age group. B) Stratified by quintile of smoking pack-years.

- Overall cancer incidence after study entry in the NLST exceeded that in the general US SEER population aged 55–79 years, but most of the excess was due to lung cancer (**Table 1**)
- The incidence rate of non-lung cancers was comparable between NLST participants and the general US SEER population, with excesses of some strongly smoking-related cancers (e.g., head/neck and esophagus) but deficits of other cancers (e.g., colon/rectum and melanoma)

Table 1. Incidence rates (per 100 000 person-years; not age-adjusted) of primary invasive cancers after randomization by type in the NLST study population and among US adults aged 55–79 years in Surveillance, Epidemiology, and End Results (SEER) 22 geographic regions, 2002–2009.

	NLST			SEER		
	All	Male	Female	All	Male	Female
All Cancers	1941	2212	1561	1543	1877	1252
Not Lung	1327	1587	960	1306	1598	1052
Lung	615	625	601	237	280	201
Prostate	428	732	–	299	642	–
Breast	166	4	392	195	4	361
Colon/Rectum	108	117	97	150	178	127
Urinary Bladder	76	108	32	71	117	31
Head/Neck	75	95	46	50	79	25
Other	69	75	59	96	109	85
Lymphoma	63	74	49	62	72	53
Kidney	58	73	36	50	69	34
Pancreas	47	57	32	39	44	35
Melanoma	37	47	24	49	69	32
Esophagus	29	43	11	17	29	7
Stomach	21	29	9	24	33	16
Liver/Intrahepatic Bile	19	29	5	24	38	13
Lymphoid Leukemia	19	23	13	19	26	14
Thyroid	18	16	22	21	14	27
Uterus	18	–	43	45	–	84
Brain/Other Nervous	17	17	16	15	19	13
Myeloma	15	16	14	21	25	18
Myeloid Leukemia	15	21	6	15	18	12
Ovary	15	–	35	20	–	38
Soft Tissue Incl. Heart	7	9	5	7	9	6
Anal	3	1	7	5	4	5
Gallbladder	3	2	5	4	3	5
Cervix	2	–	4	7	–	14

CONCLUSIONS

- In the NLST, only 32% of cancer incidence was lung; non-lung cancer comprised 68% of cancer incidence after study entry, and most cases were cancer types with no generally recommended screening strategy
- Even in a high-risk population, a single-cancer screening test misses most cancers. These results illustrate the value of multi-cancer screening tests that can detect a broad spectrum of cancers and, therefore, have the potential to address a currently inaccessible portion of cancer morbidity and mortality
- Reporting the incidence of all cancers in study populations targeted by single-cancer or selected-cancer screening strategies helps to contextualize the total burden of cancer addressed by the screening intervention. Where reported, the proportion of untargeted cancers consistently exceeds that of any single cancer[6,7]
- We encourage screening trial investigators to routinely report all cancer incidence by cancer type, and ideally by stage at diagnosis, when publishing trial results, thereby quantifying potential progress toward the overarching goal of reducing the number of lives lost to cancer

References

1. Ferlay J et al. 2020. http://gco.iarc.fr/today/home.
2. Siegel RL et al. CA Cancer J Clin. 2023;73(1):17-48.
3. The National Lung Screening Trial Research Team. N Engl J Med. 2011;365(5):395-409.
4. US Preventive Services Taskforce. 2023. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations.
5. National Cancer Institute. 2019. https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/about-rare-cancers.
6. Zhu CS et al. JNCI. 2013;105(22):1684-1693.
7. Dbouk M et al. J Clin Oncol. 2022;40(28):3257-3266.
8. Surveillance, Epidemiology, and End Results Program, National Cancer Institute. 2023. https://seer.cancer.gov/.

Disclosures

All financial relationships disclosed at abstract submission.

Acknowledgements

This study was funded by GRAIL, LLC. Randall Janairo (GRAIL, LLC) assisted with poster development. Editorial and graphics assistance was provided by Grace Wang (GRAIL, LLC) and Kristi Whitfield (PosterDocs, Oakland, CA, USA) and funded by GRAIL, LLC. The authors thank the National Cancer Institute (NCI) for access to NCI's data collected by the NLST (CDAS Project # NLST-995).

For any questions regarding this poster presentation, please contact **echang@grailbio.com.**