Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis

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ABSTRACT

OBJECTIVE
To estimate the cumulative radiation exposure and lifetime attributable risk of cancer incidence associated with lung cancer screening using annual low dose computed tomography (CT).

DESIGN
Secondary analysis of data from a lung cancer screening trial and risk-benefit analysis.

SETTING
10 year, non-randomised, single centre, low dose CT, lung cancer screening trial (COSMOS study) which took place in Milan, Italy in 2004-15 (enrolment in 2004-05). Secondary analysis took place in 2015-16.

PARTICIPANTS
High risk asymptomatic smokers aged 50 and older, who were current or former smokers (≥20 pack years), and had no history of cancer in the previous five years.

MAIN OUTCOME MEASURES
Cumulative radiation exposure from low dose CT and positron emission tomography (PET) CT scans, calculated by dosimetry software; and lifetime attributable risk of cancer incidence, calculated from the *Biological Effects of Ionizing Radiation VII* (BEIR VII) report.

RESULTS
Over 10 years, 5203 participants (3439 men, 1764 women) underwent 42 228 low dose CT and 635 PET CT scans. The median cumulative effective dose at the 10th year of screening was 9.3 mSv for men and 13.0 mSv for women. According to participants' age and sex, the lifetime attributable risk of lung cancer and major cancers after 10 years of CT screening ranged from 5.5 to 1.4 per 10 000 people screened, and from 8.1 to 2.6 per 10 000 people screened, respectively. In women aged 50-54, the lifetime attributable risk of lung cancer and major cancers was about fourfold and threefold higher than for men aged 65 and older, respectively. The numbers of lung cancer and major cancer cases induced by 10 years of screening in our cohort were 1.5 and 2.4, respectively, which corresponded to an additional risk of induced major cancers of 0.05% (2.4/5203). 259 lung cancers were diagnosed in 10 years of screening; one radiation induced major cancer would be expected for every 108 (259/2.4) lung cancers detected through screening.

CONCLUSION
Radiation exposure and cancer risk from low dose CT screening for lung cancer, even if non-negligible, can be considered acceptable in light of the substantial mortality reduction associated with screening.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Lung cancer is the leading cause of cancer death among both men and women

Screening of high risk individuals with low dose computed tomography reduces lung cancer mortality by 20% if compared with chest radiography

Excess cancer risks related to ionising radiation from low dose computed tomography are a major concern in lung cancer screening

WHAT THIS STUDY ADDS

The median cumulative radiation exposure from low dose computed tomography screening over 10 years was 9.3 mSv for men and 13.0 mSv for women

The lifetime attributable risk of major cancers from low dose computed tomography screening ranged from 2.6 to 8.1 major cancers per 10 000 participants, according to participant age and sex

One radiation induced cancer would be expected in every 108 lung cancers detected after 10 years of computed tomography screening

Radiation exposure from low dose computed tomography and the risk of radiation induced cancer can be considered acceptable in light of the substantial mortality reduction associated with lung cancer screening

Introduction

Lung cancer is the leading cause of cancer for both men and women in the USA. In 2015, the American Cancer Society expected more than 200 000 new cases of lung cancer, about 14% of the total new cancers, with a five year survival rate of 18%.[1]

The US National Lung Screening Trial has shown that screening of high risk populations with low dose computed tomography (CT) reduces lung cancer mortality by more than 20% when compared with chest radiography.[2] As a consequence, several medical societies currently recommend CT lung screening, and in the USA, the Centers for Medicare and Medicaid Services have granted a positive insurance coverage decision on screening.[3] Millions of healthy high risk individuals are therefore theoretically eligible for CT lung cancer screening.

There is concern, however, that exposure to the ionising radiation of low dose CT in lung cancer screening might increase the risk of developing solid cancers and leukaemia.[4] The concrete existence of this increased risk as related to low dose radiation (doses <50 mSv) is controversial,[5-7] although this topic deserves additional consideration because ionising radiation from CT screening is delivered to healthy people.

So far, there is limited knowledge of the levels of radiation exposure in lung cancer screening regarding both cumulative radiation exposure and the associated cancer risk, particularly in long term studies. Brenner[8]

estimated that if 50% of all current and former smokers in the US population aged 50-75 received annual CT screening, the number of lung cancers associated with radiation from screening would be about 36 000, a 1.8% (95% confidence interval 0.5 to 5.5) increase over the otherwise expected number. McCunney and Li[9] reported that lung screening participants could experience a cumulative exposure to ionising radiation over 20-30 years, which exceeds the lifetime dose experienced by nuclear power workers and atomic bomb survivors. The results of these studies cannot be considered conclusive, however, because they are based on the assumption of an arbitrary, pre-established radiation dose for all individuals, regardless of sex, age, or body size.

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

Methods

All data reported in the present study were retrospectively assembled and analysed from a 10 year, non-randomised, observational, lung cancer screening trial (COSMOS study).[10 11] In brief, 5203 asymptomatic high risk participants (age >50 and smoking history with ≥20 pack years, and no history of cancer in the past five years) underwent annual low dose CT for 10 consecutive years. Additional recalls for suspicious findings were performed with low dose CT scans and positron emission tomography (PET) CT scans, according to the study design. The COSMOS study took place in Milan, Italy, in 2004-15 (enrolment in 2004-05).A comprehensive description of the COSMOS study, as well as low dose CT protocols and PET CT scans, are reported in the supplementary material. The present study (that is, the secondary analysis), took place in 2015-16.

Radiation exposure from CT screening

To consider the overall radiation exposure in the population, the annual repeated low dose CT scans and the follow-up low dose CT scans of each patient 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 radiology information-picture archiving and communication system (RIS-PACS) and sent to Radimetrics (Bayer Healthcare), a commercially available software for monitoring and tracking patient radiation exposure.[12] Organ doses and effective doses were retrospectively estimated by Radimetrics for each low dose CT examination and for the CT acquisitions of the PET CT scans. Data and scanning parameters were collected from CT examinations, and patients were matched—according to age, sex, weight, and dimension—to six and five different adult phantoms for women and men, respectively. This size specific calculation of organ doses is more accurate than calculating from the standard reference patient used by other software.

Organ doses are calculated by use of a look-up table based on MonteCarlo simulations for the selected phantoms,[13] and are used to estimate effective dose according to weighting factors from the International Commission on Radiological Protection.[14] For PET CT scans, the contribution of the radioactive tracer to organ doses and effective doses is calculated by the absorbed dose coefficients per unit activity administered (mGy/MBq).[15]

Total estimated organ dose and effective dose for one patient were calculated as the sum of the doses of each low dose CT examination (screening rounds performed plus recalls) and PET CT scans when performed. Because cumulative organ and effective doses were non-normally distributed, median and range were considered.

Cancer risk estimation

For each age, sex, and organ, we determined the lifetime attributable risk of cancer incidence from a 100 mSv organ equivalent dose table 12D-1 of the National Research Council's *Biological Effects of Ionizing Radiation VII* (BEIR VII) report.[4] When missing, age specific lifetime attributable risk was estimated by polynomial interpolation of lifetime attributable risk values reported for ages 50, 60, 70, and 80. This lifetime attributable risk from a theoretical 100 mSv organ dose was scaled linearly on the basis of the actual organ dose measured at each CT scan. Lifetime attributable risk was calculated for each of the 42 228 low dose CT scans performed during the COSMOS trial and added together to calculate the lifetime attributable risk for the entire COSMOS population.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Radiation exposure from CT screening

During the 10 years of the COSMOS lung cancer screening trial, 5203 high risk participants underwent 42 228 low dose CT examinations, including 39 981 annual CT scans, 1965 first recall CT scans, and 282 second recall CT scans for lung cancer screening. As part of the screening protocol, 635 PET CT scans were performed in 522 participants with suspicious findings (table 1). A total of 259 lung cancers were diagnosed after 10 years of CT screening.

The median effective dose delivered at the baseline screening round was 1.0 mSv (range 0.6-16.5) for men and 1.4 mSv (0.9-14.9) for women. Median cumulative effective doses from both low dose CT and PET CT scans at the third, fifth, and 10th year of screening were 3.0 mSv (1.9-27.4), 5.2 mSv (2.9-39.6), and 9.3 mSv (5.6-42.7) for men, respectively; and 4.2 mSv (2.9-23.3), 7.2 mSv (4.1-26.8), and 13.0 mSv (8.0-33.5) for women, respectively (table 2). A PET CT scan delivered an additional

median radiation exposure of 4.0 mSv (1.2-28.8). Complete information on the effective doses and organ specific exposition doses from low dose CT scans only and from low dose CT scans plus PET CT scans are provided in appendix 2 (web tables S1 and S2).

Overall, 15 805 examinations were performed with eight detector row CT scans, 22 132 with 16 detector row CT scans, and 4291 with 64 detector row CT scans. Average effective doses for one low dose CT examination for the three CT scanners were 1.07 mSv (standard deviation 0.29), 1.05 mSv (0.27), and 0.64 mSv (0.15), respectively.

Estimated risk of cancer from CT screening

Table 3 shows lung cancers detected after 10 years of CT screening and lifetime attributable risk of lung cancer and major cancers by sex and age of COSMOS trial participants. The lifetime attributable risk of cancer incidence was extrapolated from the BEIR VII report to estimate lifetime attributable risks of lung cancer after 10 years of CT screening. This lifetime attributable risk of lung cancer after 10 years of CT screening ranged between 5.5 per 10 000 participants (1 in 1811) for women starting screening at age 50-54, and 1.4 per 10 000 participants (1 in 6908) for a man starting screening aged 65 and older. In the same two groups of women and men, lifetime attributable risks of major cancers ranged between 8.1 per 10 000 participants (1 in 1229) and 2.6 per 10 000 participants (1 in 3898), respectively (table 3).

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

The lifetime attributable risk of lung cancer was estimated to be about four times greater for women aged 50-54 years than for older men aged 65 and older (5.5 v 1.4 per 10 000 participants). However, the lifetime attributable risk of major cancers was three times higher in the corresponding groups (8.1 v 2.6 per 10 000 participants), reflecting differences in age and sex risk reported in the BEIR VII tables.

Figure 1 shows the estimated number of lung and major cancers induced by radiation for men and women, for 10 000 people screened. As expected, the risk of developing radiation induced cancer was higher for women at all ages, and the risk decreased in both sexes while the age of exposure increased. There were always fewer than five radiation induced cancers per 10 000 people screened in men, and fewer than 10 per 10 000 people screened in women.

Table 1 | Lung cancer screening rounds, annual and recall scans of low dose CT, and PET CT scans administered to COSMOS trial participants

Screening round	No of annual CT scans	No (%) of first recall CT scans per year	No (%) of second recall CT scans per year	No (%) of PET CT scans per year
Baseline	5203	482 (9.3)	75 (1.4)	160 (3.1)
2nd year	4822	142 (2.9)	23 (0.5)	68 (1.4)
3rd year	4583	198 (4.3)	32 (0.7)	74 (1.6)
4th year	4380	251 (5.7)	47 (1.1)	62 (1.4)
5th year	4120	213 (5.2)	35 (0.8)	66 (1.6)
6th year	3856	197 (5.1)	24 (0.6)	62 (1.6)
7th year	3654	170 (4.7)	16 (0.4)	41 (1.1)
8th year	3449	118 (3.4)	14 (0.4)	35 (1.0)
9th year	3182	103 (3.2)	10 (0.3)	41 (1.3)
10th year	2732	91 (3.3)	6 (0.2)	26 (1.0)
Total No of scans	39 981	1965	282	635

CT=computed tomography; PET=positron emission tomography.

Table 2 | Median cumulative organ dose and effective doses for screening and recall low dose CT scans and PET CT scans at baseline, 3rd, 5th, and 10th screening round

	Men				Women			
	Baseline	3rd year	5th year	10th year	Baseline	3rd year	5th year	10th year
No of participants	3439	3056	2768	1850	1764	1527	1352	884
Effective dose (mSv)	1.0	3.0	5.2	9.3	1.4	4.2	7.2	13.0
Organ dose (mGy):								
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
Oesophagus	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 | Number of lung cancers detected after 10 years of CT screening and number of estimated lung and major cancers associated with radiation exposure, according to age and sex of COSMOS trial participants

Participant age and sex at start of screening	No of participants	No of lung cancers detected	No of estimated radiation induced lung cancers (LAR/10 000)	No of estimated radiation induced major cancers* (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

LAR=lifetime attributable risk.
*Cumulative LAR for cancers of the stomach, colon, liver, lung, bladder, thyroid, breast, ovaries, uterus, or leukaemia.
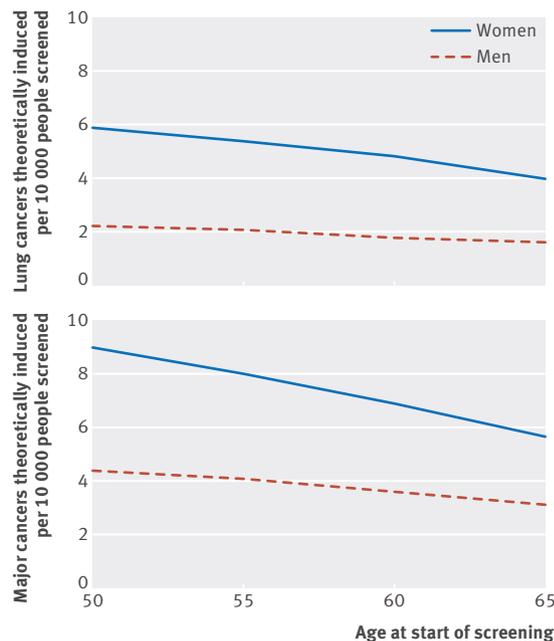
Fig 1 | Lung cancers and major cancers theoretically induced per 10 000 people screened, according to sex and age at start of CT screening for lung cancer

Discussion

Principal findings

In this study, we showed that the median cumulative effective dose after 10 years of CT screening is roughly 9 mSv for men and 13 mSv for women. By comparison with other diagnostic CT examinations, this means that an individual participating in a 10 year screening programme of low dose CT would receive a dose similar to that delivered to another undergoing one standard CT scan to the chest (7-8 mSv) or abdomen-pelvis (13-14 mSv).[16 17] Furthermore, if we consider that the 10 year average dose from background sources in the USA is about 30 mSv, we can assume that 10 years of screening delivers only a third of the exposure to natural background radiation in the same period.[18 19]

Our study estimates that, after 10 years of low dose CT screening in 5203 asymptomatic high risk patients (age >50 and smoking history ≥20 pack years) with no history of cancer in the past five years, 1.5 lung cancers and 2.4 major cancers were theoretically induced by radiation. This corresponds to an additional overall risk of major cancer of 0.05% (2.4 in 5203 screened people). When compared with the number of cancers detected by CT screening in the same period, one major cancer is theoretically induced by radiation for roughly every 100 detected.

As expected, the lifetime attributable risk for women was greater than for men at all ages, with a relative risk up to four times greater for lung cancer and up to three times greater for major cancers. This difference is related to the increased radiosensitivity of women compared with men and to the risk of breast cancer associated with chest CT scans.[4]

Strengths and weaknesses of the study

In this study, we analysed radiation exposure data assembled from a cohort of patients who were enrolled in a 10 year CT screening programme. To our knowledge, this is the first analysis in a lung cancer screening population where a specific dose has been calculated for each of the 42 228 low dose CT scans—overcoming the limitation of using a fixed radiation exposure for all participants, as seen in previous studies.

One strength of this study was the dosimetry calculation, which was provided by an advanced software program (Radimetrics) for each low dose CT scan. Although not a patient specific dosimetry, this software can calculate organ doses and hence effective doses for six groups of women and five groups of men, according to their dimensions. Therefore, this size specific calculation of organ doses provides greater accuracy than software that uses only the standard reference patient for its calculations. In this case, with a fixed acquisition protocol, we could observe no difference in organ and effective dose calculations. Variations in organ doses among participants were also related to the number of low dose CT scans and PET CT scans received during the study and to the different doses delivered by the three CT scanners.

The assessment of cancer risk according to the BEIR committee is based on the linear no-threshold model and on data collected from environmental, occupational, and medical studies, and from atomic bomb survivors. The risk estimates of the BEIR VII report are thus based on risk models generated from studies on people exposed to high levels of radiation, and they are extrapolated to low doses using the linear no-threshold model for radiation risk. Various authors have discussed the weaknesses of the BEIR VII report, focusing on the linear no-threshold model[7 20 21] and on uncertainties in the translation of risk from high doses and dose rates in the Japanese population to lower doses and dose rates in the US population.

A segment of the scientific community claims that there is a threshold for low dose radiation carcinogenesis,

and warns against quantitative estimation of health risks that might be too small to be observed or are non-existent below 50 mSv.[22-24] However, so far there is not sufficient evidence to suggest that the risk from radiation exposure is non-existent below a certain dose. Therefore, the linear no-threshold model stands as a precautionary recommendation that follows a conservative approach. Furthermore, all the risk estimates in the tables of the BEIR VII report have been obtained as a consensus opinion of a committee, and the inferred risk at lower doses probably overestimates the risk of cancer induction.[25]

To estimate the risk of cancer in individuals, the optimum approach would be to use specific organ doses and hence age and sex adjusted coefficients.[26] The effective dose has been implemented mainly for protection purposes, and its use in medical practice as a measure of individual risk goes beyond its intended purpose.[14 27] Another factor to consider is that our results are related to the specific COSMOS study design, and different patient selection (eg, by age or smoking status) might lead to dissimilar results in terms of cancer risk.

As well as study population, screening nodule management has substantial implications for the overall radiation exposure and cancer risk. In fact, different thresholds of nodule size, interval follow-up, and the use of PET CT scans are determinant sources of variations. More conservative guidelines, as suggested by the American College of Radiology (Lung-RADS version 1.0),[28] could lead to lower population doses.

Comparison with other studies

In the National Lung Screening Trial, the effective dose estimates were 1.6 mSv and 2.4 mSv for one low dose CT scan for men and women, respectively.[29] Our results show an effective dose at a baseline of 1.0 mSv for men and 1.4 mSv for women. These doses are 40% lower than in the National Lung Screening Trial, also considering the additional dose delivered by PET CT scans performed in our study. Study design, scanning parameters, and calculation methods might account for these differences. The scanning parameters at a typical study site in the National Lung Screening Trial are similar to those of our baseline data. However, the calculation method of organ dose and effective dose of the National Lung Screening Trial is based on software that does not take into account the patient's body size. The estimated organ dose in the trial was 4.9 mGy to the breast, and nearly 5 mGy to the lungs for both men and women. By comparison, taking into account the patient's body size, we found a dose of 2.5 mGy to the breast, and doses of 2.3 mGy and 2.7 mGy to the lungs for men and women, respectively. This difference between these results highlights how the estimates of organ and effective doses with software that takes into account the patient's body size is an important source of variability.

The cumulative effective dose for the National Lung Screening Trial over three years was 4.8 mSv for men and 7.2 mSv for women. In the same period, we found a cumulative effective dose of 3.0 mSv for men and 4.2 mSv for women (table 2). In our study, the cumulative effective dose, and the consequent risk of cancer, was the sum of radiation exposure both from low dose CT scans and PET CT scans. The contribution of one PET CT scan was 4.0 mSv, compared with the 10 year low dose CT cumulative exposure of 9.2 mSv and 12.9 mSv for men and women, respectively (table S2). Therefore, screening studies that do not include PET CT scans in their protocols could lead to a lower radiation exposure. The ITALUNG screening trial, after four rounds of screening, reported that 77.4% of the delivered dose was from annual low dose CT scans and 22.6% from further investigations (fluorodeoxyglucose-PET and CT guided biopsy).[30] Further investigations assessing the role of study design in measuring radiation exposure are therefore needed.

Accurate risk prediction models can now quantify an individual's risk of developing or dying from lung cancer, and help identify people at high enough risk to undergo screening.[31 32] Little is known, however, about the additional risk of cancer caused by exposure to radiation from screening itself. In a risk evaluation based on an assumed dose to the lung of 5.2 mGy, Brenner[8] estimated an additional lung cancer risk of 1.8% caused by annual lung CT screening. Our results, conversely, show a theoretical additional risk of 0.05% (2.4 cases of major cancers induced in 5203 people).

Further considerations and conclusions

Even if our results show that cumulative radiation exposure after 10 years of low dose CT screening is substantially limited, there are still possibilities for further reduction. An accurate patient selection can substantially reduce the radiation exposure of low risk individuals, and the definition of an accurate study design is essential for the improvement of the diagnostic flowchart, minimising unnecessary radiation exposure.

New CT scanners and optimised acquisitions protocols can reduce the dose by up to 40%, as seen in the differences in effective doses among 8, 16, and 64 slice scanners reported in our results. In addition, according to our protocol, CT images were reconstructed by use of the standard filtered back projection. With the introduction of a new iterative reconstruction algorithm, it is now possible to achieve the same diagnostic image quality with a dose that is reduced by up to 80% compared with standard filtered back projection.[33-36]

Another consideration is the detection of incidental findings on low dose CT scans.[37 38] New findings could lead to additional radiation exposure through further testing. In the present study, we did not consider the additional exposure from examinations performed for collateral findings, resulting in 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 substantial mortality reduction associated with screening.

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Appendix 1: Supplementary material
Appendix 2: Web tables