Chromosome Translocations and Cosmic Radiation Dose in Male U.S. Commercial Airline Pilots

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BACKGROUND: Chromosome translocations are a biomarker of cumulative exposure to ionizing radiation. We examined the relation between the frequency of translocations and cosmic radiation dose in 83 male airline pilots.

METHODS: Translocations were scored using fluorescence in situ hybridization chromosome painting. Cumulative radiation doses were estimated from individual flight records. Excess rate and log-linear Poisson regression models were evaluated.

RESULTS: Pilots' estimated median cumulative absorbed dose was 15 mGy (range 4.5–38). No association was observed between translocation frequency and absorbed dose from all types of flying [rate ratio (RR) = 1.01 at 1 mGy, 95% confidence interval (CI) 0.97–1.04]. However, additional analyses of pilots' dose from only commercial flying suggested an association (RR = 1.04 at 1 mGy, 95% CI 0.97–1.13).

DISCUSSION: Although this is the largest cytogenetic study of male commercial airline pilots to date of which the authors are aware, future studies will need additional highly exposed pilots to better assess the translocation-cosmic radiation relation.

KEYWORDS: pilots, aircrew, chromosome translocations, cosmic radiation, circadian disruption.

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Ionizing radiation is a known human carcinogen[14] and an efficient inducer of chromosome aberrations.[21] Chromosome aberrations have been shown to be associated with increased cancer risk in prospective studies[1] and are also a recognized reproductive hazard.[3] In known carriers of translocations, there is an increased risk of additional abnormal semen parameters which can increase infertility.[27,34] Translocations (the most persistent form of chromosome aberrations) can be detected in peripheral blood lymphocytes by the established method of fluorescence in situ hybridization (FISH) with whole chromosome paints and have been widely used to assess chronic low-dose ionizing radiation exposures in various occupational settings.[30]

The impact of cosmic ionizing radiation (hereafter referred to as cosmic radiation) is relevant both to commercial air crew and astronauts/commercial space travel.[22] Commercial airline pilots are occupationally exposed to levels of cosmic radiation that are higher than at ground level.[9,14] The cosmic radiation field at aircraft altitudes is a complex mixture of particles and rays of galactic and solar origin as well as secondary radiations consisting mainly of charged particles, neutrons, and gamma radiation, with some protons, alpha particles, and heavy nuclei.[7,35] Pilots are also exposed to nonionizing electromagnetic fields from cockpit instruments and chemical and physical agents in the working environment such as jet engine exhaust, cabin air pollutants, and circadian disruption.[8,12,35] Recent research suggests that the molecular circadian clock, which sets rates and periodicity for many biochemical functions, also modulates cellular response to DNA repair. Although it does not appear that disruption of the clock in itself predisposes animals to cancer, other mechanisms related to disruption may promote cancer.[28] The World Health Organization

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considers circadian disruption a probable human carcinogen based, in part, on studies of female flight attendants.[15]

During the past decades, reports of elevated risks of cancers of various sites among pilots have raised concerns about workplace exposures, particularly cosmic radiation. The epidemiological findings on cancer risks among pilots have been inconsistent. A study of German cockpit crew reported an increased risk of all cancers for those employed 30 yr or more compared to those employed under 10 yr [relative risk = 2.2, 95% confidence interval (CI), 1.2 to 4.1].[38] A 2014 mortality study of U.S. cockpit crew reported elevated mortality for malignant melanoma and increased mortality for central nervous system cancer with increasing cumulative radiation dose, but no increased mortality for other cancers considered to be associated with ionizing radiation exposure.[36] A 2014 cohort mortality study of commercial airline crew from 10 countries[11] also reported elevated mortality from malignant melanoma, but not from other cancers considered to be radiation-related. Although there have been suggestions that lifestyle and personal factors may account for the increased risk of melanoma, Rafnsson et al. reported that it was unlikely that the increase would be explained solely by excessive recreational sun exposure.[25] The inconsistent findings have been attributed to epidemiological study limitations that include the lack of direct exposure data and use of proxies such as duration of employment, limited information on potential confounding factors, and a low statistical power to detect a small radiation effect.[12]

In our previous analysis of male airline pilots and university faculty, we found no differences between the pilots and faculty, but among pilots the frequency of chromosome translocations increased significantly with increased years of self-reported flying of commercial aircraft ("commercial flight years") after adjusting for age and other potential confounders.[37] Because we were able to replace self-reported flight years from each pilot with his records-based individual flight segments, individually assessed to describe multiple exposures from his entire career,[9] we reanalyzed the chromosome translocation biomonitoring data with the records-based exposure metrics. Although these metrics do not reflect all complexities of cosmic radiation dosimetry, including the effect of location within the aircraft, personal dosimeters lack the ability to accurately measure cosmic radiation for aircrew, and records-based/calculational methods have been shown to operate in a consistent range of uncertainty compared to direct instrumentation measurements.[5] Similar methods allowed for the successful etiologic separation of flight exposures in a study of miscarriage in flight attendants, which suggested that cosmic radiation exposure of 0.1 mGy or more may be associated with an increased risk of miscarriage in weeks 9–13 of pregnancy (OR = 1.74; 95% CI = 0.95–3.20).[10] The objectives of the present study were to evaluate the relation between the frequency of translocations and the estimated cumulative cosmic radiation dose among the pilots and the university faculty members, and to conduct an internal dose-response analysis among pilots only.

METHODS

Study Population

The study protocol was approved in advance by the Institutional Review Boards of the National Institute for Occupational Safety and Health, the National Cancer Institute, and the Lawrence Livermore National Laboratory. Each participant provided written informed consent before participating. Participant recruitment and study design have been described in detail.[37] Briefly, 83 full-time male pilots of a major U.S. airline (hereafter referred to as the study airline) and a comparison group of 51 male university faculty members were recruited from a domicile (hub) city of the study airline between December 2001 and September 2002. All participants met the following eligibility criteria: 1) ages 35–56 yr; 2) a never smoker (defined as a person who smoked a lifetime total of $<$100 cigarettes) or a smoker with limited smoking history (defined as a smoker who had not smoked in the last 10 yr or who was currently smoking $<$10 cigarettes per day); 3) no personal history of cancer except for nonmelanoma skin cancer; 4) no history of chemotherapy or radiotherapy; and 5) no family history of chromosomal instability disorders. Age eligibility was restricted to limit the contribution of age to translocation frequencies. The comparison group was chosen to be comparable to the pilots, as confirmed by the questionnaire data.

All subjects provided a venipuncture blood sample and completed a self-administered questionnaire. Data collected included demographics, health and medical history, occupational flying history (from the study and nonstudy airlines and military service), height, weight, smoking and alcohol consumption history, and recreational activity. Personal diagnostic X-ray procedure information was used to estimate X-ray dose. Terrestrial background radiation was subtracted in the CARI program calculations for cosmic radiation dose.

Procedure

The analysis of chromosome translocations in peripheral blood lymphocytes using FISH whole chromosome painting was conducted by laboratory personnel without knowledge of the exposure history category of participants. Cell cultures and slides were prepared using standardized methods.[18,26] Chromosomes 1, 2, and 4 were painted red, and chromosomes 3, 5, and 6 were simultaneously painted green. The slides were then counterstained with 4',6-diamidino-2-phenylindole (blue). This combination of paints detects 56% of all chromosome exchanges.[31] All types of translocations were included and clonal exchanges were not observed. Approximately 1800 metaphase cells were evaluated per subject, and this was equivalent to $1800 \times 0.56 = 1000$ metaphase cells [defined as cell equivalents (CEs)] as if the full genome had been scored.

Methods for estimating the cumulative cosmic radiation dose of 83 male pilots and 51 university faculty members have been described previously.[9] Analyses presented here exclude one faculty member who was later determined to be ineligible. Briefly, data sources included logbooks of each flight segment flown by a pilot during his career; flight records from the study airline; summary records of hours and types of aircraft flown, generally from early training or military flights; and questionnaire self-report of commuting and recreational passenger travel. Records of fixed wing flights were categorized by flight type as study airline, military, large-aircraft commercial flights not from the study airline, small-aircraft commercial flights not from the study airline, private/nonwork flights piloted for recreational purposes, commuting flights, and recreational passenger travel. For pilots, recreational passenger travel was "pass" travel (nonwork flights flown as a passenger, at reduced fare, usually on the study airline). For faculty members, only recreational and business travel were assessed. Exposure assessment ended on the day blood was drawn for the study.

CARI6P, screen version 9/17/2005, and CARI6PM, screen version 5/1/2007 (Federal Aviation Administration, Oklahoma City, OK; http://www.faa.gov/data_research/research/med_humanfacs/aeromedical/radiobiology/cari6/), were used to estimate cosmic radiation effective, absorbed, and particle-specific doses for each flight segment. With the exception of protons, CARI6P incorporates ICRP Publication 60 based fluence-to-effective dose conversion coefficients as published by Pelliccioni.[13,24] For protons a radiation weighting factor of 2 is used in keeping with recommendations in ICRP Publication 103.[17] As recommended in ICRP Publication 103, absorbed dose was used for all analyses. The dose was calculated at a depth of 5 cm in a 30-cm tissue equivalent slab phantom and is considered to be a reasonable approximation of the red bone marrow (RBM) dose.[23]

Solar particle events (SPEs) are transient (several hours to days) sources of energetic ionizing radiation associated with eruptions of varying intensity on the sun's surface. SPEs are not evaluated by the CARI programs. Current development and validation of the National Aeronautics and Space Administration's (NASA) Nowcast of Atmospheric Ionizing Radiation for Aviation Safety (NAIRAS) model suggest that high-latitude commercial airline flights can approach or exceed ICRP annual public exposure guidelines during a SPE.[20] For this study, exposure to SPEs was assessed only for individual flight segments of the pilots by determining whether any flight segment flown by the pilots possibly traveled through any 1 of the 23 moderate or large SPEs as identified by reference to satellite data during the study period, and this was then summed as the cumulative number of SPEs.[9]

Two circadian disruption exposure metrics were calculated for pilots: nondirectional (i.e., traveling either east or west) cumulative time zones crossed and travel during the standard sleep interval (SSI) as a separate measure of sleep disturbance.[8,9] Flight segments flown for the study airline were evaluated for estimated time spent flying during SSI, defined as from 2200 to 0800 at the pilot's domicile. For each pilot, the median SSI travel (minutes/segment) over all flight segments evaluated was used to describe sleep disturbance.

In addition to evaluation of military records and logbooks to assess exposures from individual flights or summary hours of flights flown while in the military, we also examined military experience without regard to specific flight exposures. We evaluated military status as a dichotomous (never/ever) variable as used in Yong et al.[37] We also created a metric for duration of active military service to distinguish military pilots who stayed on active duty more than approximately 8 yr (who generally move to desk jobs with minimal flying) from those with less than 8 yr of active duty. We specifically excluded years spent in the military reserve from this metric. Assessment of pilot logbook records at the time of this study indicated that pilots leaving active duty and beginning a commercial flying career while continuing military service on reserve duty typically flew for the military reserve only several weeks per year (Captains M. D. Holland and J. May, Health and Safety Representatives of the Airline Pilots Association; written communication, 2012).

Statistical Analysis

For each subject, the translocations in all evaluated cells were counted and expressed as the frequency of translocations per 100 CEs. While called "frequency" for statistical purposes this should more appropriately be thought of as a rate, hence comparisons between groups are rate ratios or rate differences. Poisson regression and quasi-likelihood models were fitted by maximum likelihood.[19] The AMFIT module of EPICURE (Hirosoft, Seattle, WA) was used to construct log-linear (multiplicative) and excess rate (additive) Poisson regression models to evaluate the relation between translocation frequency (outcome variable) and cumulative cosmic radiation absorbed dose (mGy) computed from all flight types (commercial, military, private, commuting, and recreational flights). The background rate was modeled as a log-linear function of age.

Log-linear models, adjusted for age, were used to evaluate a categorical treatment of cumulative absorbed dose among all subjects. In these models, the referent group was comprised of faculty members and pilots with "low" absorbed dose. Among pilots, various metrics were similarly evaluated, including cumulative absorbed dose, absorbed dose limited to flying for the study airline, absorbed dose limited to commercial aircraft (including the study airline), military status, years of active military service, absorbed dose from military service, and estimated cumulative number of SPEs. Because the particle doses from CARI were highly correlated, analysis by particle types or linear energy transfer (LET) levels was not possible. Analyses restricted to commercial flights for the study airline were conducted since these flights were the largest source of data for the study, with the most consistent flight exposures, and least subject to potential exposure misclassification.

We also considered the circadian disruption metrics of nondirectional cumulative time zones crossed and median SSI travel as a separate measure of sleep disturbance. However, cumulative time zones crossed could not be evaluated in the regression models due to its high correlation with cosmic radiation absorbed dose (Pearson correlation coefficient = 0.89). For each pilot, the median SSI travel (minutes/segment) over all flight segments evaluated was categorized (0, >0 to <90, ≥90).

Excess rate and log-linear models evaluated absorbed dose from all flight sources as a continuous variable among all subjects and separately among pilots. In these models, confounding due to age (treated as a continuous variable) and co-exposure from estimated cumulative RBM X-ray dose score computed from personal diagnostic procedures (treated as a categorical variable with three categories: <5, 5 to <20, and ≥20 units with 1 unit approximating 1 mGy)[37] were evaluated and adjusted for as appropriate. To aid in comparison to results in Yong et al.[37] among pilots, these models also considered absorbed dose from commercial flying sources and the commercial flight years metric used in Yong et al.; since these metrics did not involve military flying, these models considered military status (never/ever served) and years of active military service (categorized as none, >0 to <6, 6 to <8, and ≥8) as potential confounders. We also evaluated the estimated cumulative number of SPEs and the estimated median SSI travel.

RESULTS

Selected characteristics of the study population and the corresponding mean frequencies of chromosome translocations were provided in Yong et al.[37] Briefly, all subjects were white men and were comparable in age: 37 to 55 yr (mean = 46.7) for pilots (N = 83) and 36 to 56 yr (mean = 46.0) for comparison subjects (N = 50). Both groups had a similar distribution for cigarette smoking (never vs. ever as well as pack-years). There was a significant increase in the mean translocation frequency with increasing age (P = 0.005) and the cumulative RBM X-ray dose score (P = 0.04) among the pilots, but not the faculty members. Translocation frequency was not associated with cigarette smoking in either group.

Translocation frequencies vs. cosmic radiation absorbed dose by employment group are graphed in **Fig. 1**. In this figure, adjustment for pilots' age and X-ray dose removed the suggestion of an increasing relation between chromosome translocations and cosmic radiation absorbed dose. The faculty members had a similar range of chromosome translocations, but minimal cosmic radiation absorbed dose.

Descriptive statistics for translocation frequencies and the exposure metrics by study group as well as by types of flying are presented in **Table I**. Table I shows similar translocation frequencies between pilots and faculty, as well as the pilots' expected higher levels of aircrew exposures, including cosmic radiation. Study airline flying accounted for about 76% of pilots' cosmic radiation exposures.

The mean frequency of translocations was 0.39 per 100 CEs (range 0 to 1.7) for pilots vs. 0.32 per 100 CEs (range 0 to 1.5) for the faculty members. Pilots' median cumulative cosmic radiation absorbed dose was 15 mGy (range 4.5 to 38); median effective dose was 34 mSv (range 10–85 mSv). Faculty cumulative cosmic radiation doses were from recreational and business travel, and were far lower, as expected (median absorbed dose: 0.37 mGy, range 0.0032–4.2; median effective dose: 0.82 mSv, range 0.01–9.4). Among the pilots, there were large variations in the doses from different types of flying. The largest contribution to cumulative pilot dose was based on data from the study airline (75.8%), followed by military service (8.1%). The

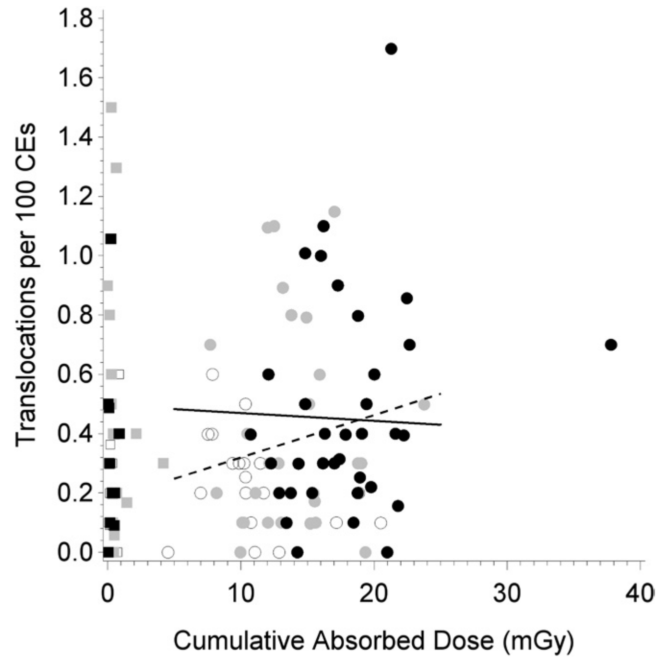

Fig. 1. Translocation frequencies per 100 cell equivalents by cumulative cosmic radiation absorbed dose for N = 83 pilots (dots) and N = 50 comparison subjects (squares). White indicates age <43 yr, grey indicates 43 to <49 yr, and black indicates age ≥49 yr. The dashed curve represents unadjusted model B1 and the solid curve represents age- and X-ray-adjusted model B3 (Table III). The two outlying data points were evaluated and deemed to not be influential.

remaining contributions were from other flight types: large-aircraft commercial flights (3.0%) and small-aircraft commercial flights (0.9%) not from the study airline; private/nonwork flights piloted for recreational purposes (0.2%); and commuting (7.4%) and recreational passenger travel (4.6%). The pilots flew through an estimated median of six SPEs (range 1–14). For SSI travel, each pilot was assigned a value based on his median minutes of SSI travel per company-recorded segment. Of the study pilots, 33% had nonzero median SSI travel ranging from 2 to 230 min/segment. The remaining 67% of pilots had a median SSI travel of 0 min/segment. Thus, the median of median SSI travel for all pilots was 0 min/segment.

Table II examines translocation frequencies with one exposure at a time, adjusting only for age. Rate ratios and P-values indicate the strength of association between each exposure level and translocation frequencies. Table II shows suggestions of a cosmic radiation association with translocations, primarily in the higher dose groups of commercial or study airline flights. For military service and estimated cosmic dose, we found a counterintuitive drop in translocation association with longest lengths of service and highest estimated cosmic radiation dose.

In analyses of all subjects and of all pilots, there was little variation in the translocation frequency with the cumulative cosmic radiation absorbed dose from all flight types. In contrast, there was a suggestion of a higher translocation frequency among pilots with a dose of ≥15 mGy compared with <10 mGy when computed from only the study airline flights; rate ratio (RR) = 1.6 (95% CI 0.9 to 2.9). This pattern was similarly observed among pilots for the dose from all commercial flights

Table I. Descriptive Statistics for Chromosome Translocation Frequency/100 Cell Equivalents, Cosmic Radiation Absorbed Dose, Effective Dose, X-Ray Dose Score, and Other Exposure Metrics Among US Commercial Airline Pilots and University Faculty Members.

GROUP EXPOSURE METRIC	MEAN	SD	MEDIAN	RANGE
Pilots (N = 83)				
Translocations/100 cell equivalents	0.39	0.33	0.30	0–1.7
Cumulative red bone marrow X-ray dose score*	11	12	7.7	0.20–60
Cumulative cosmic radiation absorbed dose, mGy (all types of flying)	15	5.0	15	4.5–38
By type of flying (% of absorbed dose)				
Commercial aircraft sources	12	3.6	13	0.44–19
Large (study airline) (75.8%)	11	3.7	11	0.44–19
Large (nonstudy airline) (3.0%)	0.45	1.0	0	0–5.5
Small nonstudy airline (0.9%)	0.13	0.46	0.0006	0–3.7
Military (8.1%)	1.2	1.3	0.84	0–5.7
Commuting (7.4%)†	1.1	2.9	0.078	0–23
Recreational (4.6%)‡	0.69	0.84	0.42	0–5.5
Private/nonwork (0.2%)§	0.031	0.052	0.0092	0–0.25
Cumulative cosmic radiation effective dose, mSv (all types of flying)¶	34	11	34	10–85
Cumulative number of solar particle events (SPEs)	6.3	2.7	6	1–14
Circadian disruption**				
Cumulative time zones crossed	5200	1800	5200	1400–11,000
Median standard sleep interval/SSI travel, (min/segment)††	32	62	0	0–230
University faculty members (N = 50)				
Translocations/100 cell equivalents	0.32	0.32	0.20	0–1.5
Cumulative red bone marrow X-ray dose score	11	16	4.0	0.40–81
Cumulative cosmic radiation absorbed dose, mGy	0.48	0.65	0.37	0.0032–4.2
Cumulative cosmic radiation effective dose, mSv	1.1	1.5	0.82	0.077–9.4

* 1 unit is approximately 1 mGy.
† Mean, SD, and range reflect high commuting hours flown by one pilot.
‡ Nonwork flights flown as a passenger, at reduced fare, usually on the study airline.
§ From personal nonwork flights logged as flown by the pilots for recreational purposes.
¶ Although all study models used absorbed dose, we also present effective dose, a radiation protection metric.
** Excludes summary hours and recreational passenger travel.
†† Flight segments flown for the study airline were evaluated for estimated time spent flying during the standard sleep interval (SSI) defined from 2200 to 0800 at the pilot's domicile (home base).

of the study and nonstudy airlines combined. Translocation frequencies did not vary significantly with either the cumulative number of SPEs or the median SSI travel, but increased with cumulative X-ray dose scores of 5 or more.

In this study, 70% of the pilots (N = 58) served as military pilots prior to working at the study airline with a median of 6.9 yr (range 2.6 to 15.8) of active duty flying, and approximately half of these continued as military reserve pilots while employed full-time with the study airline. Although not statistically significant, the translocation frequency was higher for pilots with less than 8 yr of active duty, but lower for pilots with 8 or more years of active duty, compared to pilots with no military service. A similar pattern was observed for the estimated cosmic radiation absorbed dose from military flying, with the highest rate ratios associated with absorbed dose less than 1 mGy and decreasing with higher doses ($P = 0.008$).

Table III uses two types of modeling to examine the relation between translocations and cosmic radiation dose, but adjusting to control the potential effects of age, X-rays, and military service. Table III shows no evidence of a relation between cosmic radiation dose and translocations for combined pilots and faculty or for pilots alone. However, when the source of pilot flying was limited to commercial aircraft, there was limited evidence of an association between cosmic radiation dose and translocations.

Table III provides the Poisson excess rate and log-linear regression modeling results for translocation frequencies and absorbed dose from all flying sources for all study subjects combined (models A1–A3 and E1–E3) and for pilots separately (models B1–B3 and F1–F3). For pilots, modeling was also conducted with absorbed dose from commercial aircraft and, for comparison, a proxy metric for estimated cosmic radiation dose, the commercial flight years metric used in Yong et al.[37] Unadjusted models (A1–H1) are provided for comparison with models adjusted for age and other a priori covariates. Adjustment for a priori covariates age (models A2–H2) and age and X-ray score (models A3–H3) generally reduced the excess rates or rate ratios so that the dose metric-translocation frequency relation was no longer statistically significant. Additional models which adjusted for the cumulative number of SPEs or the circadian disruption metric of median SSI travel did not modify our results (data not shown).

Because the Yong et al. models of commercial flight years and translocation frequency considered an adjustment for dichotomous military status, and because of the strong relationship with military flying in the univariate analysis (shown in Table II), these models were further adjusted in two alternative ways: ever/never military status, as defined in Yong et al., and years of active military service in four categories. In the pilot-only models, the excess rates or rate ratios for commercial

Table II. Age-Adjusted Mean Chromosome Translocation Frequency/100 Cell Equivalents and Rate Ratios by Categories of Cumulative Cosmic Radiation Absorbed Dose and Other Metrics.*

SUBJECTS	EXPOSURE METRIC	NO.	MEAN†	RATE RATIO	95% CI‡	*P*-VALUE‡
All (*N* = 133)	Absorbed dose from all flying sources (mGy)					
	<10	60	0.33	1.0§		0.52
	10 to <15	34	0.39	1.18	0.81–1.70	
	15 to <20	28	0.34	1.05	0.70–1.56	
	≥20	11	0.47	1.42	0.85–2.31	
Pilots (*N* = 83)	Absorbed dose from all flying sources (mGy)					
	<10	10	0.42	1.0§		0.66
	10 to <15	34	0.39	0.92	0.49–1.81	
	15 to <20	28	0.33	0.77	0.37–1.62	
	≥20	11	0.43	1.02	0.45–2.31	
	Absorbed dose limited to study airline flights (mGy)¶					
	<10	34	0.35	1.0§		0.12
	10 to <15	36	0.35	1.00	0.65–1.54	
	15 to <20	13	0.56	1.63	0.91–2.92	
	Absorbed dose from commercial aircraft (mGy)**					
	<10	30	0.32	1.0§		0.31
	10 to <15	37	0.38	1.20	0.76–1.91	
	15 to <20	16	0.50	1.57	0.87–2.82	
	Military status					
	Never	25	0.34	1.0§		0.45
	Ever	58	0.39	1.17	0.78–1.80	
	Duration of active military service (yr)					
	0 (no military service)	25	0.34	1.0§		0.06
	>0 to <6	16	0.43	1.26	0.76–2.09	
	6 to <8	28	0.46	1.36	0.88–2.11	
	≥8	14	0.23	0.69	0.38–1.25	
	Absorbed dose from military service (mGy)					
	0 (no military service)	25	0.34	1.0§		0.008
	>0 to <0.5	11	0.57	1.69	1.03–2.78	
	0.5 to <1	9	0.55	1.65	0.97–2.76	
	1 to <2	15	0.40	1.18	0.72–1.93	
	≥2	23	0.25	0.74	0.44–1.22	
	Number of solar particle events					
	<5	23	0.35	1.0§		0.61
	5 to 6	22	0.43	1.23	0.77–1.97	
	7 to 8	20	0.32	0.91	0.54–1.51	
	≥9	18	0.41	1.15	0.70–1.89	
	Cumulative red bone marrow X-ray dose score					
	<5	33	0.27	1.0§		0.03
	5 to <20	39	0.46	1.72	1.16–2.58	
	≥20	11	0.44	1.64	0.95–2.82	
	Median standard sleep interval travel (min/segment)					
	0	56	0.36	1.0§		0.36
	>0 to <90	13	0.34	0.95	0.56–1.54	
	≥90	14	0.49	1.36	0.87–2.08	

* From log-linear Poisson regression models using the AMFIT module of EPICURE (Hirosoft, Seattle, WA).
† Age-adjusted mean chromosome translocation frequency/100 CE (at mean pilot age of 46.7 yr).
‡ 95% profile likelihood confidence interval (CI) and likelihood ratio *P*-value adjusted for overdispersion using the deviance-based estimate of the variance inflation factor.
§ Reference category.
¶ Cumulative absorbed dose estimated from study airline flights.
** Cumulative absorbed dose estimated from study airline flights plus information from other commercial aircraft.

aircraft flying and flight years increased when the model was adjusted for dichotomous military status. These increases were significant for the commercial flight years duration metric (models D4, H4) and the log-linear model for commercial aircraft absorbed dose (G4). Note that Model H4 is similar to that reported in Yong et al.[37] In contrast, when the four-category covariate for years of active military service was added to the age- and X-ray adjusted model, risk estimates decreased in models with commercial dose, but increased in models of commercial flight years (models C5, D5, G5, H5).

Among pilots, estimated excess translocation frequency per 100 CEs was −0.003 (95% CI −0.017 to 0.014) per mGy absorbed dose from all flight sources, including military flying, adjusted for age and X-ray score (model B3). The estimated excess translocation frequency per 100 CEs was 0.007 (95% CI −0.019 to 0.033) per mGy absorbed dose from commercial

Table III. Poisson Regression Models of Chromosome Translocation Frequency/100 Cell Equivalents with Various Dose Metrics.

	EXCESS RATE MODEL*				LOG-LINEAR MODEL†			
DOSE METRIC COVARIATES‡		**EXCESS RATE**	**95% CI§**	**P§**		**RATE RATIO**	**95% CI§**	**P§**
All subjects (N = 133)								
Absorbed dose from all flying sources (mGy)¶								
None	A1	0.0070	0.0006–0.013	0.033	E1	1.02	1.00–1.04	0.029
Age	A2	0.0041	−0.0030–0.011	0.26	E2	1.01	0.99–1.03	0.18
Age, X-ray score	A3	0.0018	−0.0054–0.0091	0.63	E3	1.01	0.99–1.03	0.32
All pilots (N = 83)								
Absorbed dose from all flying sources (mGy)								
None	B1	0.0143	−0.0001–0.029	0.052	F1	1.03	1.00–1.07	0.059
Age	B2	0.0013	−0.014–0.019	0.88	F2	1.01	0.97–1.05	0.70
Age, X-ray score	B3	-0.0026	−0.017–0.014	0.75	F3	1.01	0.97–1.04	0.72
Absorbed dose from commercial aircraft (mGy)								
None	C1	0.0276	0.010–0.041	0.003	G1	1.08	1.03–1.13	0.003
Age	C2	0.0172	−0.0094–0.045	0.21	G2	1.05	0.99–1.12	0.12
Age, X-ray score	C3	0.0107	−0.014–0.034	0.40	G3	1.05	0.99–1.12	0.099
Age, X-ray score, military status	C4	0.0159	−0.011–0.034	0.24	G4	1.08	1.00–1.16	0.037
Age, X-ray score, active military years	C5	0.0067	−0.019–0.033	0.62	G5	1.04	0.97–1.13	0.28
Commercial flight years								
None	D1	0.0177	0.0063–0.027	0.003	H1	1.04	1.02–1.07	0.003
Age	D2	0.0119	−0.0067–0.030	0.21	H2	1.03	0.99–1.07	0.18
Age, X-ray score	D3	0.0123	−0.0033–0.022	0.13	H3	1.03	0.99–1.07	0.10
Age, X-ray score, military status	D4	0.0145	0.0045–0.021	0.023	H4	1.06	1.01–1.10	0.014
Age, X-ray score, active military years	D5	0.0131	0.0001–0.021	0.079	H5	1.04	0.98–1.10	0.17

* Excess rate models included a linear term for dose with all covariates in the log-linear part of the model (e.g., model A3 is given by rate = exp[$\beta_0 + \beta_1$(age-46.7) + β_2(X-ray group = 2) + β_3(X-ray group = 3)] + β_d(Absorbed dose); here, β_d is the excess rate. The background rate was modeled as a log-linear function of age, so that for individual i, the expected rate of translocations was $rate_i = exp[\beta_0 + \beta_1 age_i]$, where $rate_i$ was the rate of translocation per 100 CEs and age_i was the age (in years) of the subject at the time of blood draw (centered at 46.7 yr).

† Log-linear models included dose with the covariates in the log-linear part of the model (e.g., model E3 is given by rate = exp[$\beta_0 + \beta_1$(age-46.7) + β_2(X-ray group = 2) + β_3(X-ray group = 3) + β_d(Absorbed dose)]; here, β_d is the log rate ratio and background rate was modeled as for the excess rate models.

‡ Covariates age (centered at 46.7 yr), X-ray score (categorized as <5, 5 to <20, and ≥20 units with 1 unit approximating 1 mGy), military status (dichotomized as never/ever), and years of active military service (categorized as none, >0 to <6, 6 to <8, 8+ yr).

§ All models fit using the AMFIT module of EPICURE (Hirosoft, Seattle, WA). Likelihood ratio tests of significance were calculated using the F-statistic in the standard way for quasi-likelihood models.[19] 95% profile likelihood confidence interval (CI) and likelihood ratio P-value were adjusted for overdispersion using the deviance-based estimate of the variance inflation factor.

flying sources and 0.013 (95% CI 0.0001 to 0.021) per commercial flight year, adjusted for age, X-ray score, and active military years of service (models C5 and D5). Similarly, rate ratios were 1.01 (95% CI 0.97 to 1.04) at 1 mGy absorbed dose from all flight sources, including military flying, adjusted for age and X-ray score (model F3). Rate ratios were 1.04 (95% CI 0.97 to 1.13) at 1 mGy absorbed dose from commercial flying sources and 1.04 (95% CI 0.98 to 1.10) for 1 yr of commercial flying, adjusted for age, X-ray score, and active military years of service (models G5 and H5).

DISCUSSION

This is the largest cytogenetic study of male commercial airline pilots to date of which the authors are aware. We did not observe an association between the frequency of chromosome translocations and the cumulative cosmic radiation absorbed dose estimated from all types of flying in Poisson regression models adjusting for age and X-ray dose. However, there was some evidence for an increase in translocation frequency among pilots associated with estimated cosmic radiation absorbed dose from study-airline and all commercial flights, as well as commercial flight years as previously reported.[37] The ability of the study to detect a positive association between estimated absorbed dose and chromosome translocation frequency was limited by sample size, potential nondifferential exposure misclassification, the cytogenetic response to cosmic radiation, and sensitivity of the FISH technique.

Airline pilots have been studied previously for FISH-detected translocations using work-related metrics of exposure duration with inconsistent results. One study of a group of 48 pilots and flight technicians and 48 ground personnel found an increase in the relative risk for translocations after adjusting for age, smoking, and medication use, in the first three career flight-hour categories (<11,350, 11,350 to <15,000, 15,000–17,000); however, in the fourth category (>17,000 flight hours), the risk decreased and was not significantly higher than that of the referent group of ground personnel.[2] An earlier analysis of the airline pilots in the present study observed, after adjusting for age, X-ray dose, and military status, a statistically significant increase of 6% in the translocation frequency for a 1-yr incremental increase in commercial flight years; however, the translocation frequency was only significantly higher in the subgroup of 21 pilots in the highest quartile of commercial flight years (range 23 to 37 yr) compared to the 21 pilots in the lowest quartile (<14 yr).[37]

Our study addressed several limitations of these previous studies. First, rather than use a duration-based exposure proxy, we conducted the first exposure assessment of cosmic radiation dose for commercial pilots that considered all occupational and non-occupational flying sources.[9] Second, we increased the number of pilots studied to allow for comparisons between exposure levels of pilots. Third, we increased the sensitivity of detection of translocations by increasing the number of CEs evaluated (an average of 1039 CEs vs. 100 CEs per subject by Cavallo et al.[2]). Fourth, we accounted for several variables known to affect translocation frequency. Because age has been shown to account for as much as 70% of translocation frequency variability in a healthy population,[26] we restricted subjects to the age range of 35 to 56 yr and adjusted for age in the statistical analyses. To minimize the effect of cigarette smoking on translocation frequency variability,[29] subjects were further restricted to never smokers or limited smoking history. We also adjusted for radiation from diagnostic X-ray procedures. Although X-ray and smoking histories were self-reported, we believe that misclassification of these exposures was unlikely in our study groups.

Negative findings with respect to the analysis of estimated absorbed dose from cosmic radiation and translocation should be interpreted with caution. First, uncertainty in translocation frequencies can also be attributed to counting statistics—the number of cells scored and number of translocations observed per subject, which may be affected by cytogenetic response to cosmic radiation. Second, cosmic radiation represents a mixed radiation field containing both low- and high-LET neutrons. High-LET radiation can result in complex chromosome aberrations. Cells incurring these events are less likely to survive mitosis and thus have a shorter lifespan than cells with aberrations induced by low-LET radiation. Because these heavily damaged cells are less likely to survive and translocation frequency can decrease to some extent following radiation exposure, translocation frequency could have underestimated the dose in this study. Third, the uncertainty of cosmic radiation dose estimation is less well defined and harder to estimate. The EURADOS Working Group[5] identified several main sources of calculational uncertainty, some of which are also relevant to measurement uncertainty. Aircrew radiation exposure requires measurement or estimation of complex multicomponent fields, and total uncertainties are not fully known. EURADOS compared measurements to calculational methods and estimated calculational uncertainty at around 30%.[5] The dose estimate findings in this study refer to U.S. pilots and different results would be expected for pilots from other countries; however, the radiation programs we reference can estimate dose for pilots of any country. With this approach, differences in flight types are addressed since flights of all types have been individually assessed based on route-specific estimated radiation doses, with risk levels based on doses incurred.

The sample size and ability to recruit highly exposed pilots for this study were limited both by the cost of the FISH analyses and the logistics of participant selection and recruitment. As more studies that used FISH analysis have been published, it has become clear that larger sample sizes are needed to detect significant differences between groups due to high intra- and interindividual variability in translocation frequencies in the general population.[30,32] The magnitude of the lowest cumulative dose of radiation that can be detected by FISH is determined largely by the background level of translocations, which are mostly affected by age. Using a statistical approach for individuals unexposed to ionizing radiation and ages 20 to 69 yr for a FISH assay comparable to that used here, Tucker and Luckinbill[32] found that the minimum detectable chronic absorbed doses of ionizing radiation increased linearly with age at a rate of 15.9 mGy, 22.7 mGy, and 30.6 mGy per year at significance levels of $P = 0.05$, $P = 0.01$, and $P = 0.001$, respectively. Although these minimum doses for individuals may not be directly comparable to the lifetime doses estimated for our study pilots, the occupational dose incurred by pilots may be insufficient to be detected as translocations by FISH. In addition to age dependence of translocations, high interindividual variability of the background number of translocations complicates detecting differences between exposed and unexposed groups.[30] As with most occupational epidemiological studies, random misclassification of exposures and bias to the null are also possible explanations for negative findings.

An additional limitation of the study is the difficulty in assessment of cosmic radiation absorbed dose related to military flying, which was a component of exposure for 70% of pilots in the study. One reason for possible duration-dose differences may be that these metrics may diverge when exposures are not consistent over time, as we noted with military experience assessment of duration and dose. Among pilots who served in the military for no more than 8 yr prior to working for the study airline, there was an increase in translocation frequency compared to pilots with no military service (Table II). This reflects the higher doses incurred during initial military flying (active duty) compared to later years of diluted flying time. Military pilots who stay on active duty more than 6-8 yr generally move to desk jobs with minimal flying, and reserve duty typically requires a few weeks of flying per year. Thus, military experience/duration and dose tend to work in opposite directions: greater dose in early years of active duty military flight, followed by much lower doses in many later years of flying as a reserve pilot for brief periods while employed by the study airline. These results suggest that future studies of translocation frequencies in commercial pilots attempt to collect a more detailed military flight history, either by direct review of summary records with study pilots or by consultation with Department of Defense training resources.

We restricted some analyses to commercial flights for the study airline since these flights were the largest source of data for the study, with the most consistent flight exposures and least subject to potential exposure misclassification. The model based on commercial flying (G3) suggests an association between dose and translocation frequency. However, given the limitations described above, we cannot exclude alternate explanations for the differences between a commercial flying-based model and our models based on dose from all flying sources.

We believe that additional studies of chromosome translocation frequencies among cosmic-radiation exposed air crew are warranted. The impact of increased translocation frequencies at ionizing radiation levels in the range of aircrew exposures is still being determined. At aircraft altitudes, neutrons and protons contribute approximately 50% and 15% of the total ambient dose equivalent.[16] Interactions of protons and neutrons are primarily responsible for the high-LET component of exposure (we were not able to conduct our analysis by LET levels because neutrons and other individual particle types were highly correlated with combined dose). Although increased levels of translocations have been associated with workers exposed to high-LET radiation, issues remain regarding interpretation and analysis of the resulting translocations. As mentioned, complex chromosomal rearrangements can be more common in workers exposed to high-LET radiation, which can lead to underestimation of dose if the most damaged cells are lost to analysis.[33] Although this study's restriction to male pilots is a limitation, the results are likely relevant to female aircrew as well. Understanding the effects of cosmic radiation is relevant to other health effects unrelated to this specific study, including reproductive health outcomes such as miscarriage.[10] The implications of radiation health effects for pilots are also increasingly relevant to space workers; exposure assessment methods for space radiation are being developed from those used for aircrew.[4]

At this time, increased translocation frequencies for an individual aircrew member are not considered predictive of an increased risk of cancer. However, cosmic radiation induces structural chromosome aberrations;[6,21] some of these radiation-induced chromosome aberrations are difficult to repair,[33] and chromosome aberrations are generally associated with increased cancer risk.[1,14] Improvements in FISH methods have increased the sensitivity of the assay to detect excess translocations or complex chromosomal rearrangements. These improvements include progression of single color FISH to multicolor FISH, the use of multiple probe sets simultaneously which includes but is not limited to M-FISH, combinations of pancentromeric and telomeric probes for discriminating among translocation types, and increasing the number of cell equivalents for the same number of metaphase cells evaluated. Some of these methods could potentially be adapted for epidemiological studies to further evaluate a wide variety of chromosome aberrations and reproductive health effects in men and women.

We did not find an association between the translocation frequency and the estimated cumulative cosmic radiation absorbed dose from all sources in male commercial airline pilots, although additional analyses with absorbed dose from commercial flying sources suggested a relation between translocation frequencies and dose. Future studies will need to include larger numbers of highly exposed airline pilots and carefully consider sample size and exposure distribution issues to provide better assessment of the relation between biological dose based on translocation frequency and the estimated cosmic radiation dose.

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