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ABSTRACT

Objective: To assess the cumulative radiation exposure and lifetime attributable risk (LAR) of cancer incidence associated with low-dose CT (LDCT) from a 10-year lung cancer screening program.

Design: Retrospective evaluation of radiation exposure and estimation of LAR of cancer.

Setting: 10-year nonrandomized, single-center, CT lung cancer screening trial (COSMOS study).

Participants: 5203 asymptomatic smokers (3439 males, 1764 females). Eligibility criteria: ≥50 year-old, current/former smokers (≥20 pack-years), without history of cancer in the previous 5 years.

Intervention: Volunteers underwent annual LDCT for 10 consecutive years.

Primary and secondary outcomes measures: Cumulative radiation exposure and LAR of cancer incidence calculated from BEIR VII report.

Results: During 10 years, 5203 high-risk participants underwent a total of 42,228 LDCT and 635 PET-CT. The median cumulative effective-dose at 10^{th} year of screening was 9.3 mSv for males and 13.0 mSv for females.

According to subjects' age and sex, the LAR of lung cancer and major cancers after 10 years of CT screening ranged from 5.5/10,000 to 1.4/10,000 and from 8.1/10,000 to 2.6/10,000, respectively. In younger female (50/55-year-old) the LAR of lung cancer and major cancers is about 4-fold and 3-fold higher than older male (≥65-year-old), respectively.

The number of estimated lung cancer and major cancers induced by 10 years of screening in our cohort are 1.5 and 2.4 respectively, corresponding to an additional risk of induced major cancers of 0.05% (2.4/5203). Two hundred fifty-nine lung cancers were diagnosed in 10 years of screening: one radiation-induced major cancer is expected for every 108 (259/2.4) screening-detected lung cancers.

Conclusions: Radiation exposure and cancer risk from CT screening, even if non-negligible, can be considered acceptable in light of the significant mortality reduction associated with screening.

Strengths and limitations of this study:

- More than 5000 subjects underwent annual low-dose CT for 10 consecutive years, with more than 42.000 low-dose CT performed.
- Radiation exposure calculated for each subject with advance software
- The estimate of Lifetime Attributable Risk of cancer incidence, calculated from BEIR VII report, has intrinsic limitations
- Number of radiation-induced cancer is compared with screening-detected lung cancer

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Introduction

Lung cancer is the leading cause of cancer for both men and women in the United States. In 2015, the American Cancer Society expected over 200 thousand new cases of lung cancer, about 14% of the total new cancers, with a 5-year survival rate of 18% [1].

The National Lung Screening Trial (NLST) has demonstrated that screening of high-risk population with low-dose computed tomography (LDCT) reduces lung cancer mortality by more than 20% if compared to chest radiography [2].

As a consequence, several medical societies actually recommend CT lung screening and a positive insurance coverage decision has been granted in the United States by the Centers for Medicare and Medicaid Services (CMS) [3]. Therefore, millions of healthy high-risk subjects became theoretically eligible for CT lung cancer screening.

However, the exposure to ionizing radiation of low-dose CT still remains one of the major concerns in lung cancer screening, which might lead to an increase risk of solid cancers and leukemia [4]. Although the concrete existence of an increased risk of cancers related to low-dose radiation (doses below 50-100 mSv) is still controversial [5-7], this topic deserves additional consideration since ionizing radiations from CT screening are delivered to healthy people.

To date there is limited knowledge of the radiation exposure in lung cancer screening, particularly for a long-term exposition, regarding both cumulative radiation exposure and the associated cancer risk. Brenner estimated that if 50% of all current and former smokers in the U.S. population aged 50-75 years received annual CT screening, the number of lung cancers associated with radiation from screening would be approximately 36,000, a 1.8% (95% confidence interval: 0.5%, 5.5%) increase over the otherwise expected number [8]. McCunney and colleagues, reported that lung screening participants may experience a cumulative exposure to ionizing radiation over 20- to 30-year which can exceed lifetime doses experienced by nuclear power workers and atomic bomb survivors [9]. However, the results of the aforementioned studies cannot be considered conclusive,

as based on the assumption of an arbitrary, pre-established radiation dose for all subjects, regardless of sex, age or body habitus.

The aim of this study was therefore to retrospectively evaluate the cumulative radiation exposure and lifetime attributable risk (LAR) of cancer incidence associated with low-dose CT from a 10-year lung cancer screening program.

Material and methods

All the data reported in the present study were retrospectively collected and analyzed from a 10-year nonrandomized observational lung cancer screening trial (COSMOS Study) [10, 11]. In brief, 5203 asymptomatic high risk subjects (age > 50 years-old and smoking history ≥ 20 pack-years) underwent annual low-dose CT for 10 consecutive years. Additional recalls for suspicious findings were performed with low-dose CT and PET-CT, according to the study design.

A comprehensive description of the COSMOS study as well as LDCT protocols and PET-CT scan are reported in the Supplementary file.

Radiation exposure from CT screening

To consider the overall radiation exposure to the population, both the annual repeated LDCT and the follow-up LDCT of each subject were collected for each year of screening. In addition, all the PET-CT scans performed within the study were considered to evaluate the cumulative exposure dose. At the end of the 10th year of CT screening, all performed examinations were collected from the RIS-PACS information system and sent to Radimetrics (Bayer Healthcare AG, Leverkusen, Germany) a commercially available software for patient radiation exposure monitoring and tracking [12]. Organ and effective doses have been retrospectively estimated by Radimetrics for each LDCT examination and for the CT acquisitions of the PET- CT. Data and scanning parameters are collected from CT examinations, and patients, according to age, sex, weight and dimension, are matched to 6 and 5 different adult phantoms, for women and men, respectively: the size-specific

calculation of organ doses provides a better accuracy in comparison with software that uses only the standard reference patient.

Organ doses are calculated using look-up table built on MonteCarlo simulations for the selected phantoms [13] and hence used to estimate effective dose according to the weighting factors from ICRP 103 [14]. For PET-CT the contribution of the radioactive tracer to organ doses and effective doses is calculated using the absorbed dose coefficients per unit activity administered (mGy/MBq) [15].

Total estimated organ dose and effective dose for a single patient were calculated as the sum of the doses of each LDCT examination (screening rounds performed + recalls) and PET-CT when performed. As cumulative organ and effective doses were non-normally distributed, median and range have been considered.

Cancer risk estimation

For each age, sex, and organ, the lifetime attributable risk (LAR) of cancer incidence from a 100-mSv organ equivalent dose was determined using Table 12D-1 of the National Research Council's "Biological Effects of Ionizing Radiation" BEIR VII report. When missing, age-specific LAR were estimated using polynomial interpolation of LAR values reported for age 50, 60, 70 and 80. This LAR from a theoretical 100-mSv organ dose was scaled linearly based on the actual organ dose measured at each single CT scan. LAR were calculated for each of the 42,228 LD-CT scans performed during the COSMOS trial and added up to get the LAR for the entire COSMOS population.

Patient involvement

No patients were involved in the design of this study.

Results

Radiation Exposure from CT screening

During the 10 years of the COSMOS lung cancer screening trial, the 5203 high-risk participants underwent a total of 42,228 LDCT examinations, including 39,981 annual CTs, 1,965 first recall CTs and 282 second recall CTs. As part of the screening protocol, 635 PET-CT scans were performed in 522 subjects with suspicious findings (Table 1). Two hundred fifty-nine lung cancers were diagnosed after 10 years of CT screening.

The median effective dose delivered at baseline screening round was 1.0 mSv (range 0.6-16.5) for males and 1.4 mSv (range 0.9-14.9) for females.

The median cumulative effective doses from both LDCTs and PET-CT at 3rd, 5th and 10th year of screening were 3.0 mSv (range 1.9-27.4), 5.2 mSv (range 2.9-39.6) and 9.3 mSv (range 5.6-42.7) for males and 4.2 mSv (range 2.9-23.3), 7.2 mSv (range 4.1-26.8) and 13.0 mSv (range 8.0-33.5) for females respectively (Table 2). A single PET-CT delivered an additional median radiation exposure of 4.0 mSv (range 1.2 – 28.8 mSv). Complete information on the effective doses and organ-specific exposition doses from only LDCT scans and LDCTs + PET-CT are provided in the Supplementary file (Table S1 and Table S2).

Overall, 15,805 examinations were performed with 8-detector rows CT, 22,132 with 16-detector row CT and 4,291 with 64-detector row CT. The average effective doses (± standard deviation) for a single LDCT examination for the three CT scanners were 1.07±0.29 mSv, 1.05±0.27 mSv, 0.64±0.15 mSv respectively.

Estimated risk of cancer from CT screening

The distribution of participants enrolled in the COSMOS trial, lung cancers detected after 10 years and LAR of lung cancer and major cancers at corresponding gender and age are described in Table 3. Applying LAR of cancer incidence extrapolated from observation of atomic bomb survivors available in the BEIR VII report, the estimated LAR of lung cancer after 10 years of CT screening range between 5.5/10,000 (1 in 1811) participants for a female who starts screening at 50-54 years and 1.4/10,000 (1 in 6908) for a male who starts screening over 65-year. In the same groups, the

LAR of major cancers range between 8.1/10,000 (1 in 1229) and 2.6/10,000 (1 in 3898), respectively (Table 3).

Based on our exposure data applied to BEIR VII tables, we estimated the number of lung cancer and major cancers induced by 10 years of LDCT screening to be 1.5 and 2.4 respectively, corresponding to a theoretical risk of induced cancer of 0.05% (2.4/5203). Compared to the number of lung cancers detected over 10 years, every 173 (259/1.5) lung cancers diagnosed, one radiation-induced lung cancer is expected, while one radiation-induced major cancer is expected for every 108 (259/2.4) screening-detected lung cancers.

In a 50-54 years-old female the LAR of lung cancer is about 4-fold higher than older (65+) male (5.5 vs. 1.4/10,000), while the LAR of major cancers is 3-fold higher (8.1 vs. 2.6/10,000), reflecting differences driven by the BEIR VII tables.

The estimated lung and major cancers radiation induced for men and women, both for 10,000 people screened, are shown in Figure 1. As expected, for all ages the cancer induction risk is higher for women and the risk decreases in both sexes by increasing age of exposure. The number of induced cancers is always less than 5/10,000 for men and 10/10,000 in women.

Discussion

One of the major concerns related to lung cancer screening is the radiation dose delivered to healthy subjects.

In this study we showed that the median cumulative effective dose after 10 years of CT screening is roughly 9 mSv for male and 13 mSv for female. As a comparison to other diagnostic CT examinations, this means that a subject who participates to a 10-year LDCT screening receives a dose similar to that delivered to a patient who undergoes a single standard chest CT (7 – 8 mSv) or abdomen-pelvis CT scan (13 – 14 mSv) [16, 17].

Furthermore, if we consider that the 10-year average dose from the background sources in the U.S. is about 30 mSv, we may assume that 10-year screening delivers roughly one-third of the exposure to natural radiation background in the same period [18, 19].

In the National Lung Screening Trial (NLST), the effective dose estimated were 1.6 mSv and 2.4 mSv for a single LDCT scan, for male and female, respectively [20]. Our results show an effective dose at baseline of 1.0 mSv for male and 1.4 mSv for female. These doses are 40% lower than NLST, also considering the additional dose delivered by PET-CT scans performed in our study. Study design, scanning parameters and calculation methods may account for these differences. The scanning parameters at a typical NLST study site are quite similar to those of our baseline data. On the contrary the calculation method of organ dose and effective dose of the NLST is based on software that does not take into account the patient's habitus. Estimate of organ dose in the NLST for the breast is 4.9 mGy, while for the lungs is of nearly 5 mGy both for male and female. In comparison, taking into account subjects' dimension, we report a value for the breast of 2.5 mGy and of 2.3-2.7 mGy for the lungs, for male and female, respectively.

This highlights how the estimate of organ and effective doses with software that takes into account patient's habitus is an important source of variability. We reported a dosimetry calculation provided by advanced software (Radimetrics) for each of the 42,228 LDCT scans; although it's not a patient-specific dosimetry, the software can calculate organ doses and hence effective dose for 6 and 5 groups of patients, according to their dimension, for women and men respectively. Thus, the size-specific calculation of organ doses provides a better accuracy in comparison with software that uses only the standard reference patient for their calculations: in this case with a fixed acquisition protocol we would observe no differences in organ and effective dose calculations. Variations in organ doses among subjects were also related to the number of LDCTs and PET-CTs received during the study and to the different dose delivered by the three CT scanners.

The cumulative effective dose for NLST over 3 years was 4.8 mSv for male and 7.2 mSv for female, while in the same period we report a cumulative effective dose of 3.0 mSv for male and 4.2

mSv for female (Table 2). In our study the cumulative effective dose, and the consequent risk of cancer, is the result of the sum of radiation exposure both from LDCT and PET-CT scans. The contribution of a single PET-CT was 4.0 mSv, in comparison to the 10-year LDCT cumulative exposure of 9.2 mSv and 12.9 mSv for male and female, respectively (Table S2). Therefore, screening studies that not include PET-CT in their protocols could lead to a lower radiation exposure. The ITALUNG screening trial, after 4 rounds of screening, reported that the 77.4% of the delivered dose owed to annual LDCTs and 22.6% to further investigations (FDG-PET and CT-guided biopsy) [21]. Further studies assessing the role of different study design on radiation exposure are therefore needed in CT screening.

While accurate risk prediction models now exist to quantify an individual risk of developing or dying from lung cancer and help identifying those who are at high enough risk to undergo screening [22, 23], little is known about the additional risk of cancer that could be caused by exposure to radiations from screening itself. Brenner [8] in his risk evaluation, based on an assumed dose to the lung of 5.2 mGy, estimated an additional lung cancer risk of 1.8% due the annual lung CT screening. Our study demonstrates that after 10 years of low-dose CT screening in 5203 smoking subjects, 1.5 lung cancers and 2.4 major cancers are induced: this corresponds to an additional overall risk of 0.05% (2.4 over 5203 screened subjects).

As expected the LAR for women was greater than that for men at all ages, with a relative risk that is up to 4 times greater for lung cancer and up 3 times greater for major cancers. This is related both to the major radiosensitivities of women compared to men and to the risk of breast cancer associated with chest CT [4].

The assessment of cancer risk according to BEIR committee is based on the Linear No-Threshold (LNT) model and on the data collected from environmental, occupational, medical studies and from the atomic bomb survivor data. Risk estimate of the BEIR VII report are thus based on risk models generated from studies on subjects exposed to high levels of radiation and extrapolated to low doses using the LNT model for radiation risk. Various authors emphasized all the critical points of the

BEIR VII report, focusing, in particular, on the weaknesses of the LNT model [7, 24, 25] as well as on the uncertainties in the transport of the risk from high doses and high dose-rates in the Japanese population to lower doses and dose-rates in the American population.

A segment of the scientific community claims for the existence of a threshold for low dose radiation carcinogenesis and warns against quantitative estimation of health risks that might be too small to be observed or nonexistent below 50-100 mSv [26-28]. However, to date there is not sufficient evidence to suggests that below a certain dose the risk from radiation exposure is nonexistent and the LNT model stands as a precautionary recommendation that follows a conservative approach. It is also important to emphasize that all the risk estimates provided in the tables of the BEIR VII are obtained as a consensus opinion of a committee and the inferred risk at lower doses probably overestimates the risk of cancer induction [29].

In estimating risk for the individuals, the appropriate procedure consists in using specific organ doses and hence age-adjusted and gender-adjusted coefficients [30]. The effective dose has been implemented mainly for protection principles, and its use in medical practice as a measure of individual risk goes beyond its intended purpose [14, 31].

Even if our results demonstrate that cumulative radiation exposure after 10 years of LDCT screening is substantially limited, there are still possibilities for further reduction. The main strategy in CT screening dose reduction is targeting the patient population and optimizing the study design. An accurate patient selection can significantly reduce the radiation exposure to low-risk subjects while the definition of an accurate study design is essential for the improvement of the diagnostic flowchart, minimizing unnecessary radiation exposure.

New CT scanners and optimized acquisitions protocols can also reduce the dose by up to 40%, as we saw from the differences in effective doses between 8, 16 and 64 slice scanners reported in our results. In addition, according to our protocol, CT images were reconstructed using the standard filtered back projection (FBP). With the introduction of new iterative reconstruction algorithm, it is

currently possible to achieve the same diagnostic image quality with less dose which can be reduced up to 80% compared to standard FBP [32-35].

The results of this paper are related to the specific COSMOS study design, and different screening trials might lead to dissimilar results. In comparison to NLST population, our cohort was younger and lighter smokers, which theoretically implies a lower cancer radiation risk for NLST subjects.

As well as study population, screening nodule management has significant implications on the overall radiation exposure and cancer risk. In fact, different threshold of nodule size, interval follow-up and the use of PET-CT are determinant source of variations: more conservative guidelines, as suggested by the American College of Radiology (Lung-RADS Version 1.0) [36], could lead to lower population doses.

Another consideration that should be taken into account is the detection of incidental findings on low-dose CT [37, 38], that could lead to additional radiation risk for further testing as well as potential benefits in clinically significant findings. In the present study we did not consider the additional exposure from examinations performed for collateral findings, which could lead to a slight underestimation of overall cancer risk.

In conclusion, radiation exposure and cancer risk from CT screening, even if non negligible, can be considered acceptable in light of the significant mortality reduction associated with screening.

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Tables

Table 1. Number of screening and recall LD-CTs administered to participants to the COSMOS trial.

Screening round	Annual CTs N*	First recall CTs N (% year)	Second recall CTs N (% year)	PETs N (% year)
Baseline	5,203	482 (9.3%)	75 (1.4%)	160 (3.1%)
2nd year	4,822	142 (2.9%)	23 (0.5%)	68 (1.4%)
3rd year	4,583	198 (4.3%)	32 (0.7%)	74 (1.6%)
4th year	4,380	251 (5.7%)	47 (1.1%)	62 (1.4%)
5th year	4,120	213 (5.2%)	35 (0.8%)	66 (1.6%)
6th year	3,856	197 (5.1%)	24 (0.6%)	62 (1.6%)
7th year	3,654	170 (4.7%)	16 (0.4%)	41 (1.1%)
8th year	3,449	118 (3.4%)	14 (0.4%)	35 (1.0%)
9th year	3,182	103 (3.2%)	10 (0.3%)	41 (1.3%)
10th year	2,732	91 (3.3%)	6 (0.2%)	26 (1.0%)
Total	39,981	1,965	282	635

Table 2. Median cumulative organ doses (mGy) and effective doses E (mSv) from screening **LD-CTs, recall LD-CTs and PET-CTs** after the baseline, 3rd, 5th and 10th screening rounds received from participants who completed the correspondent screening round.

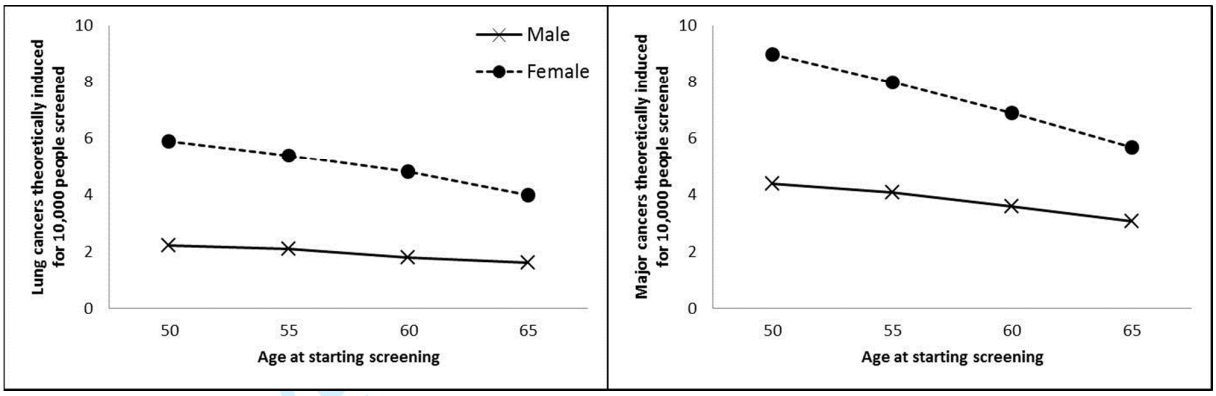
mGy (mean)	Male Baseline	3rd year	5th year	10th year	Female Baseline	3rd year	5th year	10th year
Participants	**3439**	**3056**	**2768**	**1850**	**1764**	**1527**	**1352**	**884**
E (mSv)	**1.0**	**3.0**	**5.2**	**9.3**	**1.4**	**4.2**	**7.2**	**13.0**
Breast	-	-	-	-	2.5	7.6	13.0	23.3
Bladder	0.0	0.1	0.1	0.2	0.0	0.1	0.1	0.2
Colon	0.2	0.7	1.2	2.2	0.2	0.6	1.1	2.0
Esophagus	1.4	4.5	7.7	13.6	1.8	5.6	9.5	16.9
Gallbladder	1.5	4.6	7.9	14.0	1.3	4.2	7.2	12.9
Heart	2.1	6.8	11.5	20.5	2.5	7.6	13.0	23.2
Kidney	1.9	5.9	10.1	18.0	1.8	5.6	9.7	17.4
Liver	1.9	6.1	10.4	18.4	2.1	6.6	11.2	20.0
Lung	2.3	7.1	12.2	21.7	2.7	8.3	14.2	25.3
Ovaries	-	-	-	-	0.1	0.2	0.3	0.6
Marrow	0.8	2.5	4.3	7.6	0.9	2.8	4.7	8.4
Skeleton	1.4	4.3	7.4	13.3	1.7	5.3	9.1	16.5
Spleen	2.0	6.1	10.5	18.6	2.2	6.8	11.7	20.9
Stomach	1.9	5.9	10.0	17.9	2.0	6.1	10.4	18.7
Thyroid	0.2	0.6	1.1	1.9	0.5	1.6	2.8	5.2
Uterus	-	-	-	-	0.1	0.2	0.3	0.5

Table 3. Distribution of participants enrolled in the COSMOS trial, lung cancer detected after 10 years of screening and corresponding estimated radiation-induced cancers and lifetime attributable risk (LAR) of cancers associated with radiation exposure.

Age start screening	Gender	Subjects	Lung cancers detected	Radiation induced estimated Lung cancers N (LAR/10,000)	Radiation induced estimated Major cancers[a] N (LAR/10,000)
50-54	Male	1153	35 (1 in 33)	0.24 (2.1)	0.43 (3.7)
	Female	606	19 (1 in 32)	0.33 (5.5)	0.49 (8.1)
55-59	Male	1114	56 (1 in 20)	0.21 (1.9)	0.38 (3.4)
	Female	611	31 (1 in 20)	0.31 (5.1)	0.44 (7.2)
60-64	Male	716	54 (1 in 13)	0.12 (1.7)	0.22 (3.0)
	Female	345	13 (1 in 27)	0.16 (4.5)	0.21 (6.2)
65+	Male	456	41 (1 in 11)	0.07 (1.4)	0.12 (2.6)
	Female	202	10 (1 in 20)	0.08 (3.8)	0.10 (5.1)
All ages	Both sexes	5203	259 detected	1.5 induced	2.4 induced

[a]cumulative LAR for cancer of the stomach, colon, liver, lung, bladder, thyroid, breast, ovaries, uterus or leukemia

Figure 1. Lung cancers (a) and major cancers (b) theoretically induced for 10000 people screened.



Supplementary file

Population and Study design

The screening protocol, enrollment criteria, LDCT settings, and diagnostic algorithm have been previously described [1, 2].

Briefly, between October 2004 and October 2005, 5203 asymptomatic high-risk individuals (smoking history of 20 or more pack-years) aged 50 years or more were enrolled in our single-center trial (COSMOS) and underwent baseline LDCT screening for lung cancer. This single-centre study was approved by the ethics committee of our institute. All recruited volunteers gave written consent to annual LDCT for 10 consecutive years.

Patients with non-calcified nodules detected at baseline or new nodules of 5 mm or less detected at annual screening were scheduled for repeating CT 1 year later. Patients with nodules between 5.1 and 8 mm were scheduled for repeating CT 3 to 6 months later. Patients with nodules greater than 8.1 mm, or growing lesions less than 8mm after repeated scan, were scheduled for PET-CT. Further investigations (repeat LDCT 6 months later, PET-CT, or surgical biopsy) for patients with growing nodules at subsequent annual screening depended on nodule density (non-solid, solid, or partially solid), growth rate and size.

Evolution of diagnostic protocol algorithms for the management of pulmonary nodules detected at baseline CT screening from the beginning of the study until the 10th year of screening trial has been described [3].

Low-dose CT protocols

During the 10 years of CT screening, LDCT scans were performed using 3 different scanners with 8-, 16- and 64-detector rows (Lightspeed Ultra, Lightspeed 16, Optima CT660; GE Healthcare - Waukesha, Wisconsin, USA).

Protocol parameters for both Lightspeed Ultra and Lightspeed 16 were: 120 kVp, 30 mA, rotation time of 0.8 s, 20mm collimation with 2.5mm slice thickness (1.25mm retro-reconstruction). Pitch is slightly different, being 1.675 for Lightspeed Ultra and 1.75 for Lightspeed 16. $CTDI_{vol}$ reported by the scanners are 1.21 mGy and 1.28 mGy for the 8 slice scanner and the 16 slice scanner, respectively.

Acquisitions with Optima CT660 had the following parameters: 120 kVp, 30 mA, revolution time of 0.5 s, pitch 1.375, 40mm collimation with 2.5mm slice thickness (1.25mm retro-reconstruction). The reported $CTDI_{vol}$ was 0.91 mGy.

$CTDI_{vol}$ were measured according to the AAPM Report n.96 [4] to verify that the measured values were within ±10% of the console displayed $CTDI_{vol}$.

PET-CT scan

Images were acquired with a combined PET-CT in-line system (Discovery ST and Discovery 600, GE Medical Systems) consisting of an Advance NXi PET scanner and an 8-slice Light Speed Plus CT scanner. 4 MBq/kg of 18-fluoro-deoxy-glucose were administered intravenously. CT settings were 120 kVp and mA according to body size. PET acquisition time was 3 min per table position. Three-dimensional PET image datasets were reconstructed iteratively, with segmental correction for attenuation using the CT data.

1. Veronesi G, Bellomi M, Veronesi U, et al. Role of positron emission tomography scanning in the management of lung nodules detected at baseline computed tomography screening. *Ann Thorac Surg*. 2007;84(3):959-965.

2. Veronesi G, Bellomi M, Mulshine J, et al. Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. *Lung Cancer*. 2008;61(3):340-349.

3. Veronesi G, Bellomi M, Scanagatta P, et al. Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program. *J Thorac Cardiovasc Surg*. 2008;136(3):611-617.

4. AAPM Report 96. The Measurement, Reporting, and Management of Radiation Dose in CT. 2008.

S1. Median, minimum and maximum cumulative organ doses (mGy) and effective doses (mSv) from screening **LD-CTs, recall LD-CTs and PETs** after the baseline, 3rd , 5th and 10th screening rounds received from respectively 5203, 4583, 4120, and 2734 participants who completed the 1st, 3rd, 5th and 10th screening round.

	Male				Female			
	Baseline	3rd year	5th year	10th year	Baseline	3rd year	5th year	10th year
ICRP103 (mSv)	1.0 (0.6-16.5)	3.0 (1.9-27.4)	5.2 (2.9-39.6)	9.3 (5.6-42.7)	1.4 (0.9-14.9)	4.2 (2.9-23.3)	7.2 (4.1-26.8)	13.0 (8.0-33.5)
Lung	2.3 (1.4-30.5)	7.1 (4.5-52.2)	12.2 (6.9-76.9)	21.7 (12.9-84.1)	2.7 (1.6-25.7)	8.3 (5.6-42.2)	14.2 (7.7-49.2)	25.3 (15.0-62.4)
Breast	-	-	-	-	2.5 (1.9-16.7)	7.6 (5.2-24.3)	13.0 (8.1-30.2)	23.3 (17.1-46.0)
Heart	2.1 (1.3-46.8)	6.8 (4.2-80.1)	11.5 (6.5-119)	20.5 (12.0-125)	2.5 (1.5-38.3)	7.6 (5.1-58.5)	13.0 (7.0-68.4)	23.2 (13.6-82.4)
Spleen	2.0 (1.2-23.6)	6.1 (3.9-40.5)	10.5 (5.9-59.7)	18.6 (11.1-65.8)	2.2 (1.3-20.0)	6.8 (4.5-34.0)	11.7 (6.2-39.5)	20.9 (11.9-50.5)
Liver	1.9 (1.1-27.8)	6.1 (3.7-47.6)	10.4 (5.8-70.4)	18.4 (11.0-76.6)	2.1 (1.2-23.2)	6.6 (4.3-38.1)	11.2 (5.9-43.3)	20.0 (11.4-54.0)
Stomach	1.9 (1.1-23.9)	5.9 (3.5-40.9)	10.0 (5.6-60.8)	17.9 (10.7-66.7)	2.0 (1.1-19.9)	6.1 (3.9-33.9)	10.4 (5.4-38.4)	18.7 (10.3-48.4)
Kidney	1.9 (0.9-27.0)	5.9 (3.2-46.6)	10.1 (5.6-69.3)	18.0 (10.9-75.4)	1.8 (0.9-22.2)	5.6 (3.2-36.8)	9.7 (4.7-40.4)	17.4 (9.1-50.0)
Esophagus	1.4 (0.8-14.8)	4.5 (2.7-25.7)	7.7 (4.3-37.7)	13.6 (8.0-42.0)	1.8 (1.0-13.4)	5.6 (3.7-24.7)	9.5 (5.0-29.2)	16.9 (9.6-38.4)
Skeleton	1.4 (0.8-32.8)	4.3 (2.7-53.7)	7.4 (4.2-79.7)	13.3 (8.3-84.4)	1.7 (1.1-28.5)	5.3 (3.6-40.1)	9.1 (5.1-49.8)	16.5 (10.0-55.4)
Gallbladder	1.5 (0.6-21.9)	4.6 (2.2-38.1)	7.9 (3.9-56.8)	14.0 (8.1-61.4)	1.3 (0.7-18.2)	4.2 (2.3-30.0)	7.2 (3.5-32.6)	12.9 (6.9-39.9)
Marrow	0.8 (0.5-18.5)	2.5 (1.5-31.0)	4.3 (2.4-45.9)	7.6 (4.7-48.4)	0.9 (0.5-15.5)	2.8 (1.9-22.5)	4.7 (2.6-27.4)	8.4 (5.0-29.3)
Thyroid	0.2 (0.1-34.4)	0.6 (0.3-54.2)	1.1 (0.6-77.3)	1.9 (1.1-78.1)	0.5 (0.1-26.5)	1.6 (0.7-30.0)	2.8 (1.2-45.9)	5.2 (2.2-39.9)
Colon	0.2 (0.1-19.4)	0.7 (0.3-32.3)	1.2 (0.6-48.0)	2.2 (1.2-48.9)	0.2 (0.1-16.0)	0.6 (0.4-21.3)	1.1 (0.6-28.3)	2.0 (1.1-25.4)
Ovaries	-	-	-	-	0.1 (0.0- 9.6)	0.2 (0.1-10.4)	0.3 (0.2-15.6)	0.6 (0.3-17.5)
Uterus	-	-	-	-	0.1 (0.0-10.9)	0.2 (0.1-12.3)	0.3 (0.2-18.0)	0.5 (0.3-19.5)
Bladder	0.0 (0.0-67.5)	0.1 (0.0-113)	0.1 (0.0-169)	0.2 (0.1-169)	0.0 (0.0-53.5)	0.1 (0.0-70.1)	0.1 (0.0-94.3)	0.2 (0.1-97.0)

S2. Median, minimum and maximum cumulative organ doses (mGy) and effective doses (mSv) from screening LD-CTs and recall LD-CTs after the baseline, 3rd , 5th and 10th screening rounds received from respectively 5203, 4583, 4120, and 2734 participants who completed the 1st, 3rd, 5th and 10th screening round.

	Male				Female			
	Baseline	**3rd year**	**5th year**	**10th year**	**Baseline**	**3rd year**	**5th year**	**10th year**
ICRP103 (mSv)	1.0 (0.6- 4.0)	3.0 (1.9- 9.0)	5.2 (2.9-13.4)	9.2 (5.6-17.6)	1.4 (0.9- 4.5)	4.2 (2.5-10.4)	7.2 (4.1-14.4)	12.9 (8.0-20.8)
Lung	2.3 (1.4-9.0)	7.1 (4.5-20.6)	12.1 (6.8-31.1)	21.5 (12.9-40.7)	2.7 (1.6- 9.0)	8.3 (5.0-20.3)	14.1 (7.7-28.0)	25.1 (15.0-40.8)
Breast					2.5 (1.9- 8.1)	7.6 (5.0-18.5)	12.9 (8.1-24.2)	23.3 (17.1-35.3)
Heart	2.1 (1.3- 8.8)	6.8 (4.2-20.1)	11.5 (6.4-30.8)	20.3 (12.0-39.8)	2.5 (1.5- 8.3)	7.6 (4.6-18.7)	13.0 (7.0-26.2)	23.0 (13.6-38.1)
Spleen	2.0 (1.2- 7.9)	6.1 (3.8-18.0)	10.4 (5.8-27.3)	18.4 (11.1-35.5)	2.2 (1.3- 7.3)	6.8 (4.0-16.8)	11.6 (6.2-23.7)	20.7 (11.9-34.2)
Liver	1.9 (1.1- 8.0)	6.1 (3.7-18.0)	10.3 (5.8-27.1)	18.2 (11.0-35.0)	2.1 (1.2- 6.9)	6.5 (3.7-16.2)	11.2 (5.9-22.9)	19.9 (11.4-33.0)
Stomach	1.9 (1.1- 7.8)	5.9 (3.5-17.6)	10.0 (5.6-26.2)	17.7 (10.7-34.5)	1.9 (1.1- 6.4)	6.1 (3.3-15.3)	10.4 (5.4-21.6)	18.4 (10.3-31.0)
Kidney	1.9 (0.9- 8.1)	5.9 (3.2-18.2)	10.0 (5.6-26.6)	17.8 (10.9-36.2)	1.8 (0.9- 6.2)	5.6 (2.8-14.7)	9.6 (4.7-20.5)	17.2 (9.1-29.7)
Esophagus	1.4 (0.8- 6.1)	4.5 (2.7-13.8)	7.6 (4.3-20.8)	13.4 (8.0-26.4)	1.8 (1.0- 6.0)	5.6 (3.3-13.7)	9.5 (5.0-19.7)	16.8 (9.6-28.5)
Skeleton	1.4 (0.8- 5.4)	4.3 (2.7-12.2)	7.3 (4.2-18.1)	13.2 (8.3-24.4)	1.7 (1.1- 5.6)	5.3 (3.1-13.0)	9.0 (5.1-18.0)	16.3 (10.0-26.2)
Gallbladder	1.5 (0.6- 6.7)	4.6 (2.2-14.8)	7.9 (3.9-21.7)	13.8 (8.1-29.4)	1.3 (0.7- 4.8)	4.1 (2.1-11.3)	7.1 (3.5-15.6)	12.8 (6.9-24.1)
Marrow	0.8 (0.5- 3.2)	2.5 (1.5- 7.2)	4.3 (2.4-10.7)	7.5 (4.7-14.2)	0.9 (0.5- 2.9)	2.8 (1.6- 6.8)	4.7 (2.6- 9.4)	8.4 (5.0-13.6)
Thyroid	0.2 (0.1- 2.4)	0.6 (0.3- 3.9)	1.1 (0.5- 4.9)	1.9 (1.1- 7.9)	0.5 (0.1- 2.7)	1.5 (0.7- 5.6)	2.7 (1.2-10.6)	5.1 (2.2-17.0)
Colon	0.2 (0.1- 1.0)	0.7 (0.3- 2.7)	1.2 (0.6- 4.0)	2.2 (1.2- 5.6)	0.2 (0.1- 0.8)	0.6 (0.3- 1.6)	1.1 (0.6- 2.7)	2.0 (1.1- 4.4)
Ovaries					0.1 (0.0- 0.2)	0.2 (0.1- 0.5)	0.3 (0.2- 0.8)	0.6 (0.3- 1.3)
Uterus					0.1 (0.0- 0.2)	0.2 (0.1- 0.4)	0.3 (0.2- 0.7)	0.5 (0.3- 1.1)
Bladder	0.0 (0.0- 0.1)	0.1 (0.0- 0.2)	0.1 (0.1- 0.3)	0.2 (0.1- 1.3)	0.0 (0.0- 0.1)	0.1 (0.0- 0.1)	0.1 (0.0- 0.2)	0.2 (0.1- 0.4)