SHORT COMMUNICATION

Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT

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ABSTRACT. Few data are available on the effective dose received by participants in lung cancer screening programmes with low-dose CT (LDCT). We report the collective effective dose delivered to 1406 current or former smokers enrolled in the ITALUNG trial who completed 4 annual LDCT examinations and related further investigations including follow-up LDCT, 2-[¹⁸F]flu-2-deoxy-D-glucose positron emission tomography (FDG-PET) or CT-guided fine needle aspiration biopsy (FNAB). Using the air CT dose index and Monte Carlo simulations on an anthropomorphic phantom, the whole-body effective dose associated with LDCT was determined for the eight CT scanners used in the trial. A value of 7 mSv was assigned to FDG-PET while the measured mean effective dose of CT-guided FNAB was 1.5 mSv. The mean collective effective dose in the 1406 subjects ranged between 8.75 and 9.36 Sv and the mean effective dose to the single subject over 4 years was between 6.2 and 6.8 mSv (range 1.7–21.5 mSv) according to the cranial–caudal length of the LDCT volume. 77.4% of the dose was owing to annual LDCT and 22.6% to further investigations. Considering the nominal risk coefficients for stochastic effects after exposure to low-dose radiation according to the National Radiological Protection Board, International Commission on Radiological Protection (ICRP) 60, ICRP103 and Biological Effects of Ionizing Radiation VII, the mean number of radiation-induced cancers ranged between 0.12 and 0.33 per 1000 subjects. The individual effective dose to participants in a 4-year lung cancer screening programme with annual LDCT is very low and about one-third of the effective dose that is associated with natural background radiation and diagnostic radiology in the same time period.

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Results of the National Lung Screening Trial indicating a 20.3% decrease in mortality from lung cancer in elderly heavy current and former smokers who underwent annual low-dose CT (LDCT) examination for 3 years has considerably renewed interest in lung cancer screening [1].

One important aspect of this screening is the possible hazard of radiation-induced cancers, which may have a major impact on several epidemiological and operational variables of the screening programme, including definition of the target population, the number of screening rounds needed and the screening interval [2–5].

However, very few data are available on the effective dose actually delivered to screened subjects, which is the basis for the risk calculation [2, 4].

The purpose of this paper is to report the collective effective dose delivered to subjects participating in the ITALUNG [6] randomised clinical trial who completed the four (one baseline and three repeat) annual LDCT examinations and the related further investigations that included follow-up LDCT, 2-[¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and CT-guided fine needle aspiration biopsy (FNAB).

Methods and materials

ITALUNG is a randomised clinical trial aiming to assess whether annual LDCT examination for 4 years decreases lung cancer mortality compared with usual care in smokers and former smokers. The strategy and results of the enrolment procedure were previously

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Table 1. Spiral scanners used in the ITALUNG trial

Manufacturer	Type	Rows of detectors	Number of scanners
Siemens	Somatom Plus 4 ^a	1	1
Siemens	Volume Zoom ^a	4	2
Siemens	Somatom Sensation ^a	16	1
Siemens	Somatom Sensation ^a	64	2
GE	Lightspeed ^b	4	1
GE	Lightspeed ^b	16	1

^aSiemens, Erlangen, Germany.^bGE, General Electric, Milwaukee, WI.

reported [6]. In particular the trial included smokers and former smokers aged 55–69 years with at least 20 pack-years of smoking history and no history of cancer. Former smokers should have quit smoking within the 10 years before enrolment. The technical characteristics of LDCT acquisition are those recommended for lung cancer screening [7], and follow-up LDCT and chest FDG-PET as further investigations are shared with most of the observational or randomised trials [7–11]. Conversely, CT-guided FNAB is recommended in some studies only [8, 10].

The LDCT examinations and related further investigations were carried out in three screening centres located in the Florence, Pisa and Pistoia districts of the Tuscany region in Italy. The LDCT examinations were obtained on eight different spiral scanners in three centres (Table 1). The FDG-PET examinations were performed in three centres using four scanners, two of which were dedicated PET scanners (one GE Advance PET scanner; General Electric, Milwaukee, WI, and one ECAT Exact HR+ scanner; Siemens, Erlangen, Germany) and two dual modality PET-CT scanners (one Discovery LS; General Electric, and one Gemini; Philips, Eindhoven, Netherlands). The vast majority of the CT-guided FNAB procedures were performed on the same single-detector spiral CT scanner (Somatom® Plus 4, Siemens) used for LDCT examination in one screening centre whereas the remainder were performed on the same four-detector spiral CT scanner (Somatom, Volume Zoom, Siemens) used for LDCT examination in another screening centre.

The collective effective dose delivered to the 1406 subjects (910 males with a mean age of 61.1 years and 496 females with a mean age of 60.6 years) who underwent screening with LDCT formed the basis of this report and was retrospectively computed by adding the effective doses associated to baseline, annual repeat and follow-up LDCT examinations, chest FDG-PET examinations and CT-guided FNAB procedures.

CT scanners and low-dose CT protocols

The LDCT examinations were carried out using 8 spiral scanners with 1, 4, 16 or 64 rows of detectors (Table 1). The low-dose acquisition protocols included the following parameter ranges: 120–140 kV, 20–43 mAs, pitch 1–2. The protocols were optimised taking into account beam and section collimations available in each scanner. The former was between 3 and 38.5 mm and the latter was between 0.75 (in the 64-row detector scanners) and 3 mm (in the single-detector scanner). Automatic control of the dose

delivery was not used during the data acquisition in the screened subjects in the scanners in which such an option is available.

Estimation of the dose

For the LDCT examinations the dose was computed considering the different acquisition protocols used in each CT scanner based on the air CT dose index (CTDI) values reported in the database of the CTDosimetry (release 1.0.2, <http://www.impactscan.org/>) software. This software also provides Monte Carlo simulations based on an anthropomorphic hermaphrodite phantom that was used to calculate the average dose (mGy) to the organs (thyroid, lung, breast, oesophagus) included in the field of view (FOV) and the whole-body effective dose (mSv). These calculations were performed considering two different volumes of acquisition, both defined using the anthropomorphic phantom. The first one, called the short volume (sV), had a cranial–caudal extension of 25.5 cm and covered the lung; the second one, called the long volume (lV), had a cranial–caudal extension of 29.5 cm with an additional 2 cm at each border of the acquisition volume.

There were two reasons for the lV estimation. Firstly, by this means it is possible to include variation of the delivered dose in the analysis depending on the operator's choice in prescribing the acquisition volume for the real subject at the CT scanner console. Secondly, considering lV acquisition may partially compensate for the additional dose associated with extra tube rotations that are executed by some MDCTs to improve the quality of the image reconstruction at the boundary of the acquisition volume, but are not considered in the numerical simulations of the CTDosimetry software. To estimate the whole-body effective dose the weights defined by the International Commission on Radiological Protection (ICRP) recommendation 103 [12] were used.

For chest FDG-PET, an effective dose of 7 mSv corresponding to a standard administration of 370 MBq was arbitrarily assigned to each examination [13]. This was justified by the fact that 81 of the 95 chest FDG-PET examinations were carried out using dedicated PET scanners and that in those performed on the dual modality PET/CT scanner only a low-dose acquisition volume of the chest with 5-mm-thick section collimation for attenuation correction was obtained, which implies an additional effective dose below 1 mSv.

35 CT-guided FNAB procedures were performed on a single-detector spiral CT scanner and 3 on a 4-detector CT spiral scanner. The effective dose associated with the

Table 2. Mean and range of dose to the organs (mGy) and of the whole-body effective dose (mSv) considering the different scanners used in the ITALUNG trial

Acquisition	Thyroid	Lung	Breast	Oesophagus	Effective dose
sV	0.6; 0.2–1.0	3.4; 1.2–5.4	3.0; 1.0–4.7	4.0; 1.4–6.6	1.2; 0.4–2.0
IV	1.3; 0.5–2.5	3.6; 1.3–5.7	3.0; 1.1–4.8	4.1; 1.4–6.7	1.4; 0.4–2.2

IV, long volume of acquisition of low-dose CT (LDCT); sV, short volume of acquisition of LDCT.

procedure was previously measured [4] by considering a 20-mm-thick package of thin collimation slices at full dose centred on a nodule which was multiplied by 3, corresponding to the number of scans usually required before (lesion targeting), during (needle position within the lesion before aspiration) and after (to control for possible complications) the uncomplicated procedure. The effective dose for each CT-guided FNAB procedure thus ranged between 0.7×3 (2.1) mSv for the single-detector scanner and 0.3×3 (0.9) mSv for the 4-detector scanner, yielding a mean value of 1.5 mSv.

Contrast-enhanced CT was not part of the further investigations in any subject with a suspicious lung nodule.

The risk

The effective dose associated with all the examinations involving ionising radiation adopted in the screening procedure and related further investigations was considered to calculate the risk of radiation-induced cancers. The latter was assessed using the estimates of the potential radiation-induced cancer deaths reported by the National Radiological Protection Board (NRPB) [14] and in ICRP publications 60 [15] and 103 [12], which all refer to low-dose radiation-induced cancers irrespective of gender differences. The risk was also calculated using the Biological Effects of Ionizing Radiation (BEIR) VII report [16], which allows estimation according to gender and age.

The number of potential radio-induced tumours in adult subjects is 0.035 Sv^{-1} according to NRPB, 0.048 Sv^{-1} according to ICRP 60 and 0.041 Sv^{-1} according to ICRP 103. For BEIR VII we used data from Table 12D-1 [16], which gives the coefficients for lung irradiation in males and for lung and breast irradiation in individuals aged 60 years at exposure.

Results

Table 2 reports the doses to the organs and the whole-body effective dose delivered with a single LDCT examination using the eight CT scanners employed in this study.

The total number of LDCT examinations in the ITALUNG trial, including those obtained at baseline ($n=1406$), at the three annual repeat screening rounds ($n=3924$) and the additional follow-up LDCT examinations ($n=990$) was 6320 with a mean of 5.9 LDCT examinations per subject over 4 years. Overall, 879 of the 6320 LDCT examinations (13.9%) were obtained on the single-detector CT scanner, while the remainder were obtained in MDCT scanners.

95 chest FDG-PET scans were carried out in 90 subjects for management of suspicious nodules at baseline ($n=59$)

or annual repeat ($n=36$) screening rounds. 38 CT-guided FNAB procedures were carried out in 34 subjects.

The mean collective effective dose associated with LDCT examinations in the 1406 subjects was 8.02 Sv for sV and 8.91 Sv for IV acquisitions. The collective effective dose associated with chest FDG-PET scans was 0.66 Sv. The mean collective effective dose associated with CT-guided FNAB procedures was 0.06 Sv (0.03–0.08 Sv).

The mean collective effective dose in 1406 subjects considering LDCT examinations and further investigations ranged between 8.75 and 9.36 Sv and the mean effective dose per individual subject over 4 years was between 6.2 and 6.8 mSv according to the craniocaudal length of the LDCT examination volume. The maximal individual effective dose over 4 years was 19.5–21.5 mSv delivered to two subjects examined five times with the single-detector CT scanner, twice with a multi-detector scanner and once with FDG-PET. The minimal individual effective dose corresponding to a subject with a constantly negative test examined four times with an MDCT scanner was 1.7–1.9 mSv.

Notably, a collective dose of 6.67–7.51 Sv (77.4%) was owing to the annual LDCT examinations and 1.98–2.12 Sv (22.6%) was owing to further investigations.

Considering the above mean collective effective doses associated with the screening procedure (6.22 and 6.85 Sv per 1000 subjects) and the nominal risk coefficients for stochastic effects after exposure to low-dose radiation, as indicated by NRPB, ICRP 60, ICRP 103 and BEIR VII, the corresponding mean number of radiation-induced cancers ranged between 0.12 and 0.33 per 1000 subjects (Table 3). In particular, according to BEIR VII the mean number was 0.12 or 0.13 per 1000 males and 0.31 or 0.33 per 1000 females.

Discussion

The risk of increased cancer incidence associated with low-dose ionising radiation is an extremely controversial topic [3, 17, 18]. This reflects both the limited available data, which predominantly derive from the survivors of the atomic bombs in Japan, and the scepticism on the “linear no threshold” model proposed to describe such effects. Further uncertainties derive from the adoption of the effective dose as an indicator of the cancer risk specifically for the individual subject [19, 20] and, in the case of lung cancer screening with LDCT, from the suggestion of a possible multiplicative effect of smoking and radiation exposure in increasing the incidence of lung cancer [21].

However, little is known about the actual dose exposure associated with lung cancer screening using LDCT, which is the basis for calculation of the risk of radiation-induced cancer.

Table 3. Estimation of the potential number of radiation-induced cancers per 1000 subjects participating in the ITALUNG trial undergoing 4 annual low-dose CT (LDCT) examinations and further investigations including follow-up LDCT examinations, chest 2-¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography and CT-guided fine needle aspiration biopsy

Acquisitions	NRPB	ICRP 60	ICRP 103	BEIR VII	
				Male	Female
sV	0.22; 0.09–0.33	0.29; 0.12–0.46	0.25; 0.10–0.39	0.12; 0.04–0.19	0.31; 0.11–0.49
IV	0.24; 0.10–0.37	0.33; 0.13–0.50	0.28; 0.11–0.43	0.13; 0.05–0.20	0.33; 0.12–0.52

BEIR VII, Biological Effects of Ionizing Radiation report VII; ICRP, International Commission on Radiological Protection; IV, long volume of acquisition of LDCT; NRPB, National Radiological Protection Board; sV, short volume of acquisition of LDCT. Data reported as mean; range.

In a pioneer study published in 1996, Nishizawa et al [2] used phantom measurements to determine organ or tissue doses from chest examinations performed using a prototype CT system developed for lung cancer screening, with a single row of detectors' spiral scanning capability. The effective dose per LDCT examination was 3.6 mSv and the dose to the lung was 5.2 ± 0.9 mGy. These doses were one-half to one-third lower than the doses using standard CT systems and protocols at that time and the authors concluded that "the risk-benefit analysis showed that the benefit will exceed the risk for Japanese over 40 years for men and over 45 years for women" [2]. However, using the same dose data but a different risk-benefit model, Brenner [3] concluded that "given the estimated upper limit of a 5.5% increase in lung cancer risk attributable to annual CT-related radiation exposure, a mortality benefit of considerably more than 5% may be necessary to outweigh the potential radiation risks".

10 years later we reported the effective dose delivered in a 3 year pilot study involving 60 smokers performed using a single-detector or a 4-row detector spiral CT scanner and found that the mean individual effective doses were 5.9 mSv per 3 years and 1.9 mSv per year with the single-detector scanner and 1.4 mSv per 3 years and 0.4 mSv per year with the multidetector scanner [4]. The lung dose for a single LDCT examination ranged between 3.2 mGy with the single-detector CT scanner and 0.8 mGy with the multidetector scanner. In the same study we included a risk-benefit analysis for the subjects receiving screening in the ITALUNG trial assuming not only the dose associated with LDCT examinations but also that related to further investigations, which included follow-up LDCT examinations, contrast-enhanced CT, chest FDG-PET and CT-guided FNAB, and concluded that the ratio was favourable for current smokers if screening reduces lung cancer mortality by at least 20% [4].

In the present report we computed the collective effective dose actually delivered to the 1406 subjects who, after randomisation, underwent the ITALUNG screening protocol. In particular, after software measurements of the effective dose associated with annual LDCT examinations on the eight spiral scanners, we took into account the effective dose associated with chest PET after intravenous administration of a standard quantity of FDG [13] and considered effective dose values associated with CT-guided FNAB we previously measured [4] using the scanners on which all such procedures were carried out in the trial.

As expected, the effective and organ doses for the single LDCT examination measured in all eight of the

spiral scanners of the study were considerably lower than those measured by Nishizawa et al [2], reflecting technological development. In particular, the average effective dose was 1.2 mSv for sV acquisitions and 1.4 mSv for IV acquisitions, while the corresponding average dose to the lung was 3.4 mGy for sV and 3.6 mGy for IV acquisitions.

Overall the mean collective effective dose actually delivered to the subjects who underwent LDCT in the ITALUNG trial ranged between 6.22 and 6.85 Sv per 1000 subjects depending on the length of the spiral acquisition volume of the LDCT. The corresponding mean effective dose to a single subject enrolled in the study over 4 years ranged between 6.2 and 6.8 mSv according to the cranial-caudal length of the LDCT volume. This individual effective dose falls in the very low-risk <10 mSv exposure category [19] and represents about one-third of the dose owing to natural background and diagnostic radiological procedures received by Italian subjects not undergoing screening in 4 years—that is, 18 mSv (4.5 mSv per year $\times$ 4) [22].

In only two subjects who underwent annual and follow-up LDCT mainly on a single-detector scanner and one chest FDG-PET each, the individual effective dose was approximately 20 mSv in 4 years.

The above mean collective effective dose is slightly lower than the one we previously estimated for a screening programme exclusively using a single-detector scanner (7.12 Sv), but higher than the one we estimated exclusively using a four-detector scanner (3.35 Sv) [4].

The following reasons presumably account for the discrepancy. (1) In the former analysis we hypothesised two scenarios in which screening was performed uniformly using either a single-detector or a four-detector scanner and not a combination of the two plus other multidetector scanners, as was actually the case in the ITALUNG trial. However, the proportion of LDCT examinations performed on a single-detector scanner, implying higher dose exposure than multidetector scanners [4], was small (13.9%). (2) In the trial the rate of follow-up LDCT examinations performed after baseline and annual repeat screening rounds (30% and 15%, respectively) were higher than the 10% predicted. (3) The number of further investigations involving radiation exposure, in particular chest FDG-PET, was higher than previously estimated. In fact we predicted 1.0% of further investigations at baseline and 0.5% at each annual repeat for an overall rate of 2.5% [4], but in the ITALUNG trial we carried out chest FDG-PET scans in 6.7% and CT-guided FNAB procedures in 2.5% of subjects.

Notably, in the present survey the effective dose related to further investigations for suspicious nodules

including follow-up LDCT, chest FDG-PET and CT-guided FNAB accounted for 22% of the collective effective dose.

The combination of the collective effective dose with the nominal risk coefficients for stochastic effects after exposure to low-dose radiation indicates a substantially low risk. In particular, according to NRPB estimates [14], the numbers of potential fatal cancers associated with the collective effective dose in the ITALUNG trial ranged between 0.09 and 0.37 per 1000 subjects, while they ranged between 0.11 and 0.24 per 1000 subjects in the prior projection [4]. According to BEIR VII the number of potential radiation-induced cancers might be approximately three times higher in females than in males undergoing the ITALUNG screening programme. This reflects the fact that the risk of both lung cancer and breast cancer is considerably higher in female subjects aged 50–70 years at exposure [16].

We would like to point out that the effective doses and the corresponding cancer risk we calculated in our trial are conservative and are probably overestimated for a screening programme beginning at the present time. This is because (1) multidetector CT scanners have now completely substituted single-detector spiral CT scanners in the market and their updated technology enables the delivery of a lower effective dose for each LDCT screening test compared with single-detector spiral scanners; (2) the rate of follow-up LDCT examinations we obtained at baseline and annual repeat screening rounds was on average higher than those reported in other screening programmes [23]; (3) we considered whole lung follow-up LDCT examinations, but targeted shorter volume acquisitions can be used for control of suspicious nodules; and (4) our screening protocol included four annual LDCT examinations but other dose-sparing protocols including LDCT examinations every 2–3 years as in the Dutch–Belgian lung cancer screening trial [23] and even a single LDCT examination as in the UK Lung Screen trial [24] have been proposed.

Modelling of the risk–benefit ratio based on the collective effective dose requires several assumptions and calculations and is beyond the scope of the present report. However, taking account of the fact that the present data are in line with the risk of radiation-induced cancer calculated in a prior analysis [4], and that efficacy of the screening procedure to reduce mortality from lung cancer of 20% was observed in a trial recently closed before time because of an excess of benefit in the screened subjects compared with the controls [1], we can assume that the risk–benefit ratio is favourable for elderly current smokers and probably former smokers undergoing annual LDCT for 4 years. This positive evaluation does not necessarily apply to other target populations, including younger smokers or former smokers and non-smokers and should not be extended to other screening regimens implying longer periods of active screening.

Conclusion

The mean effective dose delivered to subjects participating to the ITALUNG trial of lung cancer screening who underwent LDCT examinations and further

investigations involving radiation exposure was <7 mSv per subject over 4 years. This is about one-third of the effective dose associated with natural background radiation and diagnostic radiology in the same period of time in Italy and may constitute a reference term of the dose involved in screening programmes for lung cancer with LDCT for risk–benefit modelling.

References

1. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
2. Nishizawa K, Iwai K, Matsumoto T, Sakashita K, Iinuma TA, Tateno Y, et al. Estimation of the exposure and a risk–benefit analysis for a CT system designed for a lung cancer mass screening unit. *Radiat Prot Dosimetry* 1996;67:101–8.
3. Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. *Radiology* 2004;231:440–5.
4. Mascalchi M, Belli G, Zappa M, Picozzi G, Falchini M, Della Nave R, et al. Risk-benefit analysis of the X-ray exposure associated with lung cancer screening in the Italung-CT trial. *AJR Am J Roentgenol* 2006;187:421–9.
5. Berrington de Gonzalez A, Kim KP, Berg CD. Low-dose lung computed tomography screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk. *J Med Screen* 2008;15: 153–8.
6. Lopes Pegna A, Picozzi G, Mascalchi M, Carrozzi FM, Carozzi L, Comin C, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low dose CT. *Lung Cancer* 2009;64:34–40.
7. Aberle DR, Gamsu G, Henschke C, Naidich DP, Swensen SJ. A consensus statement of the Society of Thoracic Radiology: screening for lung cancer with helical computed tomography. *J Thorac Imaging* 2001;16:65–8.
8. Libby DM, Smith JP, Altorki NK, Pasmantier MW, Yankelevitz D, Henschke CI. Managing the small pulmonary nodule discovered by CT. *Chest* 2004;125:1522–9.
9. Veronesi G, Bellomi M, Mulshine JL, Pelosi G, Scanagatta P, Paganelli G, et al. Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. *Lung Cancer* 2008;61:340–9.
10. Infante M, Cavuto S, Lutman FR, Brambilla G, Chiesa G, Ceresoli G, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. *Am J Respir Crit Care Med* 2009;180:445–53.
11. Ashraf H, Dirksen A, Loft A, Bertelsen AK, Bach KS, Hansen H, et al. Combined use of positron emission tomography and volume doubling time in lung cancer screening with low-dose CT scanning. *Thorax* 2011;66: 315–19.
12. International Commission on Radiological Protection. The 2007 recommendations of the International Commission on Radiological Protection. ICRP Publication 103. *Ann ICRP* 2007;37:1–332.
13. Brix G, Lechel U, Glatting G, Ziegler SI, Münzing W, Müller SP, et al. Radiation exposure of subjects undergoing whole-body dual-modality ¹⁸F-FDG PET/CT examinations. *J Nucl Med* 2005;46:608–13.
14. Cox R, MacGibbon BH, Muirhead CR, Stather JW, Edwards AA, Haylock RGE, et al. Estimates of the late radiation risks to the UK population. Documents of the National Radiological Protection Board 1993;4(no.4):105–25.
15. International Commission on Radiological Protection. The 1990 recommendations of the International Commission on

- radiological Protection. ICRP Publication 60. Ann ICRP 1991;21(1–3).
16. Biological Effects of Ionizing Radiation (BEIR). Health risks from exposure to low levels of ionizing radiation. BEIR VII, Phase 2. Washington, DC: The National Academies Press; National Research Council; 2006.
 17. Cohen BL. The cancer risk from low level radiation. In: Tack D, Gevenois PA, eds. Medical radiology: radiation dose from pediatric and adult multidetector computed tomography. Berlin, Germany: Springer 2007; pp. 33–50.
 18. Tubiana M, Feinendegen LE, Yang C, Kaminski JM. The linear no-threshold relationship is inconsistent with radiation biologic and experimental data. Radiology 2009;251: 13–22.
 19. Martin CJ. 20 years of subject dose studies: where should we go from here? Br J Radiol 2005;78:477–9.
 20. Martin CJ. Effective dose: how should it be applied to medical exposures? Br J Radiol 2007;80:639–47.
 21. Darby SC, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 2005;330:223–8.
 22. ENEA. Dossier 1999 – La radioprotezione in Italia – La salvaguardia della popolazione e dell’ambiente. Rapporto ISBN 88-8286-074-4. Edizioni ENEA: Rome, Italy; 1999.
 23. Lopes Pegna A, Picozzi G. Lung cancer screening update. Curr Opin Pulm Med 2009;15:327–33.
 24. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. Thorax 2011;66:308–13.