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Measurement of chromosome translocations in peripheral blood lymphocytes has been used to quantify prior exposure to ionizing radiation, including for workers exposed to low, chronic doses. We assessed translocation frequencies in a subset of U.S. radiologic technologists to substantiate ionizing radiation dose estimates developed for 110,418 technologists who worked between 1916 and 1984. From 3,441 cohort members known to have begun working before 1950, we selected a sample of 152, stratified by estimated cumulative dose, oversampling from higher-dose categories and excluding persons with a prior cancer diagnosis, a personal or family history of chromosomal instability disorders, or a current history of smoking. Estimates of film-badge dose ranged from less than 10 cSv to more than 30 cSv. Blood samples, obtained in 2004, were analyzed by fluorescence *in situ* hybridization (FISH) whole chromosome painting by simultaneously labeling chromosomes 1, 2 and 4 in red and 3, 5 and 6 in green. Translocations were scored in 1800 well-spread metaphase cells and expressed per 100 cell equivalents (CE) per person. Linear Poisson regression models with allowance for overdispersion were used to assess the relationship between estimated occupational red bone marrow absorbed dose in cGy and translocation frequency, adjusted for age, gender and estimated red bone marrow absorbed dose score from personal diagnostic procedures. We observed 0.09 excess translocations per 100 CE per cGy red bone marrow dose (95% CI: −0.01, 0.2; $P = 0.07$), which is similar to the expected estimate based on previous cytogenetic studies (0.05 excess translocations per 100 CE per cGy). Despite uncertainty in the estimates of occupational red bone marrow absorbed doses, we found good general agreement between the doses and translocation frequencies, lending support to the credibility of the dose assessment for this large cohort of U.S. radiologic technologists.

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INTRODUCTION

Ionizing radiation exposures that occurred in the distant past as a single dose or as multiple fractionated whole- or partial-body doses have been estimated by measuring chromosome translocations (*1–7*). Translocations can be detected in peripheral blood lymphocytes by established methods using fluorescence *in situ* hybridization (FISH) with whole chromosome paints.

Translocation frequencies have been used to assess exposure in occupational settings where chronic low-dose ionizing radiation exposures were common (*8–13*). We undertook a cross-sectional study of translocation frequencies among members of a large cohort of U.S. radiologic technologists (USRT) to substantiate ionizing radiation dose estimates for individual cohort members who worked between 1916 and 1984 (*14*). Those years spanned periods when film-badge monitoring was uncommon and then became routine. Historical dosimetry records were therefore incomplete for many technologists, especially those who worked in the early years. Dose reconstruction relied on several sources of data, including published occupational radiation measurement data before 1950, hospital dosimetry badge surveys during 1950–1959, limited cohort-specific badge records for 1960–1976, extensive cohort badge records for 1977–1984, and employment information for all periods provided by technologists on three study surveys. Because of the lack of cohort monitoring data before 1960, we sought to corroborate our dose estimates by obtaining

individual biological measurements of the frequency of chromosome translocations.

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 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. During 1984–1989, 90,305 (68%) of the 132,454 presumed living radiologic technologists completed a baseline postal survey, and in 1995–1998, 90,972 (72%) of the 126,628 presumed living radiologic technologists completed a second survey (*15*). The surveys included questions related to work history as a radiologic technologist, family history of cancer, reproductive history, height, weight, other cancer risk factors (such as alcohol and tobacco use), and personal health outcomes. A third survey conducted during 2004–2005 collected more detailed work history data and updated health outcomes. To date, 110,418 technologists have responded to at least one of the surveys.

Subjects sampled for the biodosimetry study were selected from among a core group of 3441 cohort members who were known to have started working as technologists prior to 1950 and who were believed to be alive with a known address at the time of sample selection in 2003. To ensure a wide range of doses, we partitioned subjects into groups that were likely to have had high, moderate and low doses of ionizing radiation to the red bone marrow, which was the dose relevant to this study. At the time of recruitment, we used a combination of our estimates of badge doses and work history information to define these groups. Subjects were approached randomly for participation until the targeted quota for each dose group was satisfied. Subjects were excluded if they had a prior cancer diagnosis, a personal or familial history of chromosomal instability disorders (such as Bloom's syndrome or Fanconi's anemia), or reported currently smoking 10 or more cigarettes per day.

One hundred twenty subjects were identified as part of the high-dose group. This group included 104 individuals who had an estimated total cumulative badge dose in excess of 30 cSv, indicated that they had not worn a protective apron during their initial years of employment, had worked for at least 2 full years in the 1940s, or worked for at least 15 years in total and 16 individuals who reported either having exceeded an occupational exposure limit or having had a low white blood cell count attributed to occupational exposures. Among those defined as part of the high-dose group, the recruitment goal was 70 subjects; 69 were recruited. The high-dose group was augmented with the random selection and serial recruitment of 45 people with badge dose estimates greater than 20 cSv who reported that they worked 2 or more years in the 1940s or that they did not wear an apron and that they performed mostly fluoroscopic or radioisotope procedures. The moderate-dose group included 43 people who had total cumulative estimated badge doses between 10 and 19 cSv and did not wear an apron when they first worked. The recruitment goal for the moderate dose group was 15 subjects; 25 were recruited. The low-dose group represented 79 people with cumulative badge doses of 10 cSv or less and who worked between zero and 10 years. The low-dose recruitment goal was 20 individuals; 20 subjects were recruited. Of the 207 subjects approached for participation, 159 persons (77%) were successfully recruited and 48 (33%) did not agree to participate.

Each successfully recruited subject provided a venipuncture blood sample and completed a telephone survey about personal history of diagnostic and therapeutic radiologic procedures. In-home blood samples were collected using a nationwide phlebotomy service and were shipped overnight to the cytogenetics laboratory. The final sample size included 152 individuals because five samples did not grow in cell culture and two samples were unusable because of delays in shipment.

FISH Whole Chromosome Painting Assay for Chromosomal Aberrations

Laboratory personnel determined the frequency of translocations using FISH whole chromosome painting without knowledge of the exposure category of the study subjects. Cell cultures were initiated on blood samples within 24 h of blood drawing and were processed in accordance with routine cytogenetic methods (*16*). The slide preparation, staining and cell scoring were performed using standardized FISH protocols (*16, 17*).

In brief, whole blood was added to RPMI 1640 culture medium supplemented with 15% fetal bovine serum, 2 m*M* L-glutamine, penicillin/streptomycin (final concentration 100 U and 100 μg/ml, respectively), and 1% heparin and stimulated with 1% phytohemagglutinin. Cultures were incubated at 37°C in a 95% air/5% CO_2 environment for 52 h, the last 4 h with 0.1 μg/ml Colcemid to block mitosis (*16*). The cells were harvested by swelling in a hypotonic solution (0.075 *M* KCl) after centrifugation and fixed a minimum of three times with 3.1 (v/v) methanol: glacial acetic acid. The fixed cells were then dropped onto slides, taking care to minimize the presence of cytoplasm. After drying in air, the slides were stored at −20°C in sealed plastic bags in the presence of a desiccant and an N_2 atmosphere until needed for hybridization.

Chromosomes 1, 2 and 4 were painted red and chromosomes 3, 5 and 6 were painted simultaneously in green by using probes purchased from Cytocell Technologies, Ltd. (Cambridge, UK). The slides were then counterstained with 4,6-diamidino-2-phenylindole (DAPI), mounted in an antifade solution (*18*), and stored at 4°C until they were scored. This combination of paints detects 56% of all the chromosome exchanges (*19, 20*).

All cells were visualized using a fluorescence microscope with a triple band pass filter, which allowed simultaneous viewing of the labeled and DAPI-counterstained chromosomes. Only well-spread metaphase cells that met the following criteria were scored: (1) The cells appeared to be intact; (2) the centromeres of all chromosomes were readily visible; (3) the centromeres from all six painted chromosome pairs were present; and (4) the fluorescent labels were sufficiently bright along the entire length of each chromosome to detect exchanges between chromosomes labeled in different colors. Digital photographs of all abnormal cells were obtained. All chromosome aberrations (translocations, insertions, dicentrics and rings) were initially classified according to the Protocol for Aberration Identification and Nomenclature Terminology (PAINT) (*21*). Subsequently all translocations, reciprocal or non-reciprocal, were counted as single translocations based on the premise that most non-reciprocal translocations are reciprocal at the molecular level for low doses or low dose rates. For each study subject, the electronic images of all cells with translocations were evaluated to determine whether any of the cells were clones. A minimum of three cells with the same translocation were needed to qualify as a clone. Seventeen of the 152 subjects had clones, ranging in size from 0.2 to 3.5% of the total cell equivalents. Clonal cells were considered as a single translocation event. A total of approximately 1,800 metaphase cells were evaluated per subject, and this was equivalent to $1{,}800 \times 0.56 = 1{,}000$ metaphase cells as if the full genome had been scored [defined as cell equivalents (CE)].

Occupational Radiation Exposure

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 (*14*). The input data used in the current dosimetry version 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. Since the availability of radiation dose data differed by calendar period, different methods were used to estimate the badge doses in three periods (i.e. <1960, 1960–1976, 1977–1984).

For the years before 1960, estimates of individual badge dose were

based on a synthesis of evidence from the literature, being mindful of the national radiation protection standards at a time when most large institutions attempted conformity. We found 11 publications that provided information on individual badge dose readings and used those data to estimate, for each year, the median and mean annual badge doses and their uncertainties. For 1960–1976, badge dose readings were available for a small fraction of cohort members. We restricted the badge doses to approximately 2,800 badge readings taken on the outside of the apron as reported by cohort members on the baseline questionnaire. The data indicated nearly the same average annual dose for each year; therefore, we used a constant value to represent the average badge dose for each year across the entire period, modified only by type of facility where employed (i.e. hospital, physician office, or combination). The uncertainties in the badge doses were based on the distribution of the 2,800 readings. A maximum likelihood approach was used to estimate the parameters of the probability density functions (pdf) of the individual badge doses. Approximately 350,000 annual film-badge readings for cohort members were obtained from a commercial dosimetry company for the period 1977–1984, representing more than 50% of the person-years during the interval and at least one annual film-badge reading for all cohort members. For those without a film-badge reading in a particular year, a value was predicted from a regression model using responses to the most recent survey completed. The uncertainties were assumed to be due to the measurement error when the badge reading was available and to the modeling error when the badge reading was not available.

Red bone marrow dose was calculated from the badge dose in two steps: The badge dose was first used to estimate the air kerma, which was then converted to red bone marrow dose. The conversion factors depended on the X-ray energy spectrum and on whether the radiologic technologist wore an apron (and if so, the location of the badge outside or under the apron and the likely thickness of the apron). Because diagnostic X-ray practices changed over time, measured values were adjusted using 12 different X-ray spectra to reflect differences from one period to another and from one individual to another. The estimation of the uncertainty in the red bone marrow dose took into account the uncertainty in the badge dose and the uncertainties in the conversion factors. Annual mean red bone marrow doses were derived from taking the average of 100 Monte Carlo realized doses for each individual, and cumulative mean red bone marrow doses were calculated by summing their annual mean doses. Because we examined translocations in peripheral lymphocytes, occupational radiation dose to red bone marrow was the most relevant exposure, but we also evaluated estimated film-badge dose for comparison purposes.

Using interview data from questionnaires, we examined work history variables that were potential markers of exposures not explicitly accounted for in the dose reconstruction. These included the number of times that radiologic technologists held patients during diagnostic X-ray procedures and the number of times they allowed others to take practice X rays on themselves during training. In addition, we analyzed whether technologists reported having been removed from work for exceeding exposure limits and the number of times they reported their white blood cell count was found to be below normal as a result of their occupation.

The dosimetry system did not separately account for work that radiologic technologists may have performed with radioisotopes, so the badge doses were assumed to be entirely attributable to lower-energy X rays. By not accounting for the higher-energy radioisotope exposures, badge and marrow doses may have been underestimated for a small number of people. To assess the potential effect of radioisotope exposures on translocations, we included in our statistical models a variable for radioisotopes derived from survey responses about working with radium, radioactive iodine and radioactive cobalt.

Personal Diagnostic Exposure

We used self-reported information about personal diagnostic radiographic examinations, including the total number of examinations and calendar periods of exposure to assign estimated diagnostic red bone marrow absorbed dose scores. The dose estimates assigned to specific procedures in our study were taken from a study by Preston-Martin *et al.* in which published literature and expert judgment were used to assign red bone marrow dose values to a comprehensive list of radiographic procedures (*22*). For each procedure, they established a range of possible doses and assigned the midpoint value of that procedure. Since their red bone marrow dose estimates did not differ over time from 1960–2001, we assigned the procedure-specific midpoint doses to all radiographic procedures. The total number of examinations was multiplied by the corresponding dose to calculate total doses for each procedure type for each subject. Total doses were summed over all procedures to calculate an estimate of personal diagnostic red bone marrow dose. We prefer to call this estimate a dose score rather than a dose because of the uncertainties in recall of various procedures and uncertainties with the per procedure dose estimates.

Personal Therapeutic Radiation Exposure

Information on personal history of therapeutic irradiation to the head and neck ($n = 13$), pelvis ($n = 1$), extremities ($n = 9$) and chest ($n = 1$), mostly for benign conditions, was available from the baseline questionnaire. We included an indicator variable for ever having therapeutic irradiation to sites other than the extremities; the latter was excluded because it would not contribute substantially to the red bone marrow absorbed dose since the majority of adult bone marrow is located in the pelvis, torso and head (*23*).

Statistical Analysis

We used the AMFIT module of EPICURE (Hirosoft, Seattle, WA) to construct linear Poisson regression models for associations between occupational ionizing radiation exposure (badge equivalent dose and red bone marrow absorbed dose) 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 occupational ionizing radiation 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. A Pearson scale factor was added to the models to account for overdispersion of the data.

Selected covariates were included in a multivariate model to eliminate confounding. Potential confounders were identified as covariates whose inclusion in the model changed the association between badge dose or red bone marrow absorbed dose and translocation frequency, i.e., parameter β, by 10% or more. The final model included as covariates age at blood draw, personal diagnostic red bone marrow radiation exposure, and gender but not cigarette smoking, ever working with radioisotopes, holding patients, allowing others to take practice X rays, and prior therapeutic irradiation. Race was not assessed in these models because 149 of 152 subjects were Caucasian. For ordinal variables we carried out tests for trend with translocation frequency by constructing univariate linear Poisson regression models with the category series (1, 2, 3, . . .) modeled as continuous variables.

RESULTS

Responders ($n = 159$) and non-responders ($n = 48$) did not differ significantly by age at blood collection, race, cigarette smoking, alcohol consumption, education level or marital status. However, non-responders were significantly more likely to be female ($P = 0.03$) and to have worked fewer years ($P = 0.01$) than responders.

Table 1 shows several demographic and descriptive fac-

TABLE 1
Distribution of Covariates among Biodosimetry Study Subjects and Mean Translocation Frequencies by Covariate Categories, U.S. Radiologic Technologists Study

Characteristic	Subjects (n = 152)	Mean number of translocations/100 cell equivalents	95% confidence interval[a]	P trend[b]
Age at blood draw (years)				0.003
71–74	17 (11%)	0.9	0.8, 1.1	
75–78	60 (40%)	1.4	1.2, 1.6	
79–82	31 (21%)	1.3	1.1, 1.5	
83–86	31 (21%)	1.5	1.2, 1.8	
87–90	13 (9%)	1.9	1.2, 2.6	
Race				N/A
Caucasian	149 (98%)	1.4	1.2, 1.5	
African American	1 (<1%)	N/A[c]	N/A	
Other or unknown	2 (1%)	N/A	N/A	
Gender				0.003[d]
Male	46 (30%)	1.7	1.4, 2.0	
Female	106 (70%)	1.2	1.1, 1.4	
Cigarette smoking (number of pack-years)				0.4
0	89 (59%)	1.4	1.2, 1.5	
>0–20	31 (20%)	1.2	0.9, 1.6	
>20–50	17 (11%)	1.5	1.1, 1.8	
>50	14 (9%)	1.6	1.1, 2.2	
Unknown	1 (1%)	N/A	N/A	
First year worked as a radiologic technologist				0.1
≤1942	31 (20%)	1.5	1.2, 1.9	
1943 to 1944	26 (17%)	1.4	1.1, 1.6	
1945 to 1946	40 (26%)	1.5	1.2, 1.8	
1947 to 1948	34 (22%)	1.2	1.0, 1.4	
>1948	21 (14%)	1.2	0.9, 1.6	
Worked with radioisotopes				>0.5
Never	84 (55%)	1.4	1.2, 1.5	
Ever	66 (43%)	1.4	1.2, 1.6	
Unknown	2 (1%)	1.3	N/A	
Held patients during X-ray procedures				0.3
Never	11 (7%)	1.3	0.7, 2.0	
<50 times	33 (22%)	1.2	0.9, 1.4	
≥50 times	94 (62%)	1.4	1.3, 1.6	
Unknown	14 (9%)	1.6	1.1, 2.0	
Allowed others to take practice X rays				0.1
Never	89 (59%)	1.3	1.2, 1.5	
1–24 times	36 (24%)	1.4	1.1, 1.6	
≥25 times	15 (10%)	1.8	1.1, 2.4	
Unknown	12 (8%)	1.2	0.7, 1.6	
Removed from work for exceeding exposure limit				>0.5
Never	111 (73%)	1.4	1.2, 1.5	
Ever	8 (5%)	1.3	0.5, 2.0	
Unknown	33 (22%)	1.3	1.1, 1.6	
Number of times white blood cell count was below normal because of working as a radiologic technologist				0.4
Never	58 (38%)	1.4	1.2, 1.6	
≤4 times	8 (5%)	1.7	0.9, 2.4	
>4 times	5 (3%)	1.2	0.4, 1.9	
Unknown	81 (53%)	1.4	1.2, 1.5	
Estimated occupational film badge radiation dose (cSv)				0.001
≤10	24 (16%)	1.1	0.8, 1.4	
>10–20	21 (14%)	1.1	0.8, 1.4	
>20–30	36 (24%)	1.3	1.1, 1.6	
>30–40	26 (17%)	1.5	1.2, 1.9	
>40	45 (30%)	1.6	1.3, 1.9	

TABLE 1
Continued

Characteristic	Subjects (n = 152)	Mean number of translocations/100 cell equivalents	95% confidence interval[a]	P trend[b]
Estimated occupational red bone marrow radiation dose (cGy)				0.001
≤1	46 (30%)	1.1	0.9, 1.2	
>1–2.0	42 (27%)	1.4	1.2, 1.7	
>2–3.0	29 (19%)	1.7	1.3, 2.1	
>3–4.0	18 (12%)	1.3	1.0, 1.6	
>4	17 (11%)	1.7	1.2, 2.2	
Estimated personal diagnostic red bone marrow dose score (cGy)				0.002
0–2	51 (34%)	1.2	1.0, 1.4	
>2–5	51 (34%)	1.3	1.1, 1.5	
>5–10	28 (18%)	1.3	1.0, 1.5	
>10	20 (13%)	2.0	1.6, 2.4	
Unknown	2 (1%)	2.4	N/A	
History of X-ray therapy for benign conditions				
Never	135 (89%)	1.4	1.2, 1.5	0.2
Ever	17 (11%)	1.6	1.1, 2.1	

[a] The standard error (SE) of the estimated translocation frequencies (TF) can be derived based on the upper 95% confidence limit (UCL) using the formula SE = (UCL − TF)/1.96.

[b] Univariate linear Poisson regression treating ordinal categories as continuous covariates; unknown category not included.

[c] N/A: Not applicable.

[d] Univariate linear Poisson regression with dichotomous independent variable; unknown category not included.

tors. Study subjects were primarily Caucasian (98%), female (70%) and non-smokers (59%). Forty-three percent reported ever working with radioisotopes, 62% held patients 50 or more times during X-ray procedures, and 34% allowed others to take practice X rays on them. Only 5% of study subjects reported ever being removed from work for exceeding exposure limits, and 8% reported having a low white blood cell count because of their work. Eleven percent reported having therapeutic irradiation for benign conditions to body sites with appreciable red bone marrow deposition. Study subjects had an average of 1.4 translocations per 100 CE (range 0 to 4.5), a mean badge dose of 30.4 cSv, and a mean occupational red bone marrow absorbed dose of 2.1 cGy (Table 2).

Men had a higher mean number of translocations per 100 CE than women (1.7 and 1.2, respectively) (Table 1). The average number of translocations increased with increasing age (P trend = 0.003), occupational radiation badge dose (P trend = 0.001), occupational radiation red bone marrow absorbed dose (P trend = 0.001) and personal diagnostic radiation red bone marrow absorbed dose score (P trend = 0.002). Year first worked and the number of times a technologist allowed others to take practice X rays were marginally associated with increased translocation frequency (P trend = 0.1). Translocation frequency was not associated with pack-years of smoking (P trend = 0.4), working with radioisotopes (P trend > 0.5), holding patients for X rays (P trend = 0.3), removal from work for exceeding an exposure limit (P trend > 0.5), work-related below normal white blood cell count (P trend = 0.4), or prior therapeutic irradiation (P trend = 0.2).

Figure 1 shows translocation frequencies plotted as a function of occupational red bone marrow absorbed doses with the univariate dose–response trend line superimposed on the scatter plot (0.15 excess translocations per 100 CE per cGy). Univariate and multivariate regression results for translocation frequencies and occupational radiation doses are provided in Table 3. In multivariate analyses adjusted for age, gender and personal diagnostic procedures, badge dose was marginally associated with increases in translocation frequency (P = 0.10). Occupational red bone marrow absorbed dose was also borderline statistically significantly associated with translocation frequency (0.09 excess translocations per 100 CE per cGy, P = 0.07).

TABLE 2
Descriptive Statistics for Translocations and Occupational Ionizing Radiation Exposure Metrics among Biodosimetry Study Subjects, U.S. Radiologic Technologists Study

Variable	N	Mean	Standard deviation	Median	Minimum	Maximum
Translocations per 100 cell equivalents	152	1.4	0.8	1.2	0.0	4.5
Badge dose (cSv)	152	30.4	17.4	29.2	1.9	100.3
Red bone marrow dose (cGy)	152	1.9	1.4	1.6	0.06	7.4

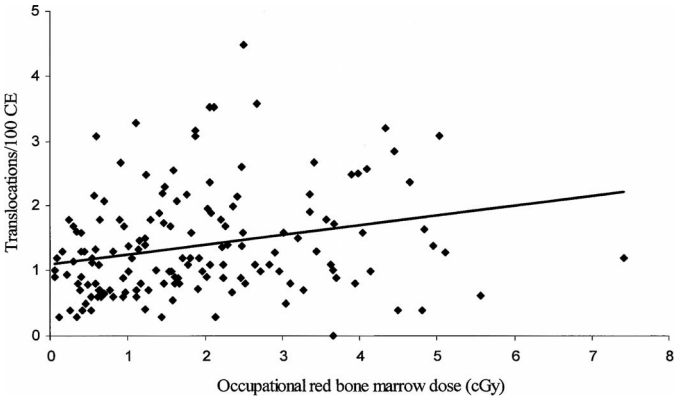

FIG. 1. Translocation frequency as a function occupational red bone marrow radiation dose among 152 U.S. radiologic technologists. The trend line is from univariate Poisson regression analysis (0.15 excess translocations per 100 CE per cGy).

As seen in Fig. 1, there were two observations that might be interpreted as outliers; one study participant had a relatively high red bone marrow dose (7.4 cGy), and another had a relatively high translocation frequency (4.5 translocations per 100 CE). When we excluded either person from multivariate regression analysis, the dose–response relationship was similar (0.1 excess translocations per 100 CE per cGy, $P = 0.05$). We individually reviewed the raw data on translocation frequencies and estimated red bone marrow radiation doses for these individuals plus a person with zero translocations and found no technical errors; thus all three individuals were retained in the final analysis.

DISCUSSION

We observed an association between increasing occupational ionizing radiation absorbed dose to the red bone marrow and increased translocation frequency that was nearly statistically significant ($P = 0.07$) after adjusting for age, gender and personal diagnostic radiation exposures. This association lends corroborative support to the dosimetry models that were used to estimate annual and cumulative occupational radiation doses in the USRT cohort. Our ability to detect this relationship, despite the older ages of the radiologic technologists, their relatively low cumulative red bone marrow absorbed doses, and the substantial interindividual variability in translocation frequencies, was likely enhanced by several study features designed to overcome poor ''signal to noise'' ratios (*24*). These features were the large number of participants, the scoring of 1828 cells (1024 cell equivalents) per person (277,890 cells in the whole study), and the ability to select participants that were homogeneous for age, smoking history, and higher badge doses. We attempted to reduce the effect of cigarette smoking on translocation frequencies by restricting the sample selected, even though studies examining the influence of cigarette smoking on translocation frequency have not been consistent (*8, 11, 12, 16, 25–27*). We also oversampled radiologic technologists who had estimated occupational radiation badge doses in excess of 30 cSv based on the dose assessment to increase the likelihood of including technologists with translocation frequencies above background levels (*28*).

In studies of exposure to γ rays of higher energy than medical X rays, the expected frequency of excess translocations per 100 CE per cGy is approximately 0.015 (*28*). The distribution of photon energies applicable to the current study included X rays with a maximum energy well below 100 keV, with most of the exposures between 25 and 60 keV. For dicentrics, which are the unstable counterpart of translocations, the linear term for X rays in the region of 50–100 keV is about three times higher than that for high-energy γ rays (*29*). Thus, for the energy of X rays relevant to this study, a calibration factor of 0.05 excess translocations per 100 CE per cGy is within reason. Our observed estimate of 0.09 excess translocations per 100 CE per cGy is consistent with the calibration factor approximation.

Annual dose estimates for cohort members were available up to 1984, and there were 47 study subjects who continued working as radiologic technologists after 1984. For these subjects, there were 1 to 20 years (mean = 7.5

TABLE 3
Occupational Radiation Dose Response for Chromosome Aberrations, U.S. Radiologic Technologists Study

	Univariate			Multivariate		
	Excess translocations/ 100 CE/unit exposure[a]	95% Wald confidence interval[b]	*P* value	Excess translocations/ 100 CE/unit exposure[a,c,d]	95% Wald confidence interval[b]	*P* value
Badge dose	0.01	0.005, 0.02	<0.001	0.007	−0.002, 0.02	0.1
Red bone marrow dose	0.15	0.05, 02	0.003	0.09	−0.01, 0.2	0.07

[a] For badge dose the unit exposure is cSv; for bone marrow dose the unit exposure is cGy.

[b] The standard error (SE) of the estimated translocation frequencies (TF) can be derived based on the upper 95% confidence limit (UCL) using the formula SE = (UCL − TF)/1.96.

[c] Adjusted for age, gender and personal diagnostic radiation exposure.

[d] Estimated translocation frequency has to be added to the estimated age-, gender-, and personal diagnostic radiation exposure-specific background translocation frequency to determine the estimated translocation frequency for a subject of given gender, age and personal diagnostic radiation exposure and a given occupational radiation exposure. The average background translocation frequency across categories of age, gender and personal diagnostic radiation exposure was 1.2 translocations per 100 CE.

years) for whom doses were not included. Because the doses after 1984 are considered to be low, they would have contributed little to the cumulative dose. Addition of a covariate to the models that accounted for these years did not significantly alter the dose–response estimate (results not shown).

Our findings should be interpreted with some caution since both the magnitude of the radiation effect estimate and the statistical significance of the results were sensitive to adjustment by the potential confounding factors considered. One must also consider the large uncertainties in individual dose estimates. There were no recorded badge dose measurements for our study subjects in the years during which they received all or almost all of their exposure. Therefore, the dosimetry system relied on data from a small number of studies to estimate typical annual badge doses for those periods. These representative badge dose estimates were adjusted to take into account what was known about each individual's work history (i.e., type of facility and decade worked). The translation of badge dose estimates to red bone marrow absorbed dose estimates introduces additional sources of uncertainty arising from the individual's ability to reliably answer questions about apron and shield use and dosimeter placement during the years they worked.

Despite these limitations, our analyses suggest that these occupational exposures were associated with persistent chromosome aberrations in this population. Furthermore, the magnitude of the effect was reasonably consistent with what one might expect based on general cytogenetic experience and knowledge of radiation quality. Kodama *et al.* found that among Hiroshima survivors the proportion of cells with at least one stable aberration increased by about 0.07 per 100 CE per cGy red bone marrow absorbed dose (*3*). For Nagasaki survivors, radiation had a somewhat smaller effect, 0.04 per 100 CE per cGy, which the authors attribute at least partially to problems estimating shielding. At these relatively low frequencies the number of cells with at least one translocation, which is the outcome measure used in the survivor studies, is almost identical to the number of translocations per cell as considered in our analyses. Because the atomic bomb survivors were primarily exposed to higher-energy γ rays (*30*), the dose–response relationship estimated in our study could be two to three times greater. Considering the uncertainties in exposure estimates for both studies and possible protraction effects in the present study, the similarity of the estimates provides some additional support for our dosimetry system.

Gender has not been associated with translocation frequencies in previous studies (*16, 31–33*); however, in our study, adding gender to the regression models changed the dose–response point estimates by more than 10%. Men had a higher mean translocation frequency than women (Table 2). It is possible that gender was a marker of some source of exposure in the study group; however, replacing gender with available employment factors (holding patients for X rays, working with radioisotopes, allowing others to take practice X rays) in the regression models did not reveal any occupational differences to explain the observed gender effect.

Because of the difficulty in detecting dose–response relationships at low radiation doses, we hoped to gain precision in our analyses by accounting for personal diagnostic exposures (*34*). Translocation frequencies increased as the estimated red bone marrow dose score from personal diagnostic procedures increased. This observation underscores the importance of collecting information on personal diagnostic procedures in low-dose occupational radiation studies. Because translocation frequencies were unknown to the technologists, any error in recalling personal diagnostic procedures should be non-differential and could only attenuate the observed relationships.

Substantial variation in translocation frequencies remained even after accounting for age, gender and ionizing radiation exposure. Given this variability, the regression point estimate from our analysis should not be used as a calibration factor to derive individual dose estimates. The identification of other major sources of variation in translocation frequencies may also further clarify the occupational radiation dose–response relationship. Genetic factors (e.g. polymorphisms in double-strand break repair genes) associated with translocation frequency warrant further exploration. A recent study among retired radiation workers did not demonstrate an effect of seven polymorphisms in DNA repair genes on radiation-induced translocation frequencies (*35*), but additional relevant pathways should be pursued.

Despite wide variation in translocation frequencies and uncertainty in the estimated occupational red bone marrow absorbed doses, we found good agreement between the dose estimates and translocation frequencies. After controlling for age, gender and personal diagnostic radiation exposure, the dose response was borderline statistically significant, and the estimated number of 0.09 excess translocations per 100 CE per cGy was consistent with expectation based on previous cytogenetic studies. The findings from this study lend credence to the accuracy of the USRT dose assessment to date.

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