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Mortality Among a Cohort of U.S. Commercial Airline Cockpit Crew

Lee C. Yong, PhD[*], **Lynne E. Pinkerton, MD, MPH**, **James H. Yiin, PhD**, **Jeri L. Anderson, PhD**, and **James A. Deddens, PhD**

Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, CDC, Cincinnati, Ohio

Abstract

Background—We evaluated mortality among 5,964 former U.S. commercial cockpit crew (pilots and flight engineers). The outcomes of a priori interest were non-chronic lymphocytic leukemia, central nervous system (CNS) cancer (including brain), and malignant melanoma.

Methods—Vital status was ascertained through 2008. Life table and Cox regression analyses were conducted. Cumulative exposure to cosmic radiation was estimated from work history data.

Results—Compared to the U.S. general population, mortality from all causes, all cancer, and cardiovascular diseases was decreased, but mortality from aircraft accidents was highly elevated. Mortality was elevated for malignant melanoma but not for non-chronic lymphocytic leukemia. CNS cancer mortality increased with an increase in cumulative radiation dose.

Conclusions—Cockpit crew had a low all-cause, all-cancer, and cardiovascular disease mortality but elevated aircraft accident mortality. Further studies are needed to clarify the risk of CNS and other radiation-associated cancers in relation to cosmic radiation and other workplace exposures.

Keywords

cancer; cockpit crew; cohort study; cosmic radiation; mortality; occupation; pilots

INTRODUCTION

Commercial airline cockpit crew (pilots and flight engineers) are occupationally exposed to cosmic ionizing radiation [IARC, 2000]. The cosmic radiation field at aircraft altitudes consists mainly of secondary neutrons and gamma radiation, with some protons, alpha particles, and heavy nuclei [Friedberg et al., 1989; Oksanen, 1998]. It has been estimated that approximately 40–65% of the cosmic radiation exposure of cockpit crew is from high linear energy transfer (LET) radiation, particularly neutrons which are generated due to

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[*] Correspondence to: Lee C.Yong, PhD, Surveillance Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, 4676 Columbia Parkway, Mail Stop R-15, Cincinnati, OH 45226. lay7@cdc.gov.

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interactions of cosmic rays [Goldhagen, 2000; IARC, 2000]. In terms of effective dose, the radiation doses for airline crew from commercial flights are estimated to be no more than 4–5 mSv per year [Bottollier-Depois et al., 2000; Verhaegen and Poffijn, 2000] and range between 0.2 and 5 mSv [O'Brien and Friedberg, 1994; Oksanen, 1998; Grajewski et al., 2011]. Cockpit crew members are also exposed to other chemical and physical agents in the working environment, such as jet fuel and engine emissions as well as electromagnetic fields (EMF) from cockpit instruments and circadian rhythm disruption [Boice et al., 2000].

Reports of elevated risks of cancers of various sites among cockpit crew have raised concerns about workplace exposures, particularly cosmic ionizing radiation. Thus far, the epidemiological findings on cancer mortality are inconsistent. The most consistent finding has been an increased risk of malignant melanoma [Sigurdson and Ron, 2004; Hammer et al., 2009]. An increased risk of cancer of the central nervous system (CNS), including brain, has also been reported in some but not in all studies [Hammer et al., 2009; Zeeb et al., 2012]. Elevated risk has been reported for leukemia, especially acute myeloid leukemia, in a few studies based on a small number of cases [Sigurdson and Ron, 2004].

In the largest mortality study reported to date, based on the pooled analysis of the data of 27,797 cockpit crew from nine European countries [Blettner et al., 2003], an increase in mortality from malignant melanoma and aircraft accidents, but a decrease in mortality from all causes, all cancer, cardiovascular diseases, and lung cancer was observed. Several previously published studies have similarly found a pattern of low all-cause [Kaji et al., 1993; Band et al., 1996; Zeeb et al., 2002, 2010; Paridou et al., 2003; Linnersjö et al., 2011; De Stavola et al., 2012], all-cancer [Band et al., 1996; Zeeb et al., 2002, 2010; Paridou et al., 2003; De Stavola et al., 2012], and cardiovascular disease [Band et al., 1996; Haldorsen et al., 2002; Zeeb et al., 2002, 2003; Linnersjö et al., 2011; De Stavola et al., 2012] mortality among cockpit crew when comparisons were made with an external general population. A high mortality from aircraft accidents has also been observed [Kaji et al., 1993; Band et al., 1996; Irvine and Davies, 1999; Haldorsen et al., 2002; Zeeb et al., 2002; Linnersjö et al., 2011; De Stavola et al., 2012], particularly among cockpit crew less than 30 years of age [Haldorsen et al., 2002].

An update of the German cohort [Zeeb et al., 2002] has been recently reported by Zeeb et al. [2010]. In this extended follow-up of one of the largest individual cohorts of male cockpit crew (n=6,017) through 2003 (an average of 22.7 years of follow-up), there was a decrease in mortality from all causes and all cancer, but an increase in mortality from cancer of the CNS (including brain). However, mortality for radiation-associated cancer (including leukemia, esophagus, stomach, large intestine, bladder/urinary tract, and thyroid gland) was not increased. A significant trend of decreased mortality from all causes but increased mortality from all cancer and CNS cancer across categories of employment duration was observed. In another analysis of this German cohort for an average of 23.5 years from 1960 to 2004 [Hammer et al., 2012], there was a decrease in total mortality (relative risk per 10mSv: 0.85, 95% CI: 0.79, 0.93) in contrast to a non-significant increase of all cancer mortality (relative risk per 10 mSv: 1.05, 95% CI: 0.91, 1.20) with increasing radiation doses, which was restricted to non-radiogenic cancers.

We evaluated the mortality of a cohort of pilots and flight engineers who were employed by the Pan American World Airways (Pan Am), a large international airline that closed in December 1991. Flight crews of this airline primarily worked on transoceanic and transpolar flights and have relatively high exposure to cosmic radiation as well as a long latency period. The objectives of this study were to evaluate the: (1) mortality experience of the cohort, and (2) relation of duration of employment and the estimated cumulative radiation dose with non-chronic lymphocytic leukemia, CNS cancer (including brain), and malignant melanoma, the outcomes of a priori interest based on previous studies.

METHODS

Study Cohort and Mortality Follow-Up

The cohort was assembled from the personnel records of Pan Am, which are available for employees who stopped working for Pan Am in 1953 or later. Employees who were employed as a pilot or/and flight engineer for at least one year before Pan Am closed in 1991, were U.S. citizens at the time of hire, and who worked at least one day at Pan Am after January 1, 1953 were included in the cohort. For 1,007 cohort members, the time employed as a pilot or/and flight engineer at other airlines prior to being transferred to Pan Am, was counted toward the 1-year minimum requirement. The study was approved by the Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH) and informed consent was waived for this study.

Vital status of each cohort member through December 31, 2008 was determined using the Social Security Administration and Internal Revenue Service records, the National Death Index, Pan Am personnel records, and ancestry.com. The causes of death for most deceased members were obtained from the National Death Index. For the period prior to 1979, the date from which death data are available from the National Death Index, the causes of death were obtained from death certificates obtained from state health departments and were coded by a nosologist according to the revision of the International Classification of Diseases (ICD) in effect at the time of death. Cohort members known to be alive after January 1, 1979 (the date from which data are available from the National Death Index) with a valid social security number and not identified as deceased or living outside of the U.S. after they last worked for Pan Am were assumed to be alive as of December 31, 2008. The National Death Index has been shown to provide complete and accurate death information in studies with known decedents [Cowper et al., 2002].

Exposure Assessment

Occupational exposures were assessed using two metrics: duration of employment and cumulative cosmic radiation dose. The duration of employment was computed from the sum of the time employed in jobs involving flying duties.

Details of the assessment of exposure to galactic cosmic radiation have been presented previously for studies of former Pan Am flight attendants [Waters et al., 2009; Anderson et al., 2011]. Briefly, a database of flight segments was created using information obtained from the Official Airline Guide^{TM} [OAG, periodical volumes 1930–1990]. Information on individual flight segments abstracted from the Official Airline Guide included the airline, origin and destination of flight, flight year, the number of flights per week for the segment, local departure and arrival times, and aircraft type. The company work history records indicated a large number of domiciles, and the Official Airline Guide indicated a large number of flights flown into those domiciles. Therefore, information was abstracted for nine Pan Am domiciles (Hong Kong, Honolulu, London, Los Angeles, Miami, New York, San Francisco, Seattle, Washington, DC) and one National Airlines domicile (Miami) for flights in the month of April for multiple years (1930, 1935, 1940, 1945, 1950, 1955, 1961, 1965, 1970, 1980, 1990) representative of flight eras [Waters et al., 2009]. Based on a preliminary analysis of electronic company records, these domiciles appeared to be the most common. Data for 1961 were used as there were no data available for 1960..

The CARI-6P code [O'Brien et al., 1996] was used to estimate the cosmic ionizing radiation effective dose for each flight segment in the database. Required inputs for the CARI-6P program (i.e., taxi time, ascent/descent times, and number/duration of cruise altitudes) were formulated based on assumptions using a modified algorithm [Grajewski et al., 2002] combined with information from former Pan Am pilots [Waters et al., 2009]. Domicile-era-specific and era-specific dose rates were then calculated using methods described in Waters et al. [2009] and Anderson et al. [2011], respectively. These dose rates (μSv/block hour) were originally weighted by block time (flight time plus taxi time), number of flights per week, and number of flight attendants per flight.

In the current study, the domicile-era-specific and era-specific dose rates were re-calculated omitting the weighting for flight attendants as it was assumed that the number of cockpit crew on a flight did not vary. As block hours were not available for this cohort, annual flight hours, which were reported in individual study subjects' medical records (and most likely estimated by the subjects) were used as a surrogate. Because the quality of flight hour data was poor for a significant portion of the cohort, the number of daily flight (block) hours was estimated by examining the distribution of annual flight hours reported in the study subjects' medical records. Study subjects were assigned daily effective doses from occupational exposure during flights using domicile-era-specific and era-specific dose rates combined with the estimated daily flight hours. These daily effective doses were summed over the duration of employment to obtain estimates of the cumulative effective dose (hereafter referred to as radiation dose).

Statistical Analyses

The mortality experience of the cohort was analyzed using a modified life table analysis system, LTAS.NET, developed by NIOSH [Schubauer-Berigan et al., 2011] to calculate standardized mortality ratios (SMRs) indirectly standardized to the U.S. population and directly standardized rate ratios (SRRs) for internal comparisons. A U.S. general population mortality rate file starting on January 1, 1960 with 52 cause-of-death categories was created from National Center for Health Statistics mortality data and U.S. census population estimates. For each subject, the person-years at risk (PYAR) began after the 1-year eligibility period, the date the mortality rate file begins, or, for a cohort member who transferred to Pan Am from other airlines, the date of transfer, whichever is later, and continued until the date of death, the date last observed in the U.S., or the study end date (December 31, 2008), whichever is earlier. Cohort members who ever lived outside the U.S. after they stopped working for Pan Am (n=21, including 12 who are known to have died outside of the U.S.) accrued PYAR until the date of their last known address in the U.S. or their date of last employment, whichever was later, because the date they emigrated was unknown. Some other cohort members only accumulated PYAR until the date last employed because they were lost to follow-up (n=217) after they stopped working at Pan Am. In addition, individuals who died outside of the U.S. but not known to have emigrated (n=50) were considered lost to follow-up in the analysis and accrued PYAR until the day before the date of death.

The PYAR were first stratified by gender (male/female), race (White/Other than White), and age and calendar year (in 5-year intervals) before being multiplied by the appropriate U.S. general population mortality rates to calculate the expected number of deaths for each stratum. The resulting expected numbers were summed across strata to obtain cause-specific expected deaths. The SMR is the ratio of observed to expected number of deaths. Ninety-five percent confidence intervals (95% CIs) of the SMRs, assuming that the observed number of deaths, D, in the cohort follows a Poisson distribution, were calculated based on exact limits when D was 10 or fewer or Byar's approximation when D was greater than 10 as described by Breslow and Day [1987].

SRR analyses were conducted to examine exposure-response relation formortality from non-chronic lymphocytic leukemia, CNS cancer, and malignant melanoma. The mortality experience of cohort members in the highest three quartiles for each exposure was compared with those in the lowest quartile (referent). Cut points were chosen so that approximately the same number of deaths occurred in each exposure quartile, thereby ensuring approximately equal precision of rate ratios [Richardson and Loomis, 2004]. Analyses were also lagged for 2 years for non-chronic lymphocytic leukemia and 10 years for CNS cancer and malignant melanoma. These lags were chosen a priori as typical for leukemia and solid tumors [UNSCEAR, 2006]. This is equivalent to assuming a minimum latency period before any exposure can cause death. In addition, we evaluated the mortality from aircraft accidents by duration of employment (<10 vs. ≥10 years). The reported 95% confidence intervals (CIs) for the SRRs across the exposure categories were estimated based on the methods described by Rothman and Greenland [1998] and Rothman [1986].

Relations between exposure metrics and mortality from non-chronic lymphocytic leukemia, CNS cancer, and malignant melanoma were further examined using Cox regression modeling. The PHREG Procedure in SAS (version 9.2, SAS Institute, Inc., Cary, NC) was used to compute the hazard ratios and 95% CIs based on full risk sets with all possible controls. In these analyses, age was the time variable (effectively matching on age). A lag for exposure of five (two for leukemia) and 10 years was also evaluated. Tests of significance for the hazard ratios, with and without adjustment for the date of birth as a potential confounder, were based on the likelihood ratio statistic.

A sensitivity analysis was also conducted to evaluate the effect of underestimation of duration of employment for cohort members who were: (1) transferred to two other U.S.

airlines when the routes were sold to these airlines in 1986 and 1991 according to the personnel records (n=1,246); or (2) laid off when Pan Am closed in 1991 (n=1,504). These members were assumed to have worked until an age of 60 years, the mandatory retirement age for pilots in the U.S. from 1959–2007 [Aerospace Medical Association, 2004], the date of death, the date last observed in the U.S., or study end date, whichever is earlier. Under these assumptions, the employment duration was changed for 2,635 (44%) of the total cohort (n=5,964) in the analysis. Because the results obtained with or without the change in the employment duration for these cohort members were similar, only the latter results are presented.

RESULTS

The analytical cohort consists of 5,964 cockpit crew after the exclusion of 23 members who died or were lost to follow-up prior to January 1, 1960, the date the mortality rate file begins (Table I). The cohort contributed a total of 202,316 PYAR. The cohort is predominantly males (97.6% White and 2.3% other than White) and 0.1% White females. Causes of deaths were obtained from the National Death Index or death certificates for 97% of the deaths. By the end of follow-up on December 31, 2008, there were a total of 2,045 U.S. deaths, which include 62 with unknown causes of death (3%) and 3 (0.1%) with an invalid underlying cause of death code. The median age at first employment was 28.8 years with the majority (62%) first employed before age 30 years. The median time since first employment was 42.2 years (mean=40.8, range 1.1–75.6); however, 90.5% had 20 or more years since first employment. The median duration of employment was 21.6 years (range 1–50.2 years).

Based on the flight hours reported in the medical records, the mean and median annual flight hours varied more by era than by domicile, although in both cases, the variation was not statistically significant (data not shown). The mean±standard deviation and median annual flight hours were 700±200 and 700, respectively, with a range of 0 to 1200 hours. Therefore, the median annual flight hours determined for each era was used for the dose estimation. The mean annual cosmic radiation dose was 1.4 mSv (median=1.4, range 0.0042–2.8) but varied from 0.081 mSv (range 0.00072–0.14) in 1940 to 1.6 mSv (range 0.059–1.8) in 1980. The cumulative radiation dose was strongly correlated with the duration of employment (Spearman correlation coefficient: 0.90). The mean cumulative radiation dose was 28 mSv (median=31; range 0.0047–71).

Table II presents the mortality results based on underlying causes as compared to the U.S. general population for the entire cohort. Mortality from all causes (2,045 deaths, SMR 0.58, 95% CI 0.56, 0.61) and all cancer (645 deaths, SMR 0.69, 95% CI 0.63, 0.74) was significantly lower than expected. Mortality was also significantly lower than expected for cardiovascular diseases. For the cancers of specific sites (Table II), a non-significant elevation of mortality was observed for CNS cancer (32 deaths, SMR 1.39, 95% CI 0.95, 1.96) and malignant melanoma (23 deaths, SMR 1.48, 95% CI 0.93, 2.21). There was a small elevation of mortality from chronic lymphocytic leukemia (9 deaths, SMR 1.14, 95% CI 0.52, 2.15) and non-melanoma skin cancer (6 deaths, SMR 1.19, 95% CI 0.44, 2.58). A non-significant reduction in mortality was observed for non-chronic lymphocytic leukemia (19 deaths, SMR 0.69, 95% CI 0.41, 1.07). Mortality was significantly less than expected for lung cancer (168 deaths, SMR 0.50, 95% CI 0.43, 0.59). Mortality from aircraft accidents was significantly elevated (52 deaths, SMR 15.95, 95% CI 11.91, 20.92).

Table III presents the internal SRR analyses stratified by duration of employment for mortality from the outcomes of a priori interest. A positive exposure-response relation was not observed for mortality from non-chronic lymphocytic leukemia or malignant melanoma (with or without a lag). For CNS cancer mortality, the SRR in the highest quartile compared to the lowest quartile of cumulative radiation dose was 1.27 (95% CI 0.39, 4.10) without a lag and 3.84 (95% CI 1.00, 14.74) with a lag of 10 years. The SRR for aircraft accidents for person-time ≥10 (30 deaths) compared to that of <10 years (22 deaths) of employment was 1.05 (95% CI 0.57, 1.93) (data not shown).

The results of Cox regression analyses for CNS cancer mortality based on the two exposure metrics as a continuous variable are shown in Table IV. Mortality from CNS cancer was not significantly associated with the duration of employment but was significantly associated with the cumulative radiation dose. The hazard ratio per 10 mSv was 2.17, 95% CI 1.06, 4.81; 2.37, 95% CI 1.09, 5.61; and 2.37, 95% CI 1.01, 6.12 when unlagged and with a lag of five and ten years, respectively. No adjustment was made for the date of birth because it did not alter the results. Non-chronic lymphocytic leukemia and malignant melanoma mortality were not significantly associated with the duration of employment or the cumulative radiation dose, with or without a lag (data not shown).

DISCUSSION

In this cohort of 5,964 cockpit crew, we observed a statistically significant lower mortality from all causes, all cancer, and cardiovascular diseases when compared with the U.S. general population. These results may reflect the high socioeconomic status and healthy worker effect of this occupational group highly selected for their health and physical fitness [Hammer et al., 2009; Zeeb et al., 2012]. Due to their job requirements, they are also under continuing medical surveillance throughout their career to maintain fitness and health in order to remain qualified to fly [Sykes et al., 2012]. This may explain the continuing healthy worker effect over time. The markedly reduced mortality from lung cancer and cardiovascular diseases in this cohort may further suggest the low prevalence of smoking as well as other lifestyle-associated cardiovascular disease risk factors among pilots and other cockpit crew members as reported by Houston et al. [2011]. However, as in previous studies [Kaji et al., 1993; Band et al., 1996; Irvine and Davies, 1999; Haldorsen et al., 2002; Zeeb et al., 2002; Blettner et al., 2003; Linnersjö et al., 2011; De Stavola et al., 2012], there is a highly elevated mortality from aircraft accidents as compared to the general population. Data from other studies suggest that this excess is due in part to occupational aircraft accidents [Haldorsen et al., 2002; Linnersjö et al., 2011] and the lack of experience of young pilots [Haldorsen et al., 2002]. In this cohort, there was no indication of a significant difference in mortality from aircraft accidents for those with ≥10 versus <10 years in duration of employment.

The number of leukemia deaths in this cohort is relatively small: 9 from chronic lymphocytic leukemia and 19 from non-chronic lymphocytic leukemia. Increased acute myeloid leukemia mortality and incidence have been observed in some studies of cockpit crew [Band et al., 1996; Gundestrup and Storm, 1999] with a fivefold increase among Danish jet pilots flying more than 5,000 hr compared to the Danish general population [Gundestrup and Storm, 1999]. As has been reported in other studies [Zeeb et al., 2002; Blettner et al., 2003; Langner et al., 2004], we did not find a significant increase in the mortality from leukemia as compared with the general population. Additionally, there was no clear association in relation to cumulative cosmic radiation dose for non-chronic lymphocytic leukemia which is considered to be induced by ionizing radiation [Sandier and Collman, 1987]. Our findings on leukemia mortality could be attributed to the somewhat limited statistical power to detect small effects due to the relatively small number of cases and low cumulative radiation dose in this occupational group.

An increase in brain cancer mortality was indicated in an earlier study of cockpit crew based on small number of cases [Band et al., 1996]. A non-significant elevation in CNS (including brain) cancer mortality was reported in the British Airways study [Irvine and Davies, 1999] and the pooled European study [Blettner et al., 2003]. CNS (including brain) cancer mortality was significantly elevated in the German cockpit crew with a significant trend for the duration of employment [Zeeb et al., 2010] and a non-significant trend for radiation dose [Hammer et al., 2012]. In this cohort, a non-significant elevation of CNS (including brain) cancer mortality based on 32 cases was observed. However, there was a significant increase in the mortality with increasing cumulative radiation dose when unlagged or lagged for 5 and 10 years. The risk factors for CNS cancer and the extent to which specific occupational exposures might influence the risk are currently unclear. Evidence for the association with ionizing radiation comes mostly from studies of atomic bomb survivors [Preston et al., 2002] and patients undergoing high therapeutic radiation doses [UNSCEAR, 2006]. There is also limited human evidence that EMF, a known exposure in the cockpit, causes CNS cancer [Cogliano et al., 2011].

An increased risk of malignant melanoma has been reported in several incidence studies [Gundestrup and Storm, 1999; Haldorsen et al., 2000; Rafnsson et al., 2000; Pukkala et al., 2002] and in some [Irvine and Davies, 1999; Blettner et al., 2003] but not all [Zeeb et al., 2010] mortality studies. We found an elevated but non-significant increase in mortality from malignant melanoma in this cohort. There was no evidence for an association with duration of employment or cumulative radiation dose. It is difficult, however, to evaluate risk of melanoma in mortality studies due to the high survival rate of this outcome. Exposure to ultraviolet radiation which is a risk factor for melanoma is considered minimal during commercial flights due to the protective materials in aircraft windows [Diffey and Roscoe, 1990]. Although a positive dose-response has been shown in relation to radiation dose among Nordic pilots, it has been suggested that this may be attributed to ultraviolet radiation from excessive sun exposure [Pukkala et al., 2002]. In a study among Icelandic flight crew and a subset of age and gender-matched general population, Rafnsson et al. [2003] found that sun exposure factors did not solely account for the difference in melanoma risk. However, in another study evaluating melanoma incidence in air traffic control officers and cockpit crew with respect to occupational exposures and lifestyle factors, the excess risk was found to reflect sun-related behavior rather than cosmic radiation exposure [dos Santos Silva et al., 2013].

The estimated cumulative (lifetime) radiation dose of this cohort is below 100 mSv. The mean cumulative dose is similar to that reported for the Pan Am flight attendants [Anderson et al., 2011], although the distribution for the cockpit crew is somewhat narrower and less skewed. In addition, the mean annual dose in this cohort is within the range previously estimated for cockpit crew [O'Brien and Friedberg, 1994; Oksanen, 1998]. On the other hand, there are several sources of uncertainty in the dose estimates for individual pilots, including the lack of individual flight histories, that is, specific routes and block hours flown, aircraft type (long-/short haul), etc. The use of average dose rates based on eras and domiciles along with using median annual flight hours could result in significant underestimation or overestimation for individual cohort members [Anderson et al., 2011]. Also, potential exposure to radiation from solar particle events was not accounted for in the dose estimates. In addition, there could be an underestimation of the duration of employment and cumulative dose because of reliance on past personnel records and the lack of data on work at other airlines. The results of the sensitivity analysis suggest that the study findings by duration of employment were unaltered by the underestimation of the duration of employment for some cohort members. The impact of the underestimation of cumulative dose for some cohort members on the study findings by cumulative dose are less clear because the mean annual cosmic radiation dose from occupational exposure during flights increased, in general, over time. However, cumulative radiation dose and employment duration at Pan Am and National Airlines were highly correlated, which suggests that the impact may have been minimal.

This study has several strengths compared to previous studies of cockpit crew. Our cohort has one of the longest average duration of employment and time since first employment to date. However, despite having one of the largest number of observed deaths to date, the numbers of many specific cancer sites are still small with limited power to detect small effects and to evaluate dose-response in relation to duration of employment and cumulative radiation dose. There are a number of study limitations, including the use of mortality rather than incidence data for the evaluation of cancer risk. In addition, we did not evaluate the effect of other occupational exposures or circadian rhythm disruption from crossing multiple time zones. Several studies have found a non-significant increase in prostate cancer mortality or incidence [Band et al., 1996; Irvine and Davies, 1999; Rafnsson et al., 2000; Pukkala et al., 2002]. In agreement with other studies [Blettner et al., 2003; Zeeb et al., 2010], we did not observe an excess in mortality from prostate cancer, a hormone-related cancer which may be associated with circadian rhythm disruption [Hammer et al., 2012]. However, cumulative time zones crossed but not work at night as a metric of circadian rhythm disruption was shown to be strongly correlated with the estimated cumulative cosmic radiation dose in the Pan Am flight attendant study [Pinkerton et al., 2012]. Thus, it is difficult to disentangle the effect of circadian rhythm disruption from that of radiation, although this may be possible in some cohorts depending on the types of routes flown, especially if data on the specific flights flown by each cohort member are available [Grajewski et al., 2002].

In conclusion, results of this study of a cohort of cockpit crew with one of the largest number of observed deaths to date are consistent with those reported in other studies. There is a significant decrease in mortality from all causes, all cancer, and cardiovascular diseases, but an elevated mortality from aircraft accidents as compared to the U.S. general population. Mortality was elevated for CNS cancer and malignant melanoma but not for non-chronic lymphocytic leukemia. In internal analyses, the estimated cumulative radiation dose was associated with mortality from CNS cancer in both unlagged and lagged analyses but not with mortality from malignant melanoma. These findings suggest a need for further studies to clarify the risk of CNS and other radiation-associated cancers in relation to cosmic radiation and other workplace exposures.

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TABLE I

Characteristics of the Study Cohort

	Total
Excluded from analysis[a]	23
Number of workers	5,964
Person-years	202,316
Race/sex	
Male	
White	5,820 (97.6%)
Other than White	138 (2.3%)
Female	
White	6 (0.1%)
Other than White	0
Vital status (as of 12/31/2008)	
Alive	3,631 (60.9%)
Emigrated[b]	21 (0.4%)
Lost to follow-up	217 (3.6%)
Foreign death[c]	50 (0.8%)
U.S. death	2,045 (34.3%)
Year of birth	
Median (range)	1934 (1896–1967)
Year of first employment[d]	
Median (range)	1965 (1929–1990)
Age at first employment[d] (years)	
<20	8 (0.1%)
20–<25	868 (14.6%)
25–<30	2,807 (47.1%)
30–<35	1,630 (27.3%)
35+	651 (10.9)
Time since first employment[d] (years)	
<10	83 (1.4%)
10–<20	486 (8.2%)
20+	5,395 (90.5)
Duration of employment[d] (years)	
<5	1,197 (20.1%)
5–<10	371 (6.2%)
10–<15	442 (7.4%)
15–<20	572 (9.6%)
20+	3,382 (56.7%)
Estimated cumulative radiation dose (mSv)	
<3	547 (9.2%)

	Total
3–<10	850 (14.3%)
10–<20	602 (10.1%)
20–<30	857 (14.4%)
30–<40	1,329 (22.3%)
40–<50	1,250 (21.0%)
50+	529 (8.9%)

[a] Died or were lost to follow-up prior to January 1,1960, the date the mortality rate file begin.

[b] Includes 12 cohort members known to have died outside of the U.S.

[c] In the analysis, these cohort members were considered lost to follow-up and accrued PYAR until the day before the date of death.

[d] Based on employment as a pilot or/and flight engineer at Pan Am or other airlines excluding leave>30 days.

TABLE II

SMRs for the Overall Cohort (1960–2008, U.S. Referent Rates)

Underlying cause of death	OBS	SMR	95% CI
All deaths[a]	2,045	0.58	0.56, 0.61
All cancers	645	0.69	0.63, 0.74
Buccal/pharynx	22	1.15	0.72, 1.74
Digestive cancers			
Esophagus	16	0.56	0.32, 0.92
Stomach	10	0.39	0.19, 0.72
Large intestine	62	0.80	0.62, 1.03
Rectum	13	0.79	0.42, 1.36
Biliary tree/liver	16	0.64	0.37, 1.04
Pancreas	36	0.76	0.53, 1.05
All respiratory cancers			
Larynx	5	0.47	0.15, 1.09
Bronchus, tree, and lung	168	0.50	0.43, 0.59
Breast cancer	2[b]	1.71	0.21, 6.18
Male genital cancers			
Prostate	77	0.90	0.71, 1.12
Testis/other male genital organs	1	0.52	0.01, 2.91
Urinary cancers			
Kidney	13	0.53	0.28, 0.90
Bladder/other urinary tract	16	0.60	0.34, 0.97
Lymphocytic and hematopoietic cancers			
Hodgkin disease	2	0.56	0.07, 2.03
Non-Hodgkin’s lymphoma	27	0.75	0.49, 1.09
Chronic lymphocytic leukemia	9	1.14	0.52, 2.15
Non-chronic lymphocytic leukemia	19	0.69	0.41, 1.07
All other and unspecified cancer			
Eye	2	4.13	0.50, 14.92
Bone	1	0.56	0.01, 3.10
Malignant melanoma	23	1.48	0.93, 2.21
Non-melanoma skin	6	1.19	0.44, 2.58
Central nervous system (including brain)	32	1.39	0.95, 1.96
Thyroid gland/other endocrine	2	0.77	0.09, 2.79
Benign neoplasms	15	0.97	0.55, 1.61
Diabetes mellitus	28	0.34	0.23, 0.49
Cardiovascular diseases			
Cerebrovascular disease	108	0.61	0.50, 0.74
Rheumatic heart disease	3	0.30	0.06, 0.88
All ischemic heart disease	231	0.49	0.43, 0.55
Acute myocardial infarction	160	0.37	0.31, 0.43

Underlying cause of death	OBS	SMR	95% CI
All other cardiovascular disease	118	0.47	0.39, 0.56
Non-malignant respiratory disease	96	0.41	0.33, 0.50
Liver cirrhosis	54	0.81	0.61, 1.05
Motor vehicle accidents	26	0.50	0.33, 0.73
Aircraft accidents	52	15.95	11.91, 20.92
Suicides	51	0.93	0.69, 1.22
Homicide/accidental death	3	0.21	0.04, 0.61
All other external causes	45	0.54	0.40, 0.73
All unknown and other causes of deaths[c]	295	0.79	0.71, 0.89

ICD, International Classification of Diseases; OBS, observed; SMR, standardized mortality ratio; CI, confidence interval.

[a] Excludes deaths that occurred outside of the U.S.

[b] Male breast cancer.

[c] Includes unknown causes of death (n=62) and others with an invalid underlying cause of death code (n =3).

TABLE III

SRRs for Non-Chronic Lymphocytic Leukemia, Cancer of the Central Nervous System (Including Brain), and Malignant Melanoma by Quartiles of Duration of Employment (Years) and Cumulative Radiation Dose (mSv)*

	Non-chronic lymphocytic leukemia		Central nervous system cancer		Malignant melanoma	
Exposure metric	**OBS**	**SRR (95% CI)**	**OBS**	**SRR (95% CI)**	**OBS**	**SRR (95% CI)**
Employment duration (Years)						
No lag						
1–<18.9	4	Referent	6	Referent	7	Referent
18.9–<26.4	4	0.68 (0.13, 3.51)	11	2.38 (0.78, 7.23)	8	0.96 (0.24, 3.83)
26.4–<31.8	6	1.02 (0.28, 3.76)	10	4.47 (1.46, 13.71)	5	0.59 (0.14, 2.46)
31.8+	5	1.65 (0.35, 7.78)	5	1.53 (0.39, 5.92)	3	0.31 (0.06, 1.57)
10-Year lag[a]						
0–<15.5	4	Referent	12	Referent	7	Referent
15.5–<25.0	4	0.67 (0.13, 3.47)	7	1.02 (0.32, 3.22)	9	3.52 (1.00, 12.42)
25.0–<31.3	8	1.43 (0.42, 4.92)	10	1.62 (0.62, 4.26)	5	1.38 (0.37, 5.10)
31.3+	3	0.25 (0.06, 1.15)	3	0.37 (0.09, 1.59)	2	0.70 (0.11, 4.61)
Cumulative radiation dose (mSv)						
No lag						
0–<22.9	5	Referent	7	Referent	6	Referent
22.9–<35.1	1	0.09 (0.01, 0.77)	6	0.84 (0.27, 2.63)	6	1.85 (0.53, 6.51)
35.1–<44.8	10	1.04 (0.35, 3.09)	11	1.50 (0.56, 4.04)	6	1.66 (0.48, 5.77)
44.8+	3	0.30 (0.07, 1.32)	8	1.27 (0.39, 4.10)	5	0.71 (0.20, 2.60)
10-Year lag[b]						
0–<18.1	5	Referent	9	Referent	6	Referent
18.1–<32.5	1	0.08 (0.01, 0.72)	8	1.29 (0.41, 4.00)	8	2.92 (0.76, 11.27)
32.5–<43.7	10	0.98 (0.33, 2.90)	6	1.13 (0.35, 3.68)	5	1.40 (0.33, 5.93)
43.7+	3	0.31 (0.07, 1.37)	9	3.84 (1.00, 14.74)	4	0.73 (0.16, 3.29)

OBS, observed; SRR, standardized rate ratio; CI, confidence interval.

[*] Quartiles of exposure metrics were based on all causes of deaths.

[a] A 2-year lag for leukemia with quartile cut points of <18.5, 18.5–<26.2, 26.2–<31.7, and 31.7+years.

[b] A 2-year lag for leukemia with quartile cut points of <22.3, 22.3–<34.8, 34.8–<44.7, and 44.7+mSv.

TABLE IV

Cox Regression Results for Cancer of the Central Nervous System (Including Brain) Mortality (n=32)*

Exposure	**Hazard ratio**	**95% CI**	***P*-value**[a]
Duration of employment per 10 years			
Unlagged	1.45	0.96–2.33	0.08
5-year lag	1.50	0.96–2.50	0.08
10-year lag	1.47	0.90–2.57	0.13
Cumulative radiation dose per 10 mSv			
Unlagged	2.17	1.06–4.81	0.03
5-year lag	2.37	1.09–5.61	0.03
10-year lag	2.37	1.01–6.12	0.05

CI, confidence interval.

*Age was the time variable and risk sets were constructed with all possible controls.

[a] Based on the likelihood ratio statistic.