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Title: Cumulative exposure to ionizing radiation from diagnostic imaging procedures: a 12-year follow-up population-based analysis.

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Abstract

Objectives: To calculate each patient's cumulative radiation exposure and the recurrent tests during a 12-year study period, according to sex and age, in a cohort of patients in routine practice.

Design: Retrospective cohort study.

Setting: A general hospital with a catchment population of 224,751 people, in the Southeast of Spain.

Participants: Population belonged to the catchment area of that hospital during the year 2007. We collected all consecutive diagnostic imaging tests undergone by this population until 31st December 2018. We excluded: imaging tests that did not involve radiation exposure and patients who had an imagen test in this hospital but did not belong to its catchment area.

Main outcome measures: The cumulative incidence radiation exposure and the recurrent imaging tests by sex and age at each at entry of study. We also collected the patients' clinical context (patients with malignancy history).

Results: Of the 224,751 people, 154,520 (68.8%) underwent an imaging test. The population had 1,335,752 imaging tests during the period of study: 1,110,077 (83.0%) plain radiography; 156,848 (11.8%) CT; 63,157 (4.8%) fluoroscopy, and 5,670 (0.4%) interventional radiography. 25.4% of the patients who had a CT, underwent 5 or more CTs (5.4% in the 0 to 15 age group); 9.7% of the patients who had a fluoroscopy examination, underwent 5 or more fluoroscopy examinations (2.1% in the 0 to 15 age group. A total of 7142 (4.6%) patients received more than 50 mSv, with differences in men and women and according to age. Out of 2,298 patients who received more than 100 mSv, 620 (27.0 %) had no malignancy history.

Conclusions: A significant proportion of patients received doses higher than 50 mSv during the 12-year period of study. The rate of recurrent examinations was high, especially in older patients, but also relevant in the 0 to 15 age group.

Article summary section: Strengths and limitations of this study.

- This is the first study that quantifies the cumulative radiation exposure and recurrent imaging test in clinical practice, following the Basic Safety Standards Directive adopted by the European Union (EU) in 2013.
- The strength of this study is that it evaluates all radiological investigations performed in a cohort of 224,751 patients in routine practice during a 12-year study period, according to sex and age.
- We used the available evidence to estimate the effective dose for each examination, as is proposed by the dosedatamed project. This is not ideal, but it does not affect the overall result.

Introduction

The Basic Safety Standards Directive was adopted by the European Union (EU) in 2013[1] to be transposed into national law by 6 February 2018. One key and innovative surveillance mechanism in this revised directive is to record the radiation dose received by each patient undergoing a medical imaging test. The directive mainly focuses on CT and procedures involving interventional radiology, all of which are associated with a relatively high dose of radiation. Other diagnostic procedures such as conventional radiography, however, are also frequently repeated in patients during their lives with a potential impact on health and could be included in these evaluations. However, these evaluations have not still been developed in the European countries.

A full evaluation of the radiation exposure from all medical diagnostic procedures in Europe has been previously carried out in the project DoseDataMed I[2] and II[3]. This project, based on national surveys, includes information on 36 European countries regarding population frequencies and radiation dose of x-ray and nuclear medicine radiodiagnostic procedures. Although this project has led to a significant advance in the evaluation of population doses, we still do not have data regarding the cumulative dose in routine practice received by patients during long time periods. Some previous studies carried out in routine practice have evaluated the cumulative incidence of effective dose by focusing on specific pathologies[4], population groups[5] or the effect of recurrent CT[6]. However, none of them have evaluated the cumulative radiation exposure derived from all diagnostic procedures carried out in routine practice during a long period of time, for both adults and children. Given that the number of people who have these examinations many times during their lifetime has increased[6], the detection of patients with high cumulative radiation derived from recurrent imaging tests will help clinicians to reduce patient-specific associated cancer risks.

The purpose of this study was to quantify the number of all radiological investigations performed in a cohort of patients in routine practice to calculate each patient's cumulative radiation exposure and the recurrent tests during a 12-year study period, according to sex and age.

Methods

Study design

We conducted a retrospective cohort study to analyse the individual cumulative effective dose in routine practice and the recurrent imaging diagnostic tests.

Setting

The target population for the study were all residents in the catchment area of San Juan Hospital (Alicante), in the Valencian Community (Spain), a general centre, with a catchment population of 234,424 people. This is a referral hospital for all individuals living in the catchment area who belong to the National Health Care System (NHS). The majority of the Spanish population uses the NHS as the main medical service (the publicly funded insurance scheme covers 98.5% of the Spanish population).

Participants

We selected the population who belonged to the catchment area of that hospital during the year 2007, and collected all consecutive diagnostic imaging tests undergone by this population until 31st December 2018 (in any care setting, inpatient, outpatient, or emergency department). We excluded: imaging tests that did not involve radiation exposure (ie, MRI and ultrasound) and patients who had an imagen test in this hospital but did not belong to its catchment area.

Sources and variables

We collected the following data from Medical Image Bank of the Valencian Community from the Department of Universal Health and Public Health Service (BIMCV-CSUSP): sex and age at entry in the study, radiological examination and date. Both the images and the patient data were anonymized and de-identified by the Health Informatics Department of the Hospital of San Juan using R&D Cloud CEIB Architecture[7] This digital register started in 2007 in our setting.

We also examined the clinical context of patients receiving the highest dose radiation. We classified patients with diagnosis of neoplasm as patients at high risk of receiving high doses of radiation, as it was previously done[6]. Thus, for all patients who underwent an imagen test, we checked if they had the ICD11 code of neoplasms through the digital register, which started in 1993.

We estimated the associated radiation effective dose using previous published evidence[8].

Patient and public involvement:

Patients and the public were not involved in the design, conduct and reporting of the research.

Statistical analysis

The average dose values for individual examinations were analysed by a frequency distribution test. Data were expressed as the median and 25–75 percentiles for non-normally distributed values. Differences were evaluated by the Mann–Whitney U test. Categorical variables were expressed as percentages and differences were evaluated by Chi squared test.

The statistical analyses of the data were performed with SPSS (Version 25.0; SPSS Inc, Chicago, IL). A p-value 0.005 was considered significant.

Results

Cohort characteristics

The cohort included 224,751 people: 53.7% women and 46.3% men. Of these, 154,520 (68.8%) underwent an imaging test associated with radiation during the period of study, with different frequency for men (66.6%) and women (70.6%) (p<0.001) (table 1). Imaging test frequency ranged from 56.5% in the 20 to 30 age group to the highest percentage, 73.1%, in the 60 to 80 year old group.

Characteristics of imaging tests undergone during period of study.

Overall, the population had a total of 1,335,752 imaging tests during the period of study.

The type of imaging tests carried out were: 1,110,077 (83.0%) plain radiography; 156,848 (11.8%) CT; 63,157 (4.8%) fluoroscopy, and 5,670 (0.4%) interventional radiography. Men were more likely to have CT (14.3%) than women (10.1%) and women were more likely to have fluoroscopy (7.1%) than men (1.6) (p= 0.035). Moreover, the percentage of people who had a CT increased with age (from 1.2% in the 0 to 5 age group to 15.4% in the 60 to 70 age group (table 2).

Recurrent imaging tests.

The population exposed undergone a median of 5 imaging tests and 52.9% of the patients who had an imagen test during the period of study underwent 5 or more examinations. Women were more likely to have more cumulative imaging tests than men during this period (maximum 221 in men and 633 in women; IQR 2-10 in men and 2-12 in women, p<0.001).

Table 3 shows distribution data for per-patient imaging tests (median and maximum) by age and sex for each type of imaging test.

Moreover, 8.2% of the patients who had an imagen test during the period of study and 25.4% (12,602/49,544) of the patients who had a CT, underwent 5 or more CTs (5.4% (112/2,063) in the 0 to 15 age group), with a maximum of 75 examinations; 1.8% of the patients who had an imagen test and 9.7% (2,849/29,314) of the patients who had a fluoroscopy examination, underwent 5 or more fluoroscopy examinations (2.1% (23/1,100) in the 0 to 15 age group), with a maximum of 18 examinations; 0.2% of the patients who had an imagen test and 5.8% of the patients who had an interventional radiography, underwent 3 or more interventional radiographies, with a maximum of 10 examinations, and 21.2% of the patients who had an imagen test and 21.6% (32,778/151,980) of the patients who had a plain radiography, underwent 10 or more plain radiographies (10.1% (2,185/21,620) in the 0 to 15 age group), with a maximum of 559 examinations.

Men were more likely to have more than 5 CTS than women (27.8% vs 23.3%, $p<0.001$), and less likely to have more than 5 fluoroscopy examinations (2.3% vs 11.6%, $p<0.001$) and more than 10 plain radiographies than women (19.6% vs 23.2%, $p<0.001$, respectively) (data not shown).

Cumulative effective dose received during the period of study.

The median total cumulative effective dose including all modalities in all population exposed was 2.10 mSv (maximum 3980.30). Women received more effective dose than men (median 2.38 vs median 1.90, $p<0.001$). The cumulative incidence of effective dose increased with age: median 0.72

(maximum 47.15) in the 0 to 5 age group and median 10.20 (maximum 3980.309) in the 70 to 80 age group ($p<0.001$) (table 4).

A total of 4,844 (3.1%) people received cumulative doses between 50-100 mSv and 2,298 (1.5%) people received doses greater than 100 mSv. Men were more likely to have cumulative effective dose above 50 mSv (both between 50 and 100 mSv (3.5%) and higher than 100 mSv (1.8%), than women (2.9% and 1.2%, respectively) ($p<0.001$). Of the 2,298 patients who received more than 100 mSv during the 12-year study period, 725 (33.3%) were patients in the 60 to 70 age group; 565 (24.6%) were patients in the 50 to 60 age group; 462 (20.1%) were patients in the 70 to 80 age group, and 350 (15.2%) were patients in the 40 to 50 age group (table 5).

Classification of high-risk patients.

Of the 154,520 patients who had an imagen test during the period of study, 11,072 (7.1%) had a diagnosis of cancer during the period of study. Out of 2,298 patients who received more than 100 mSv, 1,678 (73.0 %) had a diagnosis of cancer, compared with 43.14% of patients who received between 50 and 100 mSv and 4.9 % of patients who received less than 50 mSv.

Discussion

This study provides important information on the cumulative radiation dose received by patients in routine practice. We showed that the median total cumulative effective dose during the 12-year study period was 2.10 mSv (maximum 3,980.30), lower than the 100 mSv threshold often considered for significant risks. However, 4,844 (3.1%) people received between 50 and 100 mSv and 2,298 (1.5%) more than 100 mSv during the study period.

According to stochastic effect theory and based on the estimated incidence of fatal cancer from the International Commission of Radiation Protection (ICRP) as well as from the Biological Effects of Ionising Radiation Committee VII (BEIR VII) released in 2005, for an adult, an effective dose of 100 mSv results in a risk of fatal cancer of approximately 1 in 200, and 1 in 100 for combined fatal and non-fatal cancer[9]. In our study, we only showed data from a 12-year period, so, the percentage of patients with an effective dose higher than 100 mSv during their lifetime will be even higher. Moreover, although the BEIR VII report concludes that at doses lower than 100 mSv, the risk of cancer is small[10], the Radiation Effect Research Foundation (RERF) in Japan, defends a "linear-no-threshold" risk model, where the risk of cancer follows in a linear fashion at lower doses, without a threshold. Smallest dose, therefore, has the potential to cause a small increase in cancer risk[11].

We also found high rates of recurrent CT (25.4% of the patients who had a CT, underwent 5 or more CTs, with a maximum of 75 examinations). Previous studies have shown higher rates of recurrent CT (33% of patients underwent 5 or more CT examinations)[6], but they included a longer followed-up period (22 years vs 12 years). Moreover, 5.8% of the patients who had an interventional radiography, underwent 3 or more interventional radiographies during the period of study, with a maximum of 10 examinations. Both, interventional radiography and CT, are associated with a relatively high dose of radiation. Plain radiography and fluoroscopy, although are not associated with so high doses, also showed a high recurrent rate.

Most of our population younger than 15 years old received effective dose lower than 50 mSv during the period of study; however, more than 40% of this population underwent 5 or more imaging tests during this period and 5% of them had 5 or more CTs. Moreover, the maximum number of plain radiography, CT, fluoroscopy and interventional radiography examinations undergone was 86, 17, 8 and 7, respectively in this age group. Although the linear no-threshold model is very controversial and is considered of little relevance for doses below 100mSv, we have to take into account that children are more sensitive to ionizing radiation effects due to their high radiosensitivity[12, 13]. In addition, previous studies have shown a possible risk of cancer from radiation associated with commonly used procedures, such as computed tomography scan, in children at very young ages[14].

As in previous studies[6], most of the patients who received more than 100 mSv had history of malignancy. However, 27% of them had no underlying malignant disease. In both group of patients, clinicians should balance the risk of the cumulative exposure against the benefit of recurrent imaging.

There is increasing international interest in reducing radiation doses from imaging procedures[15]. However, previous studies showed the difficulties when implementing initiatives to reduce radiation exposure into clinical practice. For instance, communication with patients regarding associated risk is essential to get a rational use of diagnostic imaging test, but there is a lack of knowledge in the general population regarding radiation exposure and the associated risks related to imaging tests[16]. In addition, recent studies showed that most clinicians were unaware of radiation exposure associated with imaging tests[17] and that less than 50% of the imaging tests carried out in clinical practice were considered appropriate according to the available recommendations and 29.1% of the total collective effective dose was associated with inappropriate imaging tests[18].

Assessing the amount of effective dose that patients receive during their lifetime, as the European Commission of Radiological Protection recommends[6], could therefore be considered a useful tool in the reduction of cancer risk in particular groups of patients to help clinicians to reach a shared decision with patients when asking for imaging tests. However, a big effort should be done given the great variation in CT protocols and radiation doses across countries and related with technical parameters[19].

Limitations of our study included the retrospective design and lack of information regarding patients who might have been imaged outside the healthcare system, as well as radiation derived from nuclear medicine that also represents an important proportion of the collective population dose[2, 3]. We used the available evidence to estimate the effective dose for each examination, as is proposed by the dosedatamed project[2]. However, this type of estimation has inherent limitations, although it does not affect the overall result. It is also true that our results may differ from those of studies in different settings. Nevertheless, we included a general hospital and its catchment area (with a total population over 200,000 people). Even though our results could have some limited generalisability in other settings, analysing this population provides important insights, showing as far as we know, the first evaluation of the cumulative incidence of effective dose in routine practice (including adults and children) according to age and sex over a 12 year-period.

Conclusions

A significant proportion of patients received doses higher than 50 mSv during the 12-year period of study. Moreover, the rate of recurrent examinations was high, especially in older patients, but also relevant in the 0 to 15 age group. These data could help clinicians to make an informed decision when asking for each imaging test, which would lead to lower cumulative lifetime radiation, and consequently a reduction in associated risks.

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Competing interest declaration

There are not competing interest to declare.

Contributors: BL, IGA and JMS conceived of and designed the study. BL and JMS acquired the data. BL and JMS prepared the data and BL, JMS and IGA interpreted statistical analyses. BL did the statistical analyses and drafted the data tables. BL, JMS and IGA co-wrote the manuscript. All authors critically revised the paper for important intellectual content and approved the final version.

Ethical approval: The study was approved by the institutional review board at San Juan Alicante Hospital (14/301).

Data sharing: No additional data available.

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1. Characteristics of study population by final exposure status*, based on 12-year period of study (2007-2018).

Characteristics	No (%) of people exposed	Total no of people in study
Sex		
Men	69,265 (66.6)	104,056
Women	85255 (70.6)	120,695
Age at entry to study (years)		
0-5	7,631 (62.4)	12,224
5-10	7,185 (60.1)	11,965
10-15	6,978 (62.1)	11,23
15-20	6,834 (59.3)	11,526
20-30	17,590 (56.5)	31,142
30-40	27,609 (66.9)	41,287
40-50	24,364 (70.4)	34,625
50-60	18,783 (70.4)	26,671
60-70	16,093 (73.1)	22,028
70-80	14,052 (73.1)	19,225
>80	7,401 (70.3)	10,523
Total no of people in study	**154,520 (68.8)**	**224,751**

*Exposure status at end of study. All study members were classified as unexposed on entry to the study.

2- Characteristics of the imagen tests received by sex and age during the period of study.

Characteristics	Plain radiography	Computed tomography	Fluoroscopy	Interventional radiography	Total
Sex					
Men	467,373 (83.5)	79,796 (14.3)	9,159 (1.6)	3,288 (0.6)	559,616
Women	631,917 (82.6)	77,052 (10.1)	53,998 (7.1)	2,382 (0.3)	765,349
Age at entry to study (years)					
0-5	33,570 (97.2)	423 (1.2)	541 (1.6)	4	34,538
5-10	36,427 (95.5)	1,050 (2.8)	648 (1.7)	14	38,138
10-15	35,333 (93.8)	1,703 (4.5)	610 (1.6)	33 (0.1)	37,679
15-20	32,274 (92.9)	1,850 (5.3)	570 (1.6)	38 (0.1)	34,732
20-30	78,990 (90.3)	6,285 (7.2)	2,078 (2.4)	127 (0.1)	87,480
30-40	131,846 (88.1)	13,201 (8.8)	4,304 (2.9)	327 (0.2)	149,678
40-50	153,479 (80.8)	22,609 (11.9)	13,093 (6.9)	609 (0.3)	189,790
50-60	166,589 (76.6)	30,630 (14.1)	19,081 (8.8)	1,073 (0.5)	217,373

60-70	184,943 (77.9)	36,428 (15.4)	14,365 (6.1)	1,563 (0.7)	237,299
70-80	177,888 (91.4)	32,227 (14.8)	6,929 (3.2)	1,509 (0.7)	218,553
>80	69,738 (85.6)	10,442 (12.8)	938 (1.2)	373 (0.5)	81,491
Total (n/%)	**1,110,077 (83.0)**	**156,848 (11.8)**	**63,157 (4.8)**	**5,670 (0.4)**	**1,335,752**

3- Summary data for the distribution for per-patient cumulative diagnostic imaging tests counts by sex and age during the period of study (2007-2018).

Characteristics	Plain radiography		Computed tomography		Fluoroscopy		Interventional radiography	
	Median	Maximum	Median	Maximum	Median	Maximum	Median	Maximum
Sex								
Men	4	213	2	71	1	18	1	10
Women	4	559	2	75	2	14	1	9
Age at entry to study (years)								
0-5	3	41	1	5	1	8	1	1
5-10	4	86	1	17	2	8	1	2
10-15	4	72	1	11	1	8	1	7
15-20	3	64	1	14	1	6	1	2
20-30	3	165	1	36	1	7	1	9
30-40	3	112	1	39	1	10	1	4
40-50	4	373	2	57	2	13	1	6
50-60	6	160	2	62	2	18	1	7
60-70	8	213	2	75	2	14	1	9
70-80	9	139	2	69	1	11	1	10
>80	7	101	2	35	1	8	1	5

4. Cumulative incidence of effective dose (mSv) per person exposed during the period of study.

Characteristics	Median	Percentil 25	Percentil 75	Percentil 95	Maximum
Sex					
Men	1.90	0.2	10.20	51.74	629.58
Women	2.38	0.38	10.10	43.80	3980.30
Age at entry to study (years)					
0-5	0.21	0.06	1.60	7.66	47.15
5-10	0.48	0.03	2.38	10.02	94.58
10-15	0.67	0.06	2.64	13.10	196.16
15-20	0.74	0.10	2.98	14.66	159.51
20-30	1.00	0.11	4.02	18.65	222.27
30-40	1.23	0.38	5.75	25.98	297.14
40-50	2.00	0.38	10.12	44.22	716.16
50-60	4.27	0.64	17.08	73.34	629.58
60-70	8.35	1.47	25.72	93.60	506.08

70-80	10.20	2.40	26.00	80.17	3980.30
>80	5.30	1.19	15.96	45.14	204.32
Total	**2.10**	**0.36**	**10.15**	**47.22**	**3980.30**

5. Classification of population according to the cumulative incidence of effective dose during the period of study.

Characteristics	0-50 mSv	>50-100 mSv	>100 mSv	p valor
Sex				<0.001
Men	65,623 (94.7)	2,407 (3.5)	1,235 (1.8)	
Women	81,756 (95.9)	2,437 (2.9)	1,063 (1.2)	
Age at entry to study (years)				<0.001
0-5	7,631 (100.0)			
5-10	7,179 (99.9)	6 (0.1)		
10-15	6,953 (99.6)	21 (0.3)	4 (0.3)	
15-20	6,814 (99.7)	17 (0.2)	3 (0.1)	
20-30	17,450 (99.2)	97 (0.6)	43 (0.2)	
30-40	27,145 (98.3)	353 (1.3)	111 (0.4)	
40-50	23,358 (95.9)	656 (2.7)	350 (1.4)	
50-60	17,201 (91.6)	1,017 (5.4)	565 (3.0)	
60-70	14,045 (87.3)	1,323 (8.2)	725 (4.5)	

70-80	12,490 (88.9)	1,101 (7.8)	462 (3.3)	
>80	7,113 (96.1)	253 (3.4)	35 (0.5)	
Total	**147,379 (95.4)**	**4,844 (3.1)**	**2,298 (1.5)**	

STROBE Statement—checklist of items that should be included in reports of observational studies

		Item No	Recommendation
YES Pages 1 and 3	**Title and abstract**	**1**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
	Introduction		
YES Pages 5-6	Background/rationale	**2**	Explain the scientific background and rationale for the investigation being reported
YES Page 6	Objectives	**3**	State specific objectives, including any prespecified hypotheses
	Methods		
YES Page 7	Study design	**4**	Present key elements of study design early in the paper
YES Page 7	Setting	**5**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
YES page 7	Participants	**6**	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
YES Pages 7-8	Variables	**7**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
YES Pages 7-8	Data sources/ measurement	**8***	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
YES Page 8	Bias	**9**	Describe any efforts to address potential sources of bias
NA	Study size	**10**	Explain how the study size was arrived at
YES Page 8	Quantitative variables	**11**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
YES Page 8	Statistical methods	**12**	(*a*) Describe all statistical methods, including those used to control for confounding
			(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

Continued on next page

	Results		
YES Page 9	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
YES Page 9	Descriptive data	**14***	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
			(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
YES Page 9-11	Outcome data	**15***	*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
			Cross-sectional study—Report numbers of outcome events or summary measures
YES Page 9-11	Main results	**16**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
NA	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
	Discussion		
YES Page 12	Key results	**18**	Summarise key results with reference to study objectives
YES Page 14	Limitations	**19**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
YES Pages 12-13	Interpretation	**20**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
YES Page 15	Generalisability	**21**	Discuss the generalisability (external validity) of the study results
	Other information		
NA	Funding	**22**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Cumulative exposure to ionizing radiation from diagnostic imaging tests: a 12-year follow-up population-based analysis in Spain.

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Title: Cumulative exposure to ionizing radiation from diagnostic imaging tests: a 12-year follow-up population-based analysis in Spain.

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Abstract

Objectives: To calculate each patient's cumulative radiation exposure and the recurrent tests during a 12-year study period, according to sex and age, in routine practice.

Design: Retrospective cohort study.

Setting: A general hospital with a catchment population of 224,751 people, in the Southeast of Spain.

Participants: Population belonged to the catchment area of that hospital in 2007. We collected all consecutive diagnostic imaging tests undergone by this population until 31st December 2018. We excluded: imaging tests that did not involve radiation exposure.

Main outcome measures: The cumulative effective dose and the recurrent imaging tests by sex and age at entry of study.

Results: Of the 224,751 people, 154,520 (68.8%) underwent an imaging test. The population had 1,335,752 imaging tests during the period of study: 1,110,077 (83.0%) plain radiography; 156,848 (11.8%) computed tomography (CT); 63,157 (4.8%) fluoroscopy, and 5,670 (0.4%) interventional radiography. 25.4% of the patients who had a CT, underwent 5 or more CTs (5.4% in the 0 to 20 age group). The median total cumulative effective dose was 2.10 mSv (maximum 3980.30) and 16.30 mSv (maximum 1419.30 mSv) if we considered only doses associated with CT. Women received more effective dose than men (median 2.38 vs median 1.90, p<0.001). A total of 7142 (4.6%) patients received more than 50 mSv, with differences in men and women (p<0.001) and

2.5% of the patients in the 0 to 20 age group, if we considered only doses associated with CT.

Conclusions: Nearly 5% of patients received doses higher than 50 mSv during the 12-year period of study and 2.5% of the patients in the 0 to 20 age group, if we considered only doses associated with CT. The rate of recurrent examinations was high, especially in older patients, but also relevant in the 0 to 20 age group.

Article summary section: Strengths and limitations of this study.

- This study follows the Basic Safety Standards Directive adopted by the European Union (EU) in 2013 in order to assess the amount of effective dose that patients receive during their lifetime.
- The analysis of medical records allowed us to evaluate all imaging tests performed in a cohort of 224,751 patients in routine practice during a 12-year study period, according to sex and age.
- The retrospective design did not allow a detailed assessment of the longitudinal nature of the exposure.
- Instead of recording the effective dose for each individual examination, we used the available evidence, as is proposed by the Dosedatamed project.
- The inclusion of a general hospital and its catchment area could have led to some limited generalisability in other settings.

Introduction

The use of ionising radiation in medicine provides valuable diagnostic information that undoubtedly benefits many patients. However, this radiation is also the greatest source of artificial radiation exposure[1].

In the last decades, there has been an increase in utilization of X-rays, particularly of Computerized Tomography (CT). Although a single CT scan does not present a significant risk for patients' health, each additional scan increases the potential for cancer-inducing biological damage[2] and patients may receive multiple CT scans over time[3].

According to stochastic effect theory and based on the estimated incidence of fatal cancer from the International Commission of Radiation Protection (ICRP), as well as from the Biological Effects of Ionising Radiation Committee VII (BEIR VII), an effective dose of 100 mSv results in a risk of fatal cancer of approximately 1 in 200 in adults, and 1 in 100 for combined fatal and non-fatal cancer[4]. Moreover, although the BEIR VII report concludes that at doses lower than 100 mSv, the risk of cancer is small[5], the Radiation Effect Research Foundation (RERF) in Japan, defends a "linear-no-threshold" risk model, where the risk of cancer follows in a linear fashion at lower doses, without a threshold. Smaller doses, therefore, have the potential to cause a small increase in cancer risk[6].

A recent study in France[7] estimated that 0.7% of all new cancer cases in 2015 were attributable to medical ionizing radiation. In Spain, a rate of 10.9 scans per 1000 children and young adults (0 to 20 years old) was estimated in 2013, and a total of 168.6 cancer cases (95% CI: 30.1–421.1) will be attributable to these CTs[8].

Concern regarding the effects of ionizing radiation from these medical tests on population health and the estimated increased risk of cancer for the population in general, and for children and young adults in particular (0-20 years old)[9, 10] has led to several initiatives to reduce the use of ionizing radiation.

The Basic Safety Standards Directive was adopted by the European Union (EU) in 2013[11] to be transposed into national law by 6 February 2018. One key and innovative surveillance mechanism in this revised directive is to record the radiation dose received by each patient undergoing a medical imaging test. The directive mainly focuses on CT and tests involving interventional radiology, all of which are associated with a relatively high dose of radiation. Other diagnostic tests such as conventional radiography, however, are also frequently repeated in patients during their lives with a potential impact on health and could be included in these evaluations. However, these evaluations have not still been developed in the European countries as a systematically procedure.

A full evaluation of the radiation exposure from all medical diagnostic tests in Europe has been previously carried out in the project Dose DataMed I[12] and II[13]. This project, based on national surveys, includes information on 36 European countries regarding population frequencies and radiation dose of x-ray and nuclear medicine radiodiagnostic tests. Although this project has led to a significant advance in the evaluation of population doses, we still do not have data regarding the cumulative dose in routine practice received by patients during long time periods. Some previous studies carried out in routine practice have evaluated the cumulative effective dose by focusing on specific pathologies[14], population groups[15] or the effect of recurrent CT[16]. The previously mentioned study in France[7], assessed the cumulative exposure in adults of 30 years of age and older, using 2007 national frequencies of imaging tests and adjusted for changes in the use of these tests over time. However, none of them have evaluated the cumulative radiation exposure derived from all diagnostic tests carried out in routine practice during a long period of time, for both adults and children.

Given that the number of people who have these examinations many times during their lifetime has increased[16], the detection of patients with high cumulative radiation derived from recurrent imaging tests will help clinicians to reduce patient-specific associated cancer risks. Moreover, the identification of the clinical context of patients with high cumulative radiation doses due to repeat imaging could help clinicians to reduce the use of ionizing radiation[17]. According to previous literature, patients with a diagnosis of neoplasm are prone to have recurrent imaging tests[16].

The purpose of this study was to quantify the number of all radiological investigations performed in a cohort of patients in routine practice to calculate each patient's cumulative radiation exposure and the recurrent tests during a 12-year study period, according to sex. age, focusing on children and young adults (0 to 20 years old) and imaging test. In addition, we identified the clinical context of patients with potentially high cumulative radiation risks.

Methods

Study design

We conducted a retrospective cohort study to analyse the individual cumulative effective dose in routine practice and the recurrent imaging diagnostic tests.

Setting

The target population for the study were all residents in the catchment area of San Juan Hospital (Alicante), in the Valencian Community (Spain), a general centre, with a catchment population of 234,424 people. This is a referral hospital for all individuals living in the catchment area who belong to the National Health Care System (NHS). The majority of the Spanish population uses the NHS as the main medical service (the publicly funded insurance scheme covers 98.5% of the Spanish population) and hence, only a small percentage of patients are likely to have had imaging tests outside this setting.

Participants

We selected the population who belonged to the catchment area of that hospital during the year 2007, and collected all consecutive diagnostic imaging tests undergone by this population until 31st December 2018 (in any care setting, inpatient, outpatient, or emergency department). Cohort members remained in the study until their exit date or they left the catchment area. We assigned each person to the unexposed group from the date of entry until the date of the first imaging test, and to the exposed group from the date of the first imaging test until the exit date. In addition, in those patients who did not account for the 12 years of follow-up, we assumed future practice estimating the proportion of imaging tests that would have been carried out during the remaining period if the patients had been in the cohort, except for the > 80 age group, where did not implemented this strategy given that the expectancy life in Spain is 82.83 years old.

We excluded: imaging tests that did not involve radiation exposure (ie, MRI and ultrasound) and patients who had an imaging test in this hospital but did not belong to its catchment area.

We classified the population in different age groups, and we focused our estimations in the 0-20 year old group due to their increased cancer risk.

In order to check generalizability of our data, we compare our population with Spanish population on the 31st December 2007[18].

Imaging test frequency

We collected the following data from Medical Image Bank of the Valencian Community from the Department of Universal Health and Public Health Service (BIMCV-CSUSP): sex and age at entry in the study, radiological examination and date. Both the images and the patient data were anonymized and de-identified by the Health Informatics Department of the Hospital of San Juan using R&D Cloud CEIB Architecture[7] This digital register started in 2007 in our setting.

According to previous studies[16], each imaging test received was classified as a single radiation exposure. However, abdomen and pelvis tests carried out in the same process were included as a single abdomen-pelvis test, while an abdomen or pelvis test in a different process, even in the same patient, were included as two different tests. Thoracic and lumbar spine tests were included when they were performed alone but not when performed together with chest or abdominal tests.

Effective dose estimate:

Given that it was impossible to get individual machine parameters for all imaging tests, we estimated the associated radiation effective dose per test according to its region of anatomical coverage by age and using previously published evidence[19]. This review provides values of the typical effective doses associated with the 20 most frequent imaging tests for adults and children and for the most widely used set of weights (ICRP60) as well as for the most recent (ICRP103). We based our estimates on ICRP103, except in those cases where we did not have enough information. In addition, we estimated the effective dose of imaging tests different from the 20 most frequent imaging tests in Dose Datamed 2 project according to previous bibliography[20-22] (supplementary material tables 1 and 2).

Clinical classification of high-risk patients.

We examined the clinical context of patients receiving the highest dose radiation. In accordance with previous studies[16], we classified patients with diagnosis of neoplasm as patients at high risk of receiving high doses of radiation. We reviewed the digital register to establish which patients, who underwent an imaging test, had the ICD11 code of neoplasms (from 1993, when the register started, until the date of the first imaging test they underwent in our study).

Patient and public involvement:

Patients and the public were not involved in the design, conduct and reporting of the research.

Statistical analysis

We estimated the imaging test frequency as the number of people having at least 1 test during the study period until the 31st December 2018 (final exposure status) and it was classified by sex and age. We also estimated the per-patient cumulative diagnostic imaging test during the period of study by adding up the number of tests received by each patient, and then evaluated the differences by sex and age group using the Chi squared test. We also calculated the median and maximum number of imaging tests in our population and assessed the differences by sex and age using the Mann–Whitney U test.

Cumulative effective dose estimates were obtained by adding effective dose estimates received in each test in the patient's history. Data were expressed as the median, maximum and 25, 75, 95 percentiles. Differences by sex and age group were assessed using the Mann–Whitney U test.

We also classified the population according to the cumulative effective dose received during the period of study in the following way: 0-50 mSv, >50-100 mSv and >100 mSv[9] and evaluated the differences in these groups by sex and age group using the Chi squared test.

We carried out a sub-group analysis to analyse the different cumulative effective dose in patients having CT and in those having plain radiograph (supplementary material).

The statistical analyses of the data were performed with SPSS (Version 25.0; SPSS Inc, Chicago, IL). A p-value 0.05 was considered significant.

Results

Cohort characteristics

The cohort included 232,446 people: 53.7% women and 46.3% men. The distribution by sex and age was similar to Spanish general population.

Of 232,446 people included in the cohort study, 154,520 (68.8%) underwent an imaging test associated with radiation during the period of study, with different frequency for men (69,265/107,622; 66.6%) and women (85,255/123,196; 70.6%) ($p<0.001$) (table 1). The number of people having at least 1 exam during the study period (defined as imaging test frequency) ranged from 56.5% in the 20 to 30 age group to the highest percentage, 73.1%, in the 60 to 80 year old group.

Characteristics of imaging tests undergone during period of study.

Overall, the population had a total of 1,335,752 imaging tests during the period of study.

The type of imaging tests carried out were: 1,110,077 (83.0%) plain radiography; 156,848 (11.8%) CT; 63,157 (4.8%) fluoroscopy, and 5,670 (0.4%) interventional radiography. Men were more likely to have CT (14.3%) than women (10.1%) and women were more likely to have fluoroscopy (7.1%) than men (1.6) ($p= 0.035$). Moreover, the percentage of people who had a CT increased with age (from 1.2% in the 0 to 5 age group to 15.4% in the 60 to 70 age group (table 2).

Recurrent imaging tests.

The population exposed undergone a median of 5 imaging tests and 52.9% of the patients underwent 5 or more examinations. Women were more likely to have more cumulative imaging tests than men during this period (maximum 221 in men and 633 in women; interquartile range 2-10 in men and 2-12 in women, p<0.001).

Table 3 shows distribution data for per-patient imaging tests (median and maximum) by age and sex for each type of imaging test.

Moreover, 8.2% of the patients who had an imaging test during the period of study and 25.4% (12,602/49,544) of the patients who had a CT, underwent 5 or more CTs (5.5% (174/3,187) in the 0 to 20 age group), with a maximum of 75 examinations; 1.8% of the patients who had an imaging test and 9.7% (2,849/29,314) of the patients who had a fluoroscopy examination, underwent 5 or more fluoroscopy examinations (1.9% (28/1,478) in the 0 to 20 age group), with a maximum of 18 examinations; 0.2% of the patients who had an imaging test and 5.8% of the patients who had an interventional radiography, underwent 3 or more interventional radiographies, with a maximum of 10 examinations, and 21.2% of the patients who had an imaging test and 21.6% (32,778/151,980) of the patients who had a plain radiography, underwent 10 or more plain radiographies (10.1% (2,849/28,356) in the 0 to 20 age group), with a maximum of 559 examinations.

Men were more likely to have more than 5 CTS than women (27.8% vs 23.3%, p<0.001), and less likely to have more than 5 fluoroscopy examinations (2.3%

vs 11.6%, p<0.001) and more than 10 plain radiographies than women (19.6% vs 23.2%, p<0.001, respectively) (data not shown).

Cumulative effective dose received during the period of study.

The median total cumulative effective dose including all imaging tests in all population exposed was 2.10 mSv (maximum 3980.30). Women received more effective dose than men (median 2.38 vs median 1.90, p<0.001). The cumulative effective dose increased with age: median 0.72 (maximum 47.15) in the 0 to 5 age group and median 10.20 (maximum 3980.309) in the 70 to 80 age group (p<0.001) (table 4).

If we consider the cumulative effective dose associated with plain-radiograph (table S3), the median total cumulative effective dose was 0.70 mSv (maximum 2112.79). There were also differences by sex: women received more effective dose than men (median 1.02 vs median 0.64, p<0.001).

Considering the cumulative effective dose associated with CT (table S4), the median total cumulative effective dose was 16.30 mSv (maximum 1419.30). Men received more effective dose than women (median 19.80 vs median 13.20, p<0.001). 2.5% of the patients in the 0 to 20 group received more than 50 mSv.

A total of 4,844 (3.1%) people received cumulative doses between 50-100 mSv and 2,298 (1.5%) people received doses greater than 100 mSv. Men were more likely to have cumulative effective dose above 50 mSv (both between 50 and 100 mSv (3.5%) and higher than 100 mSv (1.8%), than women (2.9% and 1.2%, respectively) (p<0.001). Of the 2,298 patients who received more than 100 mSv during the 12-year study period, 725 (33.3%) were patients in the 60 to 70 age group; 565 (24.6%) were patients in the 50 to 60 age group; 462 (20.1%) were patients in the 70 to 80 age group, and 350 (15.2%) were patients in the 40 to 50 age group (table 5).

If we consider the cumulative effective dose associated with plain-radiograph, almost 100% of people received cumulative effective dose below 50 mSv. Considering the cumulative effective dose associated with CT, 17.8% of people received doses above 50 mSv (8.2% above 100 mSv).

Classification of high-risk patients.

Of the 154,520 patients who had an imaging test during the period of study, 11,072 (7.1%) had a diagnosis of cancer during the period of study. Out of 2,298 patients who received more than 100 mSv, 1,678 (73.0 %) had a diagnosis of cancer, compared with 43.14% of patients who received between 50 and 100 mSv and 4.9 % of patients who received less than 50 mSv.

Discussion

This study provides important information on the cumulative radiation dose received by patients in routine practice. We showed that the median cumulative effective dose including all the imaging tests during the 12-year study period was 2.10 mSv (maximum 3,980.30). However, the median cumulative effective dose associated with only CT was 16.30 (maximum 1419.30).

The median cumulative effective dose was therefore lower than the 100 mSv threshold often considered for significant risks in stochastic theory[23]. Nevertheless, 4,844 (3.1%) people received between 50 and 100 mSv and 2,298 (1.5%) more than 100 mSv during the study period. In addition, 17.8% of people who had CTs received doses above 50 mSv and 8.2% of them, doses above 100 mSv. A previous study evaluated CT use in general practice during an 8-year period (1998-2005) and showed that nearly 50% of the population had CT and 1.2% of them received doses >100 mSv. The longer follow-up period in our study (12 years vs 8 years) does not justify the much higher cumulative effective dose associated with CT shown in our patients.

However, our frequencies are lower than those reported in a previous study where 15% received estimated cumulative effective doses of more than 100 mSv[16]. This study included adult patients who had received CT during the previous 22 years while our cohort study included general population. In addition, we only showed data from a 12-year period, so the percentage of patients with an effective dose higher than 100 mSv during their lifetime will be even higher. Moreover, according to linear theory, smaller doses have the potential to cause a small increase in cancer risk[24]. However, the cancer rates did not change in our cohort during the period of study.

Previous research focused on patients <20 years of age[25] showed that of the 22,867 patients who had CT during an 8-year period, 1.6% received doses higher than 50 mSv. In our cohort study, the percentage was lower, but we included all imaging tests (radiography and CT). In the subgroup analysis by type of imaging test, we observed higher rates in the CT group in the 0 to 20 age group (2.5%). Greater efforts to decrease the number of recurrent CTs in children have to be implemented, taking into account that a recent study showed that even low doses of ionizing radiation increase the risk of childhood leukemia[26].

These results which show high rates of population undergoing imaging tests are in line with the DoseData Med II project[3], in which Spain had one of the greatest frequency of imaging tests per 1000 population in comparison with the European average.

We also found high rates of recurrent CT (25.4% of the patients who had a CT, underwent 5 or more CTs, with a maximum of 75 examinations). Previous studies have shown higher rates of recurrent CT (33% of patients underwent 5 or more CT examinations)[6], but they included a longer followed-up period (22 years vs 12 years). Moreover, 5.8% of the patients who had an interventional radiography, underwent 3 or more interventional radiographies during the period of study, with a maximum of 10 examinations. Both interventional radiography and CT, are associated with a relatively high dose of radiation. Plain radiography and fluoroscopy, although they are not associated with such high doses, also showed a high recurrent rate. Additional measures should be applied to control these recurrent rates, particularly to subgroups who are more prone to recurrent controls such as patients with chronic diseases like cancer.

In fact, as in previous studies[16], most of the patients who received more than 100 mSv had previous history of malignancy. However, 27% of them had no underlying malignant disease. In both groups of patients, clinicians should balance the risk of the cumulative exposure against the benefit of recurrent imaging.

Most of our population younger than 20 years old received effective dose lower than 50 mSv during the period of study; however, more than 40% of this population underwent 5 or more imaging tests during this period and 5% of them had 5 or more CTs. Moreover, the maximum number of plain radiography, CT, fluoroscopy and interventional radiography examinations undergone was 86, 17, 8 and 7, respectively in this age group. The linear no-threshold model is very controversial and is considered of little relevance for doses below 100mSv; nevertheless, we have to take into account that children are more sensitive to ionizing radiation effects due to their high radiosensitivity[27, 28]. In addition, previous studies have shown a possible risk of cancer from radiation associated with commonly used tests, such as computed tomography scan, in children at very young ages[29].

There is increasing international interest in reducing radiation doses from imaging tests[30]. Previous studies have shown difficulties when implementing initiatives to reduce radiation exposure into clinical practice. For instance, communication with patients regarding associated risk is essential to get a rational use of diagnostic imaging test, but there is a lack of knowledge in the general population regarding radiation exposure and the associated risks related to these tests[31, 32]. In addition, recent studies showed that most clinicians were unaware of radiation exposure associated with imaging tests[33-35] and that less than 50% of the imaging tests carried out in clinical practice were considered appropriate according to the available recommendations and 29.1% of the total collective effective dose was associated with inappropriate imaging tests[36].

Assessing the amount of effective dose that patients receive during their lifetime, as the European Commission of Radiological Protection recommends[11], could therefore be considered a useful tool to raise awareness among clinicians and patients regarding the risks associated, and to help them to reach a shared decision when asking for imaging tests to reduce cancer risk. However, an effort should be made to reduce the great variation in CT protocols, technical parameters and radiation doses across countries [37].

Limitations of our study included the retrospective design and lack of information regarding patients who might have been imaged outside the healthcare system, as well as radiation derived from nuclear medicine that also represents a relevant proportion of the collective population dose[12, 13]. However, as we stated previously, the publicly funded insurance scheme covers 98.5% of the Spanish population and only a small percentage of patients are likely to have had imaging tests outside this setting.

Moreover, given that we studied the imaging tests carried out during a 12-year period, some patients could have been lost to follow-up. Based on practice during this 12-year period, we estimated the proportion of imaging tests that would have been carried out during the remaining period if the patients had been in the cohort.

We used the available evidence to estimate the effective dose for each imaging test, as is proposed by the Dosedatamed project[12, 13]. However, this type of estimation has inherent limitations; it does not take into account the test date, the scanner model or the patient's characteristics. Nevertheless, it does not affect the overall result. It is also true that our results may differ from those of studies in different settings. We used effective dose to quantify the radiation exposure associated with each imaging test instead of organ doses. Absorbed organ doses are important for some procedures that either involve high doses or include sensitive tissues in the primary radiation beam[4]. However, our aim was not to assess cancer risks associated with medical ionizing radiation but to compare across the different imaging tests carried out in our population.

We included a general hospital and its catchment area (with a total population over 200,000 people). Even though our results could have some limited generalisability in other settings, analysing this population provides important insights, showing as far as we know, the first evaluation of the cumulative effective dose in routine practice (including adults and children) according to age and sex over a 12 year-period. In addition, as we showed in the result section, the population included in this study is similar to general Spanish population.

Conclusions

A total of 4,844 (3.1%) people received cumulative doses between 50-100 mSv and 2,298 (1.5%) people received doses greater than 100 mSv during the 12-year period of study. Considering only the doses associated with CT, 2.5% of the patients in the 0 to 20 age group received doses above 50 mSv. Moreover, the rate of recurrent examinations was high, especially in older patients, but also relevant in the 0 to 20 age group. These data could help clinicians to make an informed decision when asking for each imaging test, which would lead to lower cumulative lifetime radiation, and consequently a reduction in associated risks.

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Competing interest declaration

There are not competing interest to declare.

Contributors: BL, IGA and JMS conceived of and designed the study. BL and JMS acquired the data. BL and JMS prepared the data and BL, JMS and IGA interpreted statistical analyses. BL did the statistical analyses and drafted the data tables. BL, JMS and IGA co-wrote the manuscript. All authors critically revised the paper for important intellectual content and approved the final version.

Ethical approval: The study was approved by the institutional review board at San Juan Alicante Hospital (14/301).

Data sharing: Data generated by the research that supports this manuscript will be available as soon as possible wherever legally and ethically possible.

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Table 1. Characteristics of study population by final exposure status (Exposure status at end of study. All study members were classified as unexposed on entry to the study), based on 12-year period of study (2007-2018) and comparison with Spanish general population on the 31st December 2007.

Age at entry to study (years)	Number (%) of people having at least 1 imaging test in the study*			Total number (%) of people in the study			Total number (%) of Spanish general population		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
0-5	3938 (5.7)	3693 (5.3)	7,631 (4.9)	5660 (5.3)	6564 (5.3)	12,224 (5.3)	1287417 (5.6)	1213658 (5.1)	2501081 (5.3)
>5-10	3798 (5.5)	3387 (4.9)	7,185 (4.6)	5540 (5.1)	6425 (5.2)	11,965 (5.1)	1259447 (5.5)	1181161 (4.9)	2440613 (5.2)
>10-15	3611 (5.2)	3367 (4.9)	6,978 (4.5)	5199 (4.8)	6031 (4.9)	11,230 (4.8)	1269835 (5.5)	1194802 (5.0)	2464643 (5.3)
>15-20	3581 (5.2)	3253 (4.7)	6,834 (4.4)	5337 (5.0)	6189 (5.0)	11,526 (5.0)	1188946 (5.2)	1113600 (4.7)	2302551 (4.9)
>20-30	8520 (12.3)	9070 (13.1)	17,590 (11.4)	14419 (13.4)	16723 (13.6)	31,142 (13.4)	2476624 (10.8)	2418216 (10.1)	4894851 (10.4)
>30-40	11318 (16.3)	16291 (23.5)	27,609 (17.9)	19116 (17.8)	22171 (18.0)	41,287 (17.8)	3239875 (14.1)	3248190 (13.6)	6488079 (13.8)
>40-50	10119 (14.6)	14245 (20.6)	24,364 (15.8)	16031 (14.9)	18594 (15.1)	34,625 (14.9)	3914804 (17.0)	3837041 (16.0)	7751862 (16.5)
>50-60	8512 (12.3)	10271 (14.8)	18,783 (12.2)	12349 (11.5)	14322 (11.6)	26,671 (11.5)	3356615 (14.6)	3431770 (14.3)	6788400 (14.5)
>60-70	7329 (10.6)	8764 (12.7)	16,093 (10.4)	10199 (9.5)	11829 (9.6)	22,028 (9.5)	2439786 (10.6)	2650101 (11.1)	5089898 (10.8)
>70-80	5997 (8.7)	8056 (11.6)	14,052 (9.1)	8901 (8.3)	10324 (8.4)	19,225 (8.3)	1614748 (7.0)	1975175 (8.3)	3589930 (7.6)
>80	2542 (3.7)	4859 (7.0)	7,401 (4.8)	4872 (4.5)	5651 (4.6)	10,523 (4.5)	959627 (4.2)	1662367 (6.9)	2621998 (5.6)
Total (number/%)	**69,265 (100.0)**	**85,255 (100.0)**	**154,520 (100.0)**	**107,622 (100.0)**	**123,196 (100.0)**	**232,446 (100.0)**	**23,007,724 (100.0)**	**23,926,081 (100.0)**	**46,933,905 (100.0)**

*p-value <0.05: differences in the number of people having at least 1 imaging test in the study by sex in all age groups and in the total.

Table 2. Number and percentage of each type of imaging test received, classified by sex and age during the period of study.

Age at entry to study (years)	Number (%) of plain radiography*			Number (%) of computed tomography*			Number (%) of fluoroscopy*			Number (%) of interventional radiography*		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
0-5	17411 (3.7)	16159 (2.6)	33,570 (3.0)	235 (0.3)	188 (0.2)	423 (0.3)	239 (2.6)	302 (0.6)	541 (0.9)	4 (0.1)	0	4 (0.1)
5-10	20124 (4.3)	16303 (2.6)	36,427 (3.3)	577 (0.7)	473 (0.6)	1,050 (0.7)	362 (4.0)	286 (0.5)	648 (1.0)	8 (0.2)	6 (0.3)	14 (0.2)
10-15	20053 (4.3)	15280 (2.4)	35,333 (3.2)	955 (1.2)	748 (1.0)	1,703 (1.1)	298 (3.3)	312 (0.6)	610 (1.0)	21 (0.6)	12 (0.5)	33 (0.6)
15-20	18408 (3.9)	13866 (2.2)	32,274 (2.9)	1070 (1.3)	780 (1.0)	1,850 (1.2)	214 (2.3)	356 (0.7)	570 (0.9)	21 (0.6)	17 (0.7)	38 (0.7)
20-30	40301 (8.6)	38689 (6.1)	78,990 (7.2)	3162 (4.0)	3123 (4.1)	6,285 (4.0)	617 (6.7)	1461 (2.7)	2,078 (3.3)	58 (1.8)	69 (2.9)	127 (2.2)
30-40	57707 (12.3)	74139 (11.7)	131,846 (12.0)	6604 (8.3)	6597 (8.6)	13,201 (8.4)	1139 (12.4)	3165 (5.9)	4,304 (6.8)	217 (6.6)	110 (4.6)	327 (5.8)
40-50	61353 (13.1)	92126 (14.5)	153,479 (13.9)	10918 (13.7)	11691 (15.2)	22,609 (14.4)	1347 (14.7)	11746 (21.8)	13,093 (20.7)	401 (12.2)	208 (8.7)	609 (10.7)
50-60	67366 (14.4)	99223 (15.7)	166,589 (15.1)	16560 (20.8)	14070 (18.3)	30,630 (19.5)	1809 (19.8)	17272 (32.0)	19,081 (30.2)	671 (20.4)	402 (16.9)	1,073 (18.9)
60-70	75355	109588	184,943	19665	16763	36,428	1754	12611	14,365	981	582 (24.4)	1,563

	(16.1)	(17.3)	(16.8)	(24.6)	(21.8)	(23.2)	(19.2)	(23.4)	(22.7)	(29.8)		(27.6)
70-80	67088 (14.3)	110800 (17.5)	177,888 (16.2)	15925 (20.0)	16302 (21.2)	32,227 (20.5)	1130 (12.3)	5799 (10.7)	6,929 (11.0)	766 (23.3)	743 (31.2)	1,509 (26.6)
>80	22730 (4.9)	47008 (7.4)	69,738 (6.3)	4125 (5.2)	6317 (8.2)	10,442 (6.7)	250 (2.7)	688 (1.3)	938 (1.5)	140 (4.3)	233 (9.8)	373 (6.6)
Total (n/%)	**467,373 (100.0)**	**631,917 (100.0)**	**1,110,077 (100.0)**	**79,796 (100.0)**	**77,052 (100.0)**	**156,848 (100.0)**	**9,159 (100.0)**	**53,998 (100.0)**	**63,157 (100.0)**	**3,288 (100.0)**	**2,382 (100.0)**	**5,670 (100.0)**

*p valor<0.05: differences by sex in in all age groups and in the total.

Table 3. Cumulative diagnostic imaging tests per person exposed by sex and age during the period of study.

Age at entry to study (years)	Plain radiography (median/maximum)			Computed tomography (median/maximum)			Fluoroscopy (median/maximum)			Interventional radiography (median/maximum)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
0-5	3 (40)	3 (41)	3 (41)	1 (4)	1 (5)	1 (5)	1 (8)	1 (7)	1 (8)	1 (1)	-	1 (1)
5-10	4 (40)	4 (86)	4 (86)*	1 (17)	1 (11)	1 (17)	2 (8)	1 (5)	2 (8)	1 (2)	1 (1)	1 (2)
10-15	4 (72)	3 (49)	4 (72)*	1 (11)	1 (11)	1 (11)*	1 (8)	1 (5)	1 (8)*	1 (7)	1 (3)	1 (7)
15-20	4 (47)	3 (64)	3 (64)*	1 (14)	1 (13)	1 (14)*	1 (6)	1 (6)	1 (6)	1 (2)	1 (2)	1 (2)
20-30	3 (165)	3 (62)	3 (165)*	1 (36)	1 (21)	1 (36)	1 (5)	1 (7)	1 (7)*	1 (3)	1 (9)	1 (9)
30-40	3 (112)	3 (80)	3 (112)*	1 (29)	2 (39)	1 (39)*	1 (8)	1 (10)	1 (10)*	1 (4)	1 (3)	1 (4)
40-50	4 (101)	4 (373)	4 (373)*	1 (44)	2 (57)	2 (57)*	1 (7)	2 (13)	2 (13)*	1 (6)	1 (5)	1 (6)
50-60	5 (160)	7 (95)	6 (160)*	2 (62)	2 (49)	2 (62)*	1 (18)	2 (13)	2 (18)*	1 (7)	1 (5)	1 (7)
60-70	7 (213)	9 (173)	8 (213)*	2 (71)	3 (75)	2 (75)*	1 (10)	2 (14)	2 (14)*	1 (9)	1 (6)	1 (9)
70-80	8 (139)	10 (559)	9 (559)*	2 (69)	3 (74)	2 (69)*	1 (8)	1 (11)	1 (11)*	1 (10)	1 (7)	1 (10)

>80	6 (85)	7 (101)	7 (101)*	2 (23)	2 (35)	2 (35)*	1 (5)	1 (8)	1 (8)*	1 (4)	1 (5)	1 (5)
Total	**4 (213)**	**4 (559)**	**4 (559)***	**2 (71**	**2 (75)**	**2 (75)***	**1 (18)**	**2 (14)**	**2 (18)***	**1 (10)**	**1 (9)**	**1 (10)**

[a]p valor<0.05

Table 4. Cumulative effective dose (mSv) per person exposed during the period of study.

Age at entry to study (years)	Total			Men			Women			p-valor
	Median	Percentil 25-75	Maximum	Median	Percentil 25-75	Maximum	Median	Percentil 25-75	Maximum	
0-5	0.21	0.06-1.60	47.15	0.20	0.06-1.28	37.38	0.21	0.06-1.93	47.15	0.579
5-10	0.48	0.03-2.38	94.58	0.42	0.04-2.26	94.58	0.52	0.02-2.48	55.19	0.128
10-15	0.67	0.06-2.64	196.16	0.64	0.06-2.56	196.16	0.77	0.07-2.78	143.51	0.001
15-20	0.74	0.10-2.98	159.51	0.65	0.10-2.80	159.51	0.83	0.10-3.08	104.15	0.001
20-30	1.00	0.11-4.02	222.27	0.69	0.10-3.18	222.27	1.38	0.22-4.83	221.10	<0.001
30-40	1.23	0.38-5.75	297.14	1.09	0.16-5.14	297.14	1.29	0.38-6.04	259.56	0.002
40-50	2.00	0.38-10.12	716.16	2.03	0.30-10.87	389.44	1.96	0.38-9.70	716.16	0.417
50-60	4.27	0.64-17.08	629.58	4.17	0.62-18.05	629.58	4.32	0.65-16.26	430.68	0.514

60-70	8.35	1.47-25.72	506.08	9.80	1.47-29.21	506.08	7.63	1.48-23.46	489.57	<0.001
70-80	10.20	2.40-26.00	3980.30	12.05	2.60-30.46	502.08	8.81	2.18-23.21	3980.30	<0.001
>80	5.30	1.19-15.96	204.32	6.54	1.28-18.98	183.80	5.00	1.10-4.58	204.32	<0.001
Total	**2.10**	**0.36-10.15**	**3980.30**	**1.90**	**0.2-10.20**	**629.58**	**2.38**	**0.38-10.10**	**3980.30**	**<0.001**

Table 5. Number and percentage of people exposed according to the cumulative effective dose during the period of study.

Age at entry to study (years)	Total (number, percentage)			Men (number, percentage)			Women (number, percentage)			p-valor
	0-50 mSv	>50-100 mSv	>100 mSv	0-50 mSv	>50-100 mSv	>100 mSv	0-50 mSv	>50-100 mSv	>100 mSv	
0-5	7,631 (100.0)			3938 (100.0)			3693 (100.0)			
5-10	7,179 (99.9)	6 (0.1)		3793 (99.9)	5 (0.1)		3386 (100.0)			0.135
10-15	6,953 (99.6)	21 (0.3)	4 (0.3)	3597 (99.6)	11 (0.3)	3 (0.1)	3356 (99.7)	10 (0.3)	1	0.647
15-20	6,814 (99.7)	17 (0.2)	3 (0.1)	3570 (99.7)	9 (0.3)	2 (0.1)	3244 (99.7)	8 (0.2)	1	0.884
20-30	17,450 (99.2)	97 (0.6)	43 (0.2)	8462 (99.3)	39 (0.5)	19 (0.2)	8988 (99.1)	58 (0.6)	24 (0.3)	0.227
30-40	27,145 (98.3)	353 (1.3)	111 (0.4)	11101 (98.2)	158 (1.4)	59 (0.5)	16044 (98.5)	195 (1.2)	52 (0.3)	0.011
40-50	23,358 (95.9)	656 (2.7)	350 (1.4)	9678 (95.6)	295 (2.9)	146 (1.4)	13680 (96.0)	361 (2.5)	204 (1.4)	0.193
50-60	17,201 (91.6)	1,017 (5.4)	565 (3.0)	7681 (90.2)	506 (5.9)	325 (3.8)	9520 (92.7)	511 (5.0)	240 (2.3)	<0.001
60-70	14,045 (87.3)	1,323 (8.2)	725 (4.5)	6227 (85.0)	694 (9.5)	408 (5.6)	7818 (89.2)	629 (7.2)	317 (3.6)	<0.001
70-80	12,490 (88.9)	1,101 (7.8)	462 (3.3)	5151 (85.9)	594 (9.9)	252 (4.2)	7339 (91.1)	507 (6.3)	210 (2.6)	<0.001

>80	7,113 (96.1)	253 (3.4)	35 (0.5)	2425 (95.4)	96 (3.8)	21 (0.8)	4688 (96.5)	157 (3.2)	14 (0.3)	0.003
Total	**147,379 (95.4)**	**4,844 (3.1)**	**2,298 (1.5)**	**65623 (94.7)**	**2407 (3.5)**	**1235 (1.8)**	**81756 (95.9)**	**2437 (2.9)**	**1063 (1.2)**	**<0.001**

Table S1. Imaging tests included and doses used per examination (mSv) (adults).

Tests	Anatomical sites	Doses (mSv)
Plain radiography		
	Abdomen	0.5
	Cervical spine	0.05
	Chest/Thorax	0.05
	Lumbar spine	0.8
	Pelvis/Hip	0.37
	Breast (incl. mammography)	0.64
	Thoracic spine	0.50
	Skull	0.1
	Knee	0.005
	Other extremities	0.001
	Shoulder	0.01
Fluoroscopy		
	Hysterosalpingography	1.95
	Urography	3.5
	Ba enema	5.8
	Ba meal	3.6
	Ba follow-through	3.5
	Endoscopic retrograde cholangiopancreatography	4.0
Computed tomography		
	Abdomen	6.8
	Chest	7.0
	Chest for pulmonary embolism	15.0
	Abdomen-chest	15.3
	Head	1.7
	Neck	3.0
	Pelvis	7.4
	Abdomen and pelvis	10.0
	Cervical spine	7.0
	Trunk	12.3
	Skull	2.0
	Lumbar spine	6.0
	Thoracic spine	7.0
Interventional radiology		
	Head and/or neck angiography	5.0
	Coronary angiography (diagnostic)	7.0
	Coronary percutaneous transluminal angioplasty, stent placement, or radiofrequency ablation	15.0
	Thoracic angiography of pulmonary artery or aorta	5.0

	Abdominal angiography or aortography	12.0

Table S2. Imaging tests included and doses used per examination (mSv) (children).

Tests	Anatomical sites	<1 year old	>1-5 years old	>5-10 years old	>10-15 years old
Plain radiography					
	Abdomen	0.07	0.09	0.15	0.27
	Cervical spine	0.02	0.03	0.05	0.10
	Chest/Thorax	0.05	0.05	0.05	0.06
	Lumbar spine	0.4	0.5	0.6	0.8
	Pelvis/Hip	0.08	0.10	0.15	0.21
	Thoracic spine	0.39	0.41	0.77	1.18
Fluoroscopy					
	Hysterosalpingography				
	Urography	0.5	0.5	0.7	1.0
	Ba enema	2.3	2.3	2.3	2.3
	Ba meal	0.7	0.6	0.9	1.0
	Ba follow-through	1.2	1.2	1.2	1.2
Computed tomography					
	Abdomen	7.9	7.9	7.9	7.9
	Chest	3.9	2.8	4.2	6.8
	Head	1.7	1.6	1.8	1.6
	Pelvis	7.9	7.9	7.9	7.9
	Trunk	3.9	3.0	5.6	8.3

Table S3. Cumulative effective dose (mSv) per person exposed during the period of study (plain radiography).

Age at entry to study (years)	Total			Men			Women			p-valor
	Median	Percentil 25-75	Maximum	Median	Percentil 25-75	Maximum	Median	Percentil 25-75	Maximum	
0-5	0.20	0.06-1.01	47.14	0.20	0.06-0.90	26.34	0.20	0.06-1.16	47.14	0.453
5-10	0.39	0.04-1.42	24.90	0.38	0.04-1.30	24.90	0.40	0.02-1.53	23.40	0.456
10-15	0.64	0.10-1.28	14.64	0.64	0.10-1.28	14.64	0.64	0.10-1.38	13.14	0.097
15-20	0.64	0.20-1.28	23.26	0.64	0.12-1.28	14.96	0.64	0.30-1.38	23.26	0.043
20-30	0.64	0.38-1.88	30.01	0.64	0.20-1.34	22.51	0.64	0.46-1.92	30.01	<0.001
30-40	0.74	0.48-2.08	46.73	0.64	0.26-1.58	36.48	0.64	0.64-2.86	46.73	<0.001
40-50	1.02	0.64-2.16	716.15	0.64	0.48-1.92	26.39	1.28	0.64-2.56	716.15	<0.001
50-60	1.28	0.64-2.54	54.27	0.94	0.64-1.92	41.31	1.28	0.64-2.56	54.27	<0.001
60-70	1.28	0.64-2.68	51.02	1.28	0.64-2.56	44.78	1.28	0.64-3.20	51.02	<0.001
70-80	1.28	0.64-3.10	2112.79	1.28	0.64-2.56	27.22	1.32	0.64-3.20	2112.79	<0.001
>80	1.28	0.64-2.66	33.34	1.28	0.64-2.56	19.97	1.28	0.64-3.08	33.34	<0.001
Total	**0.70**	**0.30-2.00**	**2112.79**	**0.64**	**0.20-1.90**	**44.78**	**1.02**	**0.40-2.56**	**2112.79**	**<0.001**

Table S4. Cumulative effective dose (mSv) per person exposed during the period of study (CT).

Age at entry to study (years)	Total			Men			Women			p-valor
	Median	Percentil 25-75	Maximum	Median	Percentil 25-75	Maximum	Median	Percentil 25-75	Maximum	
0-5	3.80	1.90-7.70	50.20	3.80	1.90-9.70	50.20	2.00	1.90-7.30	32.10	0.834
5-10	3.90	1.90-9.70	93.00	4.00	1.90-9.70	93.00	3.80	1.90-9.70	74.40	0.414
10-15	5.90	1.90-13.20	195.40	6.60	1.90-13.20	195.40	4.50	1.90-14.60	156.80	0.239
15-20	5.80	1.90-19.35	316.40	6.60	1.90-17.00	316.40	5.00	1.90-22.60	165.00	0.146
20-30	7.70	1.90-22.60	414.40	8.80	1.90-22.60	345.60	7.60	1.90-22.60	414.40	0.004
30-40	9.70	1.90-22.60	558.30	9.70	3.80-22.60	558.30	9.70	1.90-22.60	458.60	0.439
40-50	17.90	5.00-35.30	710.80	18.60	6.60-38.90	710.80	15.00	5.00-33.90	703.30	0.003
50-60	22.60	6.60-45.90	1083.10	22.60	7.30-54.55	1083.10	19.80	6.60-41.20	732.40	<0.001
60-70	22.60	5.70-54.40	891.40	24.50	7.70-67.10	754.20	22.40	5.70-45.20	891.40	<0.001
70-80	22.60	3.80-45.20	1419.30	22.60	7.30-53.70	957.50	17.35	3.80-39.60	1419.30	<0.001
>80	13.20	3.80-28.30	393.00	19.10	3.80-33.45	316.60	10.40	3.80-26.40	393.00	<0.001
Total	**16.30**	**3.80-35.90**	**1419.30**	**19.80**	**5.70-43.50**	**1083.10**	**13.20**	**3.80-31.80**	**1419.30**	**<0.001**

STROBE Statement—checklist of items that should be included in reports of observational studies

		Item No	Recommendation
YES Pages 1 and 3	**Title and abstract**	**1**	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
	Introduction		
YES Pages 5-6	Background/rationale	**2**	Explain the scientific background and rationale for the investigation being reported
YES Page 6	Objectives	**3**	State specific objectives, including any prespecified hypotheses
	Methods		
YES Page 7	Study design	**4**	Present key elements of study design early in the paper
YES Page 7	Setting	**5**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
YES page 7	Participants	**6**	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
YES Pages 7-8	Variables	**7**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
YES Pages 7-8	Data sources/ measurement	**8***	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
YES Page 8	Bias	**9**	Describe any efforts to address potential sources of bias
NA	Study size	**10**	Explain how the study size was arrived at
YES Page 8	Quantitative variables	**11**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
YES Page 8	Statistical methods	**12**	(*a*) Describe all statistical methods, including those used to control for confounding
			(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses

Continued on next page

	Results		
YES Page 9	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
YES Page 9	Descriptive data	**14***	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
			(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
YES Page 9-11	Outcome data	**15***	*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
			Cross-sectional study—Report numbers of outcome events or summary measures
YES Page 9-11	Main results	**16**	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
NA	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
	Discussion		
YES Page 12	Key results	**18**	Summarise key results with reference to study objectives
YES Page 14	Limitations	**19**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
YES Pages 12-13	Interpretation	**20**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
YES Page 15	Generalisability	**21**	Discuss the generalisability (external validity) of the study results
	Other information		
NA	Funding	**22**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.