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Increased Frequency of Chromosome Translocations Associated with Diagnostic X-Ray Examinations

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Abstract

Informative studies of cancer risks associated with medical radiation are difficult to conduct owing to low radiation doses, poor recall of diagnostic X rays, and long intervals before cancers occur. Chromosome aberrations have been associated with increased cancer risk and translocations are a known radiation biomarker. Seventy-nine U.S. radiologic technologists were selected for blood collection, and translocations were enumerated by whole chromosome painting. We developed a dose score to the red bone marrow for medical radiation exposure from X-ray examinations reported by the technologists that they received as patients. Using Poisson regression, we analyzed translocations in relation to the dose scores. Each dose score unit approximated 1 mGy. The estimated mean cumulative red bone marrow radiation dose score was 42 (range 1–265). After adjustment for age, occupational radiation, and radiotherapy for benign conditions, translocation frequencies significantly increased with increasing red bone marrow dose score with an estimate of 0.007 translocations per 100 CEs per score unit (95% CI, 0.002 to 0.013; $P = 0.01$). Chromosome damage has been linked with elevated cancer risk, and we found that cumulative radiation exposure from medical X-ray examinations was associated with increased numbers of chromosome translocations.

INTRODUCTION

Structural chromosome aberrations, specifically translocations enumerated using whole chromosome paints by fluorescence *in situ* hybridization (FISH) in peripheral blood lymphocytes, have been used extensively as biodosimeters of past radiation exposure (1–8). Cytogenetic damage is caused by radiation exposure, and chromosome aberrations have been associated with increased cancer risk (9,10). Some studies have found increased chromosome abnormalities immediately after radiation exposure from CT scanning (11) or in patients with unusually high numbers of diagnostic procedures (12).

Typical radiation doses to patients from routine diagnostic X-ray procedures have diminished over time; however, there has been a rapid increase in the use of new procedures that confer much higher doses, such as helical and multi-slice CT scanning (13–15). Estimated dose to the lungs from a typical full-body CT scan was approximately 15 mGy (16) and from a 64-slice

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CT for coronary angiography was between 42 and 91 mSv (14). The number of CT scans performed in the U.S. has increased from 18.3 million in 1993 to 62 million in 2006 (17), and concern about the long-term cancer risks associated with medical radiation has widened (13, 14,16,18,19). To our knowledge, studies to detect chromosome damage from long-term cumulative modest radiation doses (under 300 mGy) from medical radiographic examinations have not been attempted in the general public because the doses were previously considered too low and inaccuracies in self-reported X-ray procedure histories were likely (15).

To determine whether chromosome damage was associated with self-reports of routine and specialized diagnostic X-ray procedures, we evaluated the relationship between chromosome translocation frequency (as measured by FISH whole chromosome painting) and cumulative lifetime red bone marrow radiation dose scores from diagnostic X-ray procedures that 79 radiologic technologists received as patients. While the benefit of radiation in disease diagnosis and patient treatment is undisputed, findings of increased chromosomal damage associated with diagnostic X-ray examinations may indicate increased health risks such as cancer and would argue against non-essential use of diagnostic X-ray examinations.

MATERIALS AND METHODS

Study Population

In 1982, the National Cancer Institute, in collaboration with the University of Minnesota and the American Registry of Radiologic Technologists, initiated a study of cancer incidence and mortality among 146,022 U.S. radiologic technologists (USRT) who were certified for at least 2 years between 1926 and 1982. This study has been approved annually by the human subjects review boards of the National Cancer Institute and the University of Minnesota. In brief, during 1984–1989, 1994–1998 and 2003–2005, postal surveys were conducted that included questions related to several health outcomes, work history, cancer risk factors, and history of diagnostic X-ray procedures [for questionnaires, see http://www.radtechstudy.org/; for participation details, see Sigurdson *et al.* (20)]. To date, 110,418 technologists have responded to one or more surveys.

Subject selection and recruitment for the biodosimetry study were based on electronic film badge dose records that were obtained from a nationwide dosimetry provider and spanned the years 1977 to 1984. A sample of 200 living technologists with high (over 350 mGy) recorded badge doses were randomly selected and approached for participation. Another 130 technologists with low recorded badge doses (10 mGy or less) who worked for 1 year or less were also randomly sampled. Subjects underwent a brief screening telephone interview to confirm and update their work history information and to exclude subjects with a previous cancer diagnosis or who had undergone radiation therapy for malignancy. Those selected for the low-dose group were additionally excluded if they had worked in a radiation therapy department, had worked in another occupation with radiation exposure, or had worked more than 10 years as a technologist. Recruitment goals were approximately 65–70 technologists in the high-dose group and 20–25 in the low-dose group until 90 technologists were successfully recruited and were based on considerations given from similar studies being conducted among radiation-exposed workers (8). Ultimately 62 “high” and 28 “low” dose individuals provided a venipuncture blood sample. Collection kits were mailed to each consenting technologist and peripheral whole blood was drawn by their health care provider. The blood tubes were shipped overnight with an ice pack to the cytogenetics laboratory.

FISH Assay for Chromosome Aberrations

Laboratory personnel determined the frequency of translocations using FISH whole chromosome painting without knowledge of ionizing radiation exposure of the technologists.

Cell cultures were initiated on blood collected in heparinized vacutainer tubes within 24 h of phlebotomy and were processed according to routine cytogenetic methods (21). The slide preparation, staining and cell scoring were performed using standardized chromosome painting protocols (21,22). All translocations, reciprocal or non-reciprocal, were counted as single translocations. Because standard practice is to apply whole chromosome paints to a portion of the genome (single-color painting of chromosomes 1, 2 and 4), the number of meta-phases counted was converted to whole genome equivalents and is defined as cell equivalents (CEs), as if the full genome had been scored. The average number of CEs per person used for analysis was 432 (range 100 to 1108).

Occupational Radiation Exposure

The occupational dosimetry system used to estimate absorbed dose to the red bone marrow has been described in detail elsewhere (23), with some significant refinements (1) introduced for this work. The dose reconstruction methods involved first estimating annual badge doses for individuals with missing data, then estimating red bone marrow doses on the basis of measured or predicted badge readings. The input data included 350,000 cohort member film-badge measurements from a commercial dosimetry provider, 20,000 annual badge readings from military dose registries, 2,800 dose records provided by employers, and 125 cohort records from Massachusetts General Hospital, individual work history and protection practices from three cohort surveys, and measurement and other data derived from the literature.

The present version of the dosimetry system incorporates new dose factors (i.e., Gy to red bone marrow per Sv of badge dose) that reflect temporal changes in X-ray machine tube potentials and filtration, more reliable estimates of photon transmission through protective aprons and shields, more precise estimates of individual-specific apron use during the years worked, and substantially greater number of occupational radiation monitoring badge readings from cohort members in the period before 1977. To derive a cumulative occupational red bone marrow dose for each person, we summed their derived arithmetic mean doses from each year they worked. The occupational radiation doses are shown in summary form in Table 1.

Medical Diagnostic Exposure

We used self-reported information about medical diagnostic X-ray procedures that technologists received as patients from the first and second cohort surveys to assign weighted red bone marrow dose scores. The doses associated with specific radiographic procedures were assigned midpoint red bone marrow dose values from a comprehensive list of examination types (24). We used the midpoint doses and, as appropriate, the frequencies to weight the dose scores for the types of radiographic procedures reported by the technologists on the first and second surveys (see Table 2 and footnotes), multiplied the number of examinations by the corresponding dose, and then summed the doses over all procedures to estimate the total cumulative medical diagnostic X-ray red bone marrow dose score. While one dose score unit is approximately 1 mGy, because of the uncertainties in recall of various procedures and uncertainties of the direct application of dose estimates per procedure, we prefer the term “cumulative medical diagnostic red bone marrow radiation dose score” rather than dose. Dose scores ranged from 0.05 for a chest X ray to 12.7 for a coronary angiogram.

We excluded 11 of the 90 subjects because a cumulative red bone marrow radiation dose score at the time of blood collection could not be calculated for them. These 11 individuals did not complete the second survey that contained additional information on medical diagnostic X-ray examinations and other covariates such as cigarette smoking and therapeutic radiologic procedures. Therefore, the final sample size for the present study was 79 radiologic technologists, with 53 from the high-dose and 26 from the low-dose groups.

To assess the reproducibility of recall of medical diagnostic procedures by cohort members, we compared self-reports from 354 radiologic technologists who completed the same questionnaire twice during a 4-year period. The distribution by age, gender, race and selected work history characteristics was similar for these technologists when compared with the full study cohort. We evaluated the number of reported procedures and the decade they first occurred for the following common or high-dose examinations: upper gastrointestinal series, angiography, CT scans, mammography (among women age 50 or older), and chest X rays.

Medical Therapeutic Radiation Exposure

We included an indicator variable in the statistical model for having therapeutic irradiation for benign conditions (ever/never). Information on personal history of therapeutic irradiation to the head and neck, pelvis, extremities and chest was available from the first survey or baseline questionnaire. The majority of adult bone marrow is located in the pelvis, torso and head (25), so we excluded radiation to extremities since it would not contribute substantially to the red bone marrow dose.

Statistical Analysis

We used the AMFIT module of EPICURE (HiroSoft, Seattle, WA) to construct linear Poisson regression models for associations between cumulative medical diagnostic X-ray red bone marrow dose score and translocation frequency. The models were of the following general form:

$$\lambda(a, d)=\lambda_0(a)+\beta d,$$

where λ is the expected number of translocations per cell, *a* represents covariates affecting translocation frequency, *d* is the medical diagnostic X-ray red bone marrow dose, $\lambda_0(a)$ is the covariate specific background number of translocations per cell, and β is the increase in translocations per cell per unit dose score. A Pearson scale factor was added to the models to account for overdispersion of the data.

Age at blood drawing, occupational radiation dose, prior X-ray therapy, and history of radioisotope therapy were included as covariates in the multivariate model. Gender, race, cigarette smoking, past history of allowing others to take practice X rays, and working with radioisotopes were assessed as potential confounders but did not change parameter β by 10% or more and were not included in the final model.

RESULTS

Descriptive features of the study population are shown in Table 1. Technologists ranged in age from 34 to 76 years at blood drawing, were predominately female (65%), were former or current cigarette smokers (59%), and worked an average of 21 (range 1 to 45) years before blood collection. Work history characteristics included a past history of allowing others to take practice X rays during training (9%), holding patients for X-ray procedures (75%), and working with radioisotopes (27%). Sixteen percent reported having had a therapeutic radioisotope procedure performed on them, and 10% reported having X-ray therapy for benign conditions to the pelvis, torso or head, adult body sites with the most red bone marrow.

Mean translocation levels by categories of covariates and age-adjusted translocation rate ratios comparing categories of these covariates are also presented in Table 1. History of X-ray therapy for benign conditions was associated with an increased frequency of translocations, and there was a statistically significant increased trend of translocation frequencies with increasing medical diagnostic red bone marrow dose score (*P* trend 0.005).

Study technologists had an average of 1.6 translocations/100 CEs (median 1.3, range 0–4.4), a mean occupational red bone marrow dose of 7 mGy (median 4, range 0.0–30 mGy), and a mean cumulative medical diagnostic red bone marrow radiation dose score of 42 (median 26, range 1.0–265). The three procedures that most contributed to the collective medical diagnostic red bone marrow dose score among study participants were barium enemas (19%), upper gastrointestinal series (16%), and unspecified CT scans (10%) (see Table 2). Cumulative medical diagnostic red bone marrow radiation dose score was correlated with occupational red bone marrow dose ($r = 0.38$, $P < 0.001$).

Translocation frequencies plotted as a function of diagnostic red bone marrow radiation dose score are shown in Fig. 1 with the superimposed univariate dose–response trend line. In univariate analysis, a one unit increase in medical radiographic radiation dose score was associated with an increase of 0.013 excess translocations/100 CEs per unit red bone marrow radiation dose score ($P < 0.001$). After adjustment for age at blood drawing, occupational radiation dose, and radiotherapy for benign conditions, this association was reduced to 0.007 excess translocations/100 CEs per unit red bone marrow radiation dose score (95% CI 0.001–0.013, $P = 0.01$) Occupational radiation dose was marginally significantly associated with an increase in translocation frequencies, with an adjusted point estimate of 0.03 excess translocations/100 CEs per mGy (95% CI −0.007–0.07, $P = 0.1$).

We reanalyzed the data first excluding the eight participants that reported receiving X-ray therapy for benign conditions and then again after excluding the 13 participants that reported receiving therapeutic radioisotope procedures. In both cases, the point estimate changed slightly and remained statistically significant (0.008 excess translocations/100 CEs per unit red bone marrow radiation dose score, $P = 0.01$ and 0.009 excess translocations/100 CEs per unit red bone marrow radiation dose score, $P = 0.02$, respectively). We also reanalyzed the data excluding 22 individuals who had less than 300 CEs evaluated because scoring additional cells usually results in more stable estimates of translocation frequency. The multivariate dose response was slightly reduced to 0.005 excess translocations/100 CEs per unit red bone marrow radiation dose score ($P = 0.12$).

Consistency in reporting the numbers of medical diagnostic procedures ranged from agreement of 51% for chest X rays (within two) to 100% for angiography. If the criteria for chest X-ray agreement were relaxed (within five), the agreement reached 92%. Complete agreement for the number of mammograms was 68%. Agreement for decade in which the reported procedure first occurred ranged from 79% for upper gastrointestinal series to 86% for angiography. Agreement percentages for decade of first chest X ray and first mammogram were 84% and 81%, respectively.

DISCUSSION

Among radiologic technologists we found a statistically significant increase in translocation frequency ($P = 0.01$) with increasing cumulative medical diagnostic red bone marrow radiation dose score after adjustment for age at blood drawing, occupational radiation dose, and radiotherapy for benign conditions. The same magnitude of the association was still observed after excluding several individuals with less than 300 CEs evaluated. Although the smaller sample size caused a loss in power, the similar magnitude suggested that the estimate was relatively insensitive to these exclusions.

Our analysis of the reproducibility of self-reporting among 354 technologists who completed the same questionnaire twice within a 4-year period showed an overall 80% agreement, suggesting radiologic technologists are consistent in their recall of the number of past diagnostic procedures (78% agreement) and the time they first occurred (83% agreement).

Because the technologists did not know their translocation frequencies, any recall error should be non-differential and would probably attenuate relationships observed, not introduce them.

In studies of high-energy γ rays, the expected frequency of excess translocations/100 CEs per mGy is 0.0015 (26). The distribution of photon energies applicable to the present study was X rays of approximately 100 keV or less. For dicentrics, the unstable counterpart of translocations, the linear term for X rays of 50–100 keV is about two to three times higher than that for high-energy γ rays (27). So, for the relevant energies from diagnostic X rays, an estimated frequency of 0.005 excess translocations/100 CE per mGy is reasonable. Assuming one unit of the exposure score approximated 1 mGy, the observed association of 0.007 excess translocations/100 CE per unit diagnostic red bone marrow radiation dose score (95% CI, 0.001–0.013) was consistent with this estimate and generally similar to the occupational red bone marrow estimate of 0.009 excess translocations/100 CEs per mGy (95% CI −0.001–0.02, $P = 0.07$) reported previously (1), lending further support to our findings.

In the present study, we observed a marginally significant association between occupational doses and translocation frequency, generally supporting our reconstruction of past occupational radiation exposure. The point estimate (0.03 excess translocations/100 CEs per mGy, 95% CI −0.007–0.07) was an order of magnitude higher than expected but was within the bounds of possible values considering uncertainty in the dose assignments.

At the time the FISH laboratory work was performed, an average of 432 CEs per person constituted a substantial number of analyzed cells. This number may be considered small compared to those achievable by more modern, automated analyses (1000 CEs) (1), but this should not bias our results, because counting a greater number of cells would serve to increase the sensitivity of the analysis to detect lower radiation doses rather than change the proportion of cells with translocations. Nonetheless, we were able to detect a relatively robust relationship with the generally low levels of cumulative red bone marrow radiation exposure from medical diagnostic procedures, possibly because we minimized confounding by adjusting for several other variables in the model. Alternatively, it may be that the radiation doses were actually higher because the radiologic technologists under-reported X-ray examinations (28,29), low-quality images had to be repeated and were under-counted, or realistic working conditions in radiology practice resulted in higher patient doses (30). While the absolute numbers may not be known precisely, we still detected evidence of cytogenetic damage associated with diagnostic X-ray examinations. Cytogenetic damage is concerning because increased frequencies of chromosome aberrations have been associated with elevated cancer risk (9, 10).

Reports of individuals who had many diagnostic X-ray examinations resulting in high cumulative doses, such as tuberculosis patients who underwent multiple chest fluoroscopies (0.5 to 1.0 Gy to the targeted body sites) (31,32) and scoliosis patients who had frequent diagnostic X-ray examinations in adolescence (33), have been informative (15,34). However, these studies do not address the potential risks of routine diagnostic X-ray exposures that individuals undergo over their lifetime that would result in cumulative doses considerably lower than 0.5 Gy.

We are unaware of truly comparable studies in the published literature. We found that radiation from routine X-ray examinations among radiologic technologists was associated with increased chromosome damage, which is thought to be related to elevated cancer risk. These findings underscore the potential future contribution of this cohort for understanding cancer risks associated with radiographic procedures. The enormous benefit of radiation in disease diagnosis and patient treatment is undisputed, but it is important to be mindful that potential

long-term chromosome damage and other health risks such as cancer argue against nonessential use or unnecessary repeats of diagnostic X-ray examinations.

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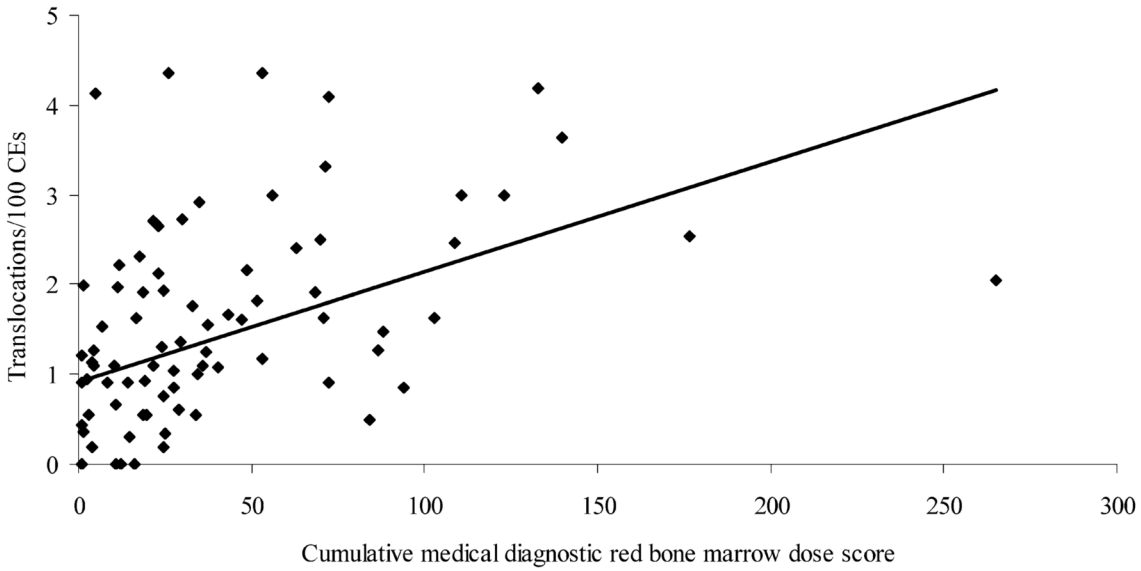

FIG. 1.

Translocation frequency as a function of the cumulative diagnostic red bone marrow radiation dose score among 79 U.S. radiologic technologists. The trend line is from univariate Poisson regression analysis [0.013 translocations/100 cell equivalents (CEs)/red bone marrow dose score].

TABLE 1

Distribution of Covariates among Biodosimetry Study Subjects and Mean Translocation Frequencies by Covariate Categories, U.S. Radiologic Technologists Study, 1994–1995

Characteristic	Subjects n = 79 (%)[a]	Mean number of translocations/100 cell equivalents	Translocation rate ratios (95% CI)[b]
Age at blood collection (years)			
<45	11 (14)	0.8	0.7[c] (0.4, 1.1)
45–54	27 (34)	1.2	1.0
55–64	21 (27)	1.9	1.5 (1.0, 2.1)
≥65	20 (25)	2.3	2.0 (1.5, 2.8)
Gender			
Female	51 (65)	1.5	1.0
Male	28 (35)	1.7	1.2 (0.9, 1.6)
Smoking status			
Never	31 (39)	1.8	1.0
Former	27 (34)	1.8	1.1 (0.8, 1.5)
Current	20 (25)	1.1	0.8 (0.6, 1.2)
Unknown	1 (1)	N/A	N/A
Years worked before blood drawing			
≤10	22 (28)	1.5	1.0
11–20	26 (33)	1.2	0.9 (0.7, 1.4)
21–30	20 (25)	2.2	1.4 (1.0, 2.0)
≥30	22 (28)	1.6	0.8 (0.6, 1.2)
Ever allowed others to take practice X rays			
No	62 (78)	1.6	1.0
Yes	7 (9)	1.9	1.2 (0.7, 1.5)
Unknown	10 (13)	1.5	0.6 (0.4, 1.0)
Ever held patients			
No	14 (18)	1.5	0.7 (0.5, 1.1)
Yes	59 (75)	1.6	1.0
Unknown	6 (8)	1.5	0.7 (0.4, 1.1)
Ever worked with radioisotopes			
No	55 (70)	1.6	1.0
Yes	21 (27)	1.6	0.9 (0.7, 1.2)
Unknown	3 (4)	1.5	0.9 (0.5, 1.8)
Ever had therapeutic radioisotope procedure			
No	53 (67)	1.6	1.0
Yes	13 (16)	1.8	1.1 (0.8, 1.6)
Unknown	13 (16)	1.5	0.7 (0.5, 1.1)
Ever had X-ray therapy			
No	71 (90)	1.5	1.0
Yes	8 (10)	2.3	1.6 (1.1, 2.2)
Estimated occupational red bone marrow radiation dose			
≤5 mGy	45 (57)	1.3	1.0[d]
>5–10 mGy	11 (14)	1.5	1.0 (0.6, 1.5)
>10–20 mGy	15 (19)	2.4	1.3 (0.9, 1.8)
>20 mGy	8 (10)	1.9	1.1 (0.7, 1.9)
Estimated medical diagnostic red bone marrow dose score[e]			
≤10	15 (19)	1.1	1.0[d]
>10–20	15 (19)	1.0	0.8 (0.5, 1.3)
>20–40	22 (28)	1.6	1.3 (0.8, 2.0)
>40	27 (34)	2.2	1.4 (0.9, 2.2)

[a] May not always sum to 100% due to rounding.

[b] Poisson regression adjusted for age.

[c] Age at blood collection P trend < 0.001; age categories treated as continuous variable in Poisson regression.

[d] Estimated occupational red bone marrow dose P trend = 0.3; estimated medical diagnostic red bone marrow dose score P trend = 0.005; dose (dose score) categories treated as continuous variables in age-adjusted Poisson regression.

[e] One unit is approximately 1 mGy.

TABLE 2

Estimated Red Bone Marrow Radiation Doses for Medical Diagnostic X-Ray Procedures Reported by Technologists and the Corresponding Weighted RBM Radiation Dose Score, U.S. Radiologic Technologists Study

Diagnostic procedures reported by radiologic technologists on the first and second survey or second survey only	Red bone marrow dose[a] score[b] assigned to each procedure	Number of procedures reported (n = 3591)	Percentage contribution to collective dose among study group[c]
Abdomen X ray	0.4	161	2.00
Cervical spine X ray	0.1	133	0.41
Chest X ray	0.05	1396	2.17
Coccyx X ray	2	1	0.06
Collar bone X ray	0.6	56	1.05
Kidneys/ureters/bladder X ray	0.5	192	2.99
Lumbar spine X ray	1.5	145	6.77
Lumbosacral spine X ray	1.1	108	3.70
Other head and neck X ray	0.1	79	0.25
Pelvis X ray	0.4	51	0.63
Ribs X ray	0.4	48	0.60
Shoulder X ray	0.06	125	0.23
Skull X ray	0.5	102	1.59
Thoracic spine X ray	0.7	66	1.44
Upper gastrointestinal series	3.6	139	15.57
Mammogram of the breast	0.07	358	0.78
Barium enema	6.3	96	18.82
Barium swallow	3.6	50	5.60
Cholangiogram/cholecystogram	2	55	3.42
Coronary angiogram	12.7	20	7.91
Cystography	1.7	10	0.53
Hysterosalpinogram	2	1	0.06
Myelogram	3.7	10	1.15
Renal arteriogram	2.1	1	0.07
Retrograde pyelogram	2.2	85	5.82
Urethrogram	2.6	9	0.73
Shoulder arthrogram	3.3	2	0.21
Head and neck CT scan	3	2	0.19
Liver CT scan	5.5	1	0.17
Fluoroscopic or multi-film procedure, other than above	3.6[d]	45	5.04
Unspecified CT scan	7.5[d]	43	10.04

[a] From ref. (24) and is an approximation of mGy.

[b] Because of the uncertainties in recall of various procedures and the application of uncertain radiation doses per procedure, we prefer using the term “medical diagnostic red bone marrow radiation dose score” rather than standard dose units.

[c] For each procedure calculated as the product of the red bone marrow dose score and number of procedures reported divided by the sum of this product across all procedures.

[d] Determined by weighting each examination dose in ref. (24) by the frequency with which the examination type occurred in their study population and is an approximation of mGy.