AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 55:25–36 (2012)

Cause-Specific Mortality Among a Cohort of U.S. Flight Attendants

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Background *We evaluated mortality among 11,311 former U.S. flight attendants. The primary a priori outcomes of interest were breast cancer and melanoma.*
Methods *Vital status was ascertained through 2007, and life table analyses was conducted. Cumulative exposure to cosmic radiation and circadian rhythm disruption were estimated from work history data and historical published flight schedules.*
Results *All-cause mortality was less than expected among women but was elevated among men, primarily due to elevated HIV-related disease mortality. Mortality from breast cancer among women and melanoma was neither significantly elevated nor related to metrics of exposure. Mortality was elevated for non-Hodgkin's lymphoma among men; for alcoholism, drowning, and intentional self-harm among women; and for railway, water, and air transportation accidents.*
Conclusions *We found no evidence of increased breast cancer or melanoma mortality. Limitations include reliance on mortality data and limited power resulting from few melanoma deaths and relatively short employment durations.* Am. J. Ind. Med. 55:25–36, 2012. *© 2011 Wiley Periodicals, Inc.*

KEY WORDS: flight attendants; cancer; mortality; cohort; cosmic radiation; circadian rhythm disruption

INTRODUCTION

Flight attendants may have an increased risk of breast and other cancers due to workplace exposures including cosmic radiation and circadian rhythm disruption from traveling across multiple time zones and working at night. For flight attendants and other air crew members flying 600–1,000 hr/year, annual effective doses to cosmic radiation range from approximately 0.2–6 mSv [Friedberg and Copeland, 2003]. Cosmic radiation is qualitatively different from terrestrial ionizing radiation and consists primarily of charged particles and neutrons with neutrons contributing 40–65% of the dose equivalent at average flight altitudes [Goldhagen, 2000]. The relative biological effectiveness (RBE) of neutrons (i.e., the ratio of the absorbed doses of low-linear energy transfer radiation (e.g., X- or gamma (γ)-rays) to the dose of neutron radiation that results in the same biological effects) increases with decreasing dose and appears to range from 5 to 20; the RBE is expected to be close to 20 for the low-dose exposure experienced by flight crew [Sigurdson and Ron, 2004]. The International Agency for Research on Cancer (IARC) has designated X-, gamma, and neutron radiation as known human carcinogens [IARC, 2000]. However, no direct evidence exists in humans of carcinogenicity of neutrons [IARC, 2000].

Flight attendants may also have an increased risk of cancer due to hormonal alterations resulting from

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Contract grant sponsor: Office of Women's Health of the U.S. Department of Health and Human Services (partial support).
Disclosure Statement: The authors report no conflicts of interest.
The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.
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Accepted 29 August 2011
DOI 10.1002/ajim.21011. Published online 10 October 2011 in Wiley Online Library (wileyonlinelibrary.com).

disruption of circadian rhythms; substantial evidence exists indicating that the risk of breast cancer is influenced by endogenous hormones [Bernstein and Ross, 1993]. It has also been hypothesized that circadian rhythm disruption may reduce melatonin production and increase the likelihood of breast cancer [Stevens and Davis, 1996] and other cancers [Pukkala et al., 2002; Buja et al., 2005]. An association between breast cancer and decreased melatonin, and a protective effect against breast cancer of supplementary melatonin has been observed in animal studies [Stevens and Davis, 1996; Mawson, 1998]. In addition, epidemiologic studies suggest that women who work at night have an increased risk of breast cancer [Megdal et al., 2005]. In 2007, an IARC working group concluded that shift work that involves circadian rhythm disruption is probably carcinogenic to humans based on sufficient evidence in experimental animals for the carcinogenicity of light during biological night and limited human evidence [IARC, 2010].

In 1995, Pukkala et al. [1995] reported an increased risk of breast cancer among Finnish female flight attendants. Since then, a number of studies of cancer among flight crew have been conducted [Sigurdson and Ron, 2004]. Overall, the studies suggest that female flight attendants may have an increased risk of breast cancer and that both flight attendants and pilots may have an increased risk of melanoma [Sigurdson and Ron, 2004; Buja et al., 2005; Buja et al., 2006; Tokumaru et al., 2006].

We conducted a retrospective cohort mortality study to evaluate the risk of cancer among a cohort of former flight attendants who worked for Pan American World Airways (Pan Am), a large, U.S.-based international airline that declared bankruptcy and ceased operations in December 1991. Flight crews of this airline worked primarily on international flights with relatively greater exposure to cosmic radiation than domestic crew since dose increases with altitude (doubling every 1,500 meters at flight altitudes) and near the poles. The primary cancers of a priori interest were breast cancer and melanoma. Other radiogenic and hormonally related cancers were also of a priori interest. In addition, we were interested in evaluating the overall mortality experience of the cohort.

METHODS

The study was reviewed and approved by the Human Subjects Review Board of the National Institute for Occupational Safety and Health (NIOSH). Informed consent was waived.

Cohort Description

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 for at least 1 year as a flight attendant before Pan Am ceased operation in 1991, were U.S. citizens when they were hired, and who worked at least 1 day after January 1, 1953 were included in the cohort (n = 11,324). In 1981, Pan Am bought National Airlines, another U.S.-based airline. For cohort members who transferred to Pan Am when Pan Am bought National (n = 1,393), the time employed as a flight attendant at National was counted towards the 1-year minimum.

Exposure Assessment

The domiciles (i.e., cities/airports) where cohort members were based and the corresponding dates were available from company records, but information on the specific flights flown for individual flight attendants was not available. Duration of employment was calculated as the sum of time spent in flight attendant jobs at Pan Am and National excluding training periods. We reduced duration of employment by 50% for periods spent working part-time as a flight attendant at Pan Am. For 362 flight attendants for whom only the first and last date employed at National was available, we reduced duration of employment while working at National by 12%, the average percent of time that flight attendants at National with detailed work history information spent away from work while employed.

In addition to duration of employment, estimates of three other exposure metrics were considered: cumulative cosmic ionizing radiation effective dose, cumulative number of time zones crossed, and cumulative time spent working in the standard sleep interval (i.e., between 10 p.m. and 8 a.m. at the flight attendant's home base domicile). Duration of employment was computed for all cohort members while the other three exposure metrics were estimated as described elsewhere [Waters et al., 2009] for a subset of the cohort, specifically flight attendants with 100% of their work history at one or more of the following nine domiciles: Hong Kong, Honolulu, London, Los Angeles, Miami, New York, San Francisco, Seattle, and Washington DC.

Briefly, flight schedule data were abstracted from the Official Airline Guide™ [OAG, periodical volumes 1930–1990] for the nine domiciles for the years 1930, 1935, 1940, 1945, 1950, 1955, 1961 (1960 data unavailable), 1965, and 1970 when flight schedules existed. Additionally, data were abstracted for 1980 and 1990 for five of the nine domiciles, excluding Hong Kong, London, Seattle, and Washington. The use of a 10-year interval and a smaller number of domiciles for 1980 and 1990 was due to the large increase in flights per domicile in these years and limits on the amount of data that could be abstracted and coded. In addition to data for Pan Am, flight data for the Miami domicile of National were abstracted and coded separately. Only data on flights arriving at the domicile were abstracted because it was assumed that computation of only flights either arriving or departing would lead to similar domicile-based estimates. Radiation effective dose was calculated using the Federal Aviation Administration (FAA) program CARI6P, which estimates effective radiation dose for an individual flight segment [Friedberg and Copeland, 2003]. Assumptions were made to predict taxi time, ascent and descent times, and number and duration of cruise altitudes from block time (flight time plus taxi time) for historical Pan Am routes by modifying a validated algorithm [Grajewski et al., 2002] with information provided by former Pan Am pilots. Time zones crossed and standard sleep interval travel, metrics related to both melatonin desynchronization and sleep displacement, were defined and calculated as described in Grajewski et al. [2003].

Next, the segment-specific estimates of rates of radiation effective dose (μSv/block hr), time zones crossed (# of time zones/block hr), and standard sleep interval travel (standard sleep interval travel min/block hr) were frequency weighted (by the number of block hours per flight segment, the number of times the flight segment occurred per week, and the number of flight attendants that worked on the specific aircraft for that flight segment) to obtain domicile-era-specific rates. Work history information was then merged with the weighted domicile-era-specific exposure rates, assuming an 80 block hr month, to obtain estimates of cumulative radiation effective dose, time zones crossed, and time spent working during the standard sleep interval for each flight attendant.

Follow-Up

The vital status of all persons in the cohort was determined through December 31, 2007. Follow-up included inquiry through the Social Security Administration, Internal Revenue Service, U.S. Postal Service, and the National Death Index (NDI). The causes of death for most deceased members of the cohort were obtained from the NDI. Death certificates were obtained from state vital records offices for other deceased members of the cohort and coded by a trained 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 that the NDI began) with a valid social security number and not identified as deceased or residing outside the United States were assumed to be alive as of December 31, 2007. The sensitivity of the NDI is over 95% when social security numbers are available [Cowper et al., 2002].

Analysis

The mortality experience of the cohort was analyzed with the NIOSH LTAS.NET, a modified person-time analysis program [Schubauer-Berigan et al., 2011]. In LTAS.NET, ICD codes were mapped to cause of death categories as described by Robinson et al. [2006] and on the NIOSH website (http://www.cdc.gov/niosh/ltas/net200808/NIOSH-119%20table_20080418.pdf). Each cohort member accumulated person-years-at-risk (PYAR) for each year of life after the 1-year eligibility period, the date the U.S. mortality rate files begin (1/1/1960), or, for flight attendants who transferred to Pan Am from National, the date of transfer from National, whichever was later. Most cohort members accumulated PYAR until the date of death, the date last observed in the United States, or the ending date of the study (December 31, 2007), whichever was earliest. A few cohort members only accumulated PYAR until the date last employed because they were lost to follow-up (n = 60) or lived outside of the United States after they stopped working for Pan Am (n = 63). The PYAR were stratified into 5-year intervals by age and calendar time and were then multiplied by the appropriate U.S. gender, race, and cause-specific mortality rates [Robinson et al., 2006] to calculate the expected number of deaths for that stratum. The resulting expected numbers were summed across strata to obtain cause-specific and total expected number of deaths. The ratio of observed to expected number of deaths was expressed as the standardized mortality ratio (SMR). Ninety-five percent confidence intervals (CI) were computed for the SMRs assuming a Poisson distribution for observed deaths.

We stratified SMRs for female breast cancer and melanoma by time since first employment (<10, 10–19, 20+ years), duration of employment, cumulative radiation dose, cumulative time zones crossed, and cumulative time spent working in the standard sleep interval. For analyses stratified by duration of employment and the other three exposure metrics, the cohort was divided into four groups using quartiles of exposure based on all flight attendants.

We also calculated standardized rate ratios (SRRs) to compare female breast cancer among cohort members in the highest three quartiles with those in the lowest quartile for each exposure metric. We also evaluated the association between female breast cancer and the four exposure metrics using 10- and 20-year lags. Stratified SMRs and/or SRRs were also calculated for other non-accidental causes of death that were elevated in the cohort and plausibly related to cosmic radiation or circadian rhythm disruption.

Mortality from female breast cancer was further evaluated in internal analyses with Poisson log-linear regression modeling using the GENMOD procedure in SAS (version 9.2, SAS Institute, Inc., Cary, NC). Rate ratios, adjusted for race (non-white vs. white), time since first employment (20+ years vs. <20 years), and age and year of birth using natural regression splines (i.e., restricted cubic splines with $k = 3$ knots at the 10th, 50th, and 90th percentiles) were calculated for each of the four exposure metrics, using the lowest category as the reference group. For each exposure metric, the cohort was divided into six groups based on sextiles of exposure among the female breast cancer cases. A test for trend was performed by treating the categorical exposure groups as a continuous variable and assigning a weight equal to the PYAR-weighted mean exposure level for the groups [Richardson and Loomis, 2004].

A sensitivity analysis of the life table results was performed to evaluate the impact of underestimating duration of employment for some cohort members, as described in the Appendix.

RESULTS

A total of 11,311 workers contributing 350,771 person-years were included in the analysis. One worker was excluded from the analysis because date of birth was missing; another 12 were excluded because their date last observed was prior to 1960 when the mortality rate files begin. The distribution of the cohort by race, sex, vital status, first year of employment, time since first employment, and duration of employment is presented in Table I. The cohort is primarily white (89.5%) and female (85.0%). Causes of death were obtained from death certificates or the NDI for 989 (96.8%) of 1,022 individuals known to have died in the United States. Twenty-three cohort members died outside of the United States. Of these, 15 died outside of the United States while they were employed by Pan Am and 14 were due to aircraft accidents. The duration of employment of the cohort is

TABLE I. Characteristics of the Study Population

	Total
Excluded from analysis	13
Number of workers	11,311
Race/Sex	
White male	1,503 (13.3%)
Non-white male	198 (1.8%)
White female	8,621 (76.2%)
Non-white female	989 (8.7%)
Vital status (as of 12/31/2007)	
Alive	9,953 (88.0%)
Deceased	1,045 (9.2%)
U.S. death	1,022 (97.8%)
Foreign death	23 (2.2%)
Unknown	313 (2.8%)
Year of birth	
Median (range)	1948 (1896–1970)
Year of first employment[a]	
Median (range)	1971 (1929–1990)
Age at first employment[a] (years)	
<20	273 (2.4%)
20–<25	8,493 (75.1%)
25–<30	1,939 (17.1%)
30–<35	404 (3.6%)
35+	202 (1.8%)
Time since first employment[a] (years)	
<10	193 (1.7%)
10–<20	1,903 (16.8%)
20+	9,215 (81.5%)
Duration of employment[a] (years)	
<1	224 (2.0%)[b]
1–<5	4,861 (43.0%)
5–<10	2,352 (20.8%)
10–<15	1,649 (14.6%)
15–<20	1,122 (9.9%)
20+	1,103 (9.8%)
Estimated cumulative radiation dose (mSv)	
Unknown	1,156 (10.2%)
<3	781 (6.9%)
3–<10	3,720 (32.9%)
10–<20	1,866 (16.5%)
20–<30	1,336 (11.8%)
30–<40	1,038 (9.2%)
40–<50	715 (6.3%)
50+	699 (6.2%)
Estimated cumulative time zones crossed	
Unknown	1,156 (10.2%)
<1,000	2,205 (19.5%)
1,000–<2,000	2,324 (20.5%)
2,000–<5,000	2,675 (23.6%)
5,000–<10,000	2,350 (20.8%)
10,000+	601 (5.3%)
Estimated cumulative time spent working in the standard sleep interval (hr)	
Unknown	1,156 (10.2%)
<500	3,137 (27.7%)
500–<1,000	1,928 (17.0%)
1,000–<2,000	1,973 (17.4%)
2,000–<4,000	2,451 (21.7%)
4,000+	666 (5.9%)

[a]Based on employment as a flight attendant at Pan Am and National excluding training.

[b]These flight attendants met the 1 year minimum employment requirement; however, their employment duration was adjusted to reflect training and part-time work.

relatively short with a median of 5.9 years. According to the personnel records, 2178 (19.3%) of the cohort members transferred to two other U.S. airlines when routes were sold to these airlines. Only 7.7% of the cohort was first employed as a flight attendant prior to 1958 when jet aircraft were first used. The time since first employment was 20 years or more for 81.5% of the cohort.

Of the 11,311 cohort members in the analysis, 10,155 (89.8%) were always based at domiciles for which domicile-era specific exposure estimates were calculated. Employment duration, cumulative radiation dose, and cumulative time zones crossed were highly correlated (Pearson correlation coefficient: 0.92–0.98; Spearman correlation coefficient: 0.96–0.99); cumulative time spent working in the standard sleep interval was moderately correlated with the other exposure estimates (Pearson correlation coefficient: 0.76–0.83; Spearman correlation coefficient: 0.89–0.92). The median estimated cumulative radiation dose was 12.7 mSv (range 0.33–102 mSv).

The results of the analysis for all underlying causes of death are shown in Table II. Mortality from all causes among women (SMR 0.59; 95% CI 0.54, 0.64) was significantly less than expected, consistent with the healthy worker effect. However, mortality from all causes among men (SMR 1.09; 95% CI 0.99, 1.19) was elevated, primarily due to an elevation in HIV-related diseases (SMR 16.0; 95% CI 13.1, 19.2). Mortality from all cancers was less than expected among both women (SMR 0.71; 95% CI 0.62, 0.81) and men (SMR 0.83; 95% CI 0.67, 1.02). Mortality from breast cancer among women (78 deaths; SMR 1.01; 95% CI 0.80, 1.26) and melanoma (7 deaths; SMR 0.90; 95% CI 0.36, 1.85) was not elevated. Mortality from non-melanoma skin cancer (3 deaths; SMR 4.93; 95% CI 1.02, 14.4) and brain cancer (6 deaths; SMR 1.97; 95% CI 0.72, 4.30) was elevated among men. Only one death from non-melanoma skin cancer was observed among women (SMR 1.63; 95% CI 0.04, 9.09). Mortality from railway, water, and air transport injuries (SMR 3.59; 95% CI 1.64, 6.81) was elevated. Eight of the nine deaths in this death category were due to air transport injuries. When 14 foreign deaths due to aircraft accidents identified from sources including company records and aircraft accident internet sites were included in the analysis, the SMR for railway, water and air transport injuries increased to 9.17 (95% CI 5.81, 13.8). Among outcomes other than those of a priori interest, mortality from non-Hodgkin's lymphoma (10 deaths; SMR 2.30; 95% CI 1.10, 4.23), and other causes (residual codes) (27 deaths; SMR 2.48; 95% CI 1.63, 3.61) among men and alcoholism (12 deaths; SMR 2.87; 95% CI 1.48, 5.01), drowning (8 deaths; SMR 6.41; 95% CI 2.77, 12.6), and intentional self-harm (34 deaths; SMR 1.51; 95% CI 1.05, 2.11) among women were elevated. Mortality from alcoholism (5 deaths; SMR 1.92; 95% CI 0.62, 4.49) and intentional self-harm (16 deaths; SMR 1.37; 95% CI 0.78, 2.23) was also elevated among men, but less so and not significantly; there were no observed deaths from drowning among men.

Pneumocystosis, deficiency of cell mediated immunity, diseases of other mycobacteria, and/or unspecified immune deficiency was the underlying cause of death or a contributing cause of death for 22 of the 27 deaths from other causes (residual codes) among men. Alcohol or other substances were a contributing cause to several of the eight drowning deaths but small numbers preclude reporting the exact numbers.

There was no evidence of an exposure–response relationship when SMRs and SRRs for female breast cancer and SMRs for melanoma were stratified by employment duration, cumulative radiation dose, cumulative time zones crossed, or cumulative time spent working in the standard sleep interval (Table III). This finding was unchanged when these metrics were lagged by 10 and 20 years (data not shown). The SMRs for melanoma were elevated in the highest exposure category for cumulative radiation dose, cumulative number of time zones crossed, and cumulative time spent working in the standard sleep interval, but these results were based on three observed deaths and the CIs were wide. Results based on duration of employment were essentially unchanged when the analysis was repeated under the alternative assumption about the duration of employment for cohort members who transferred to other airlines when those airlines bought Pan Am routes and for cohort members who were still employed when Pan Am ceased operations (data not shown). We also calculated SMRs stratified by the four exposure metrics for brain cancer among men (Table III) and SRRs stratified by the four exposure metrics for non-Hodgkin's lymphoma among men and alcoholism (data not shown). The SMRs for brain cancer among men were elevated in the highest category of each exposure metric but the CIs were wide and the SMRs were also elevated in the lowest category based on one observed death. Mortality from non-Hodgkin's lymphoma among men was not associated with any of the four exposure metrics (data not shown). Mortality from alcoholism was associated with cumulative time spent working in the standard sleep interval but not with the other three exposure metrics. The SSRs for alcoholism mortality among cohort members in the highest three quartiles compared to the lowest quartile were 1.06 (95% CI 0.14, 7.90), 1.11 (95% CI 0.19, 6.67), and 1.94 (95% CI 0.38, 9.80), respectively (trend P-value <0.01).

In analyses stratified by time since first employment, SMRs for female breast cancer were 0.39 (1 death; 95% CI 0.01, 2.16), 1.21 (15 deaths; 95% CI 0.68, 2.00), and 0.99 (62 deaths; 95% CI 0.76, 1.27) for cohort members with <10, 10–19, and 20 or more years since first employment, respectively and the SMRs for melanoma were 1.48 (1 death; 95% CI 0.04, 8.24), 0.64 (1 death; 95% CI 0.02,

TABLE II. SMRs by Gender and for the Overall Cohort (1960–2007, U.S. Referent Rates)

	Men (n = 1,701)			Women (n = 9,610)			Overall (n = 11,311)		
Underlying cause of death[a]	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
All deaths[b]	492	1.09	0.99, 1.19	530	0.59[d]	0.54, 0.64	1,022	0.76[d]	0.71, 0.80
All cancers	90	0.83	0.67, 1.02	241	0.71[d]	0.62, 0.81	331	0.74[d]	0.66, 0.83
Buccal and pharyngeal ca	2	0.82	0.10, 2.95	1	0.31	0.01, 1.73	3	0.53	0.11, 1.55
All digestive ca	22	0.83	0.52, 1.25	44	0.78	0.56, 1.04	66	0.79	0.61, 1.01
Esophagus	2	0.63	0.08, 2.26	2	0.72	0.09, 2.60	4	0.67	0.18, 1.72
Stomach	1	0.31	0.01, 1.74	7	1.38	0.56, 2.85	8	0.97	0.42, 1.91
Intestine (except rectum)	12	1.31	0.67, 2.28	17	0.78	0.45, 1.24	29	0.93	0.62, 1.34
Rectum	2	1.00	0.12, 3.62	2	0.44	0.05, 1.60	4	0.61	0.17, 1.57
Biliary passages, liver and gallbladder	3	0.93	0.19, 2.73	2	0.28	0.03, 1.02	5	0.49	0.16, 1.14
Pancreas	0	0.00[d]	0.00, 0.68	13	0.92	0.49, 1.58	13	0.67	0.35, 1.14
Peritoneum and other and unspecified digestive organs	2	5.46	0.66, 19.73	1	0.83	0.02, 4.61	3	1.90	0.39, 5.56
All respiratory ca	25	0.66[e]	0.43, 0.98	41	0.50[d]	0.36, 0.68	66	0.55[d]	0.43, 0.70
Trachea, bronchus and lung	25	0.69	0.45, 1.02	40	0.50[d]	0.36, 0.68	65	0.56[d]	0.43, 0.71
Breast ca	1	7.40	0.19, 41.24	78	1.01	0.80, 1.26	79	1.02	0.81, 1.27
Female genital ca	—	—	—	33	0.79	0.54, 1.11	33	0.79	0.54, 1.11
Cervix uteri	—	—	—	2	0.18[d]	0.02, 0.64	2	0.18[d]	0.02, 0.64
Other unspecified parts of uterus	—	—	—	3	0.39	0.08, 1.14	3	0.39	0.08, 1.14
Ovary, fallopian tube, and broad ligament	—	—	—	26	1.21	0.79, 1.77	26	1.21	0.79, 1.77
Male genital ca	5	0.51	0.17, 1.20	—	—	—	5	0.51	0.17, 1.20
Prostate	4	0.42	0.11, 1.08	—	—	—	4	0.42	0.11, 1.08
Testes	1	3.94	0.10, 21.96	—	—	—	1	3.94	0.10, 21.96
All urinary ca	4	0.70	0.19, 1.79	5	0.64	0.21, 1.50	9	0.67	0.31, 1.27
Kidney	1	0.36	0.01, 2.00	4	0.75	0.20, 1.92	5	0.62	0.20, 1.44
Bladder and other urinary organs	3	1.03	0.21, 3.00	1	0.41	0.01, 2.30	4	0.75	0.20, 1.91
Lymphatic and hematopoietic ca	15	1.37	0.77, 2.26	14	0.52[d]	0.28, 0.86	29	0.76	0.51, 1.09
Hodgkin's dz	0	0.00	0.00, 6.34	1	0.54	0.01, 3.01	1	0.41	0.01, 2.29
Non-Hodgkin's lymphoma	10	2.30[e]	1.10, 4.23	4	0.38[e]	0.10, 0.98	14	0.95	0.52, 1.59
Multiple myeloma	1	0.55	0.01, 3.09	2	0.45	0.05, 1.63	3	0.48	0.10, 1.41
Leukemia and aleukemia	4	0.95	0.26, 2.43	7	0.67	0.27, 1.38	11	0.75	0.37, 1.34
All other and unspecified ca	16	1.09	0.62, 1.78	25	0.58[d]	0.38, 0.86	41	0.71[e]	0.51, 0.97
Bone	0	0.00	0.00, 13.66	0	0.00	0.00, 5.17	0	0.00	0.00, 3.75
Melanoma	2	1.02	0.12, 3.69	5	0.85	0.28, 1.99	7	0.90	0.36, 1.85
Non-melanoma skin	3	4.93[e]	1.02, 14.40	1	1.63	0.04, 9.09	4	3.27	0.89, 8.38
Brain and other parts of the nervous system	6	1.97	0.72, 4.30	8	0.76	0.33, 1.49	14	1.03	0.56, 1.73
Thyroid gland	0	0.00	0.00, 19.13	1	1.28	0.03, 7.12	1	1.02	0.03, 5.71
Benign and unspecified neoplasms	0	0.00	0.00, 2.59	1	0.23	0.01, 1.31	1	0.18[e]	0.00, 0.98
Tuberculosis and HIV-related dz	113	14.87[d]	12.25, 17.87	3	0.41	0.09, 1.21	116	7.81[d]	6.45, 9.36
HIV-related	112	15.96[d]	13.14, 19.20	3	0.45	0.09, 1.33	115	8.44[d]	6.97, 10.14
Diseases of the blood and blood forming organs	0	0.00	0.00, 2.09	2	0.47	0.06, 1.68	2	0.33	0.04, 1.19
Diabetes mellitus	3	0.31[e]	0.06, 0.92	0	0.00[d]	0.00, 0.13	3	0.08[d]	0.02, 0.23
Mental psychoneurotic and personality disorders	9	1.31	0.60, 2.49	14	1.44	0.79, 2.42	23	1.39	0.88, 2.08
Alcoholism	5	1.92	0.62, 4.49	12	2.87[d]	1.48, 5.01	17	2.51[d]	1.46, 4.01
Nonmalignant nervous system and sense organs dz	12	1.22	0.63, 2.14	13	0.58[e]	0.31, 0.98	25	0.77	0.50, 1.14
Heart dz	113	0.78[d]	0.64, 0.93	42	0.28[d]	0.20, 0.38	155	0.52[d]	0.44, 0.61
Ischemic heart dz	95	0.81[e]	0.65, 0.98	25	0.24[d]	0.16, 0.36	120	0.55[d]	0.45, 0.65
Circulatory system dz	21	0.61[e]	0.38, 0.94	28	0.44[d]	0.29, 0.63	49	0.50[d]	0.37, 0.66
Nonmalignant respiratory dz	24	0.66[e]	0.42, 0.99	27	0.44[d]	0.29, 0.63	51	0.52[d]	0.39, 0.68

(*Continued*)

TABLE II. (*Continued*)

Underlying cause of death[a]	Men (n = 1,701)			Women (n = 9,610)			Overall (n = 11,311)		
	OBS	SMR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
Chronic obstructive pulmonary dz	13	0.69	0.37, 1.18	15	0.45[d]	0.25, 0.74	28	0.54[d]	0.36, 0.77
Nonmalignant digestive dz	12	0.61	0.31, 1.06	31	0.72	0.49, 1.02	43	0.69[e]	0.50, 0.92
Cirrhosis and other chronic liver dz	7	0.69	0.28, 1.41	18	0.84	0.50, 1.33	25	0.79	0.51, 1.17
Nonmalignant skin and subcutaneous tissue dz	2	4.70	0.57, 16.98	1	0.72	0.02, 4.02	3	1.66	0.34, 4.84
Nonmalignant genitourinary dz	6	0.85	0.31, 1.84	2	0.14[d]	0.02, 0.49	8	0.37[d]	0.16, 0.72
Symptoms and ill-defined conditions	4	0.76	0.21, 1.95	12	1.02	0.53, 1.79	16	0.94	0.54, 1.53
Transportation injuries	13	0.92	0.49, 1.57	20	0.62[e]	0.38, 0.96	33	0.71	0.49, 1.00
Railway, water and air transport[c]	4	3.12	0.85, 7.99	5	4.08[e]	1.32, 9.51	9	3.59[d]	1.64, 6.81
Falls	3	0.95	0.20, 2.79	7	1.94	0.78, 4.01	10	1.48	0.71, 2.73
Other injury	4	0.33[e]	0.09, 0.84	17	0.74	0.43, 1.18	21	0.60[e]	0.37, 0.91
Drowning	0	0.00	0.00, 3.42	8	6.41[d]	2.77, 12.63	8	3.44[d]	1.49, 6.78
Intentional self-harm	16	1.37	0.78, 2.23	34	1.51[e]	1.05, 2.11	50	1.46[e]	1.09, 1.93
Assault and homicide	3	0.49	0.10, 1.44	6	0.53	0.19, 1.15	9	0.52[e]	0.24, 0.98
Other causes	27	2.48[d]	1.63, 3.61	13	0.37[d]	0.20, 0.63	40	0.86	0.62, 1.18
Unknown cause of death	17			16			33		

ICD, International Classification of Diseases; OBS, observed number of deaths; SMR, standardized mortality ratio; CI, confidence interval; ca, cancer; dz, disease.
[a]ICD codes were mapped to cause of death categories as described by Robinson and colleagues (2006) and as described on the NIOSH website (http://www.cdc.gov/niosh/ltas/net200808/NIOSH-119%20table.20080418.pdf). One major category (musculoskeletal and connective system diseases) was omitted because no deaths occurred.
[b]Excludes 23 deaths that occurred outside the United States.
[c]When 14 deaths outside the United States due to aircraft accidents were included, the overall SMR (95% CI) for railway, water, and air transport injuries was 9.17 (95% CI 5.81, 13.76).
[d]99% CI excludes 1.0.
[e]95% CI excludes 1.0.

3.54), and 0.90 (5 deaths; 95% CI 0.29, 2.10) for cohort members with < 10, 10–19, and 20 or more years since first employment, respectively. All six brain cancer deaths among men occurred among men with 20 or more years since first employment (SMR 2.60; 95% CI 0.95, 5.65).

There was also no evidence of an exposure–response relation between female breast cancer with the exposure metrics in internal analyses based on Poisson regression (Table IV).

DISCUSSION

We observed a marked increase in HIV-related mortality among male flight attendants. A marked increase in AIDS mortality was also observed among male flight attendants in a large collaborative study of flight attendants in eight European countries [Zeeb et al., 2003], and the incidence of Kaposi's sarcoma, which is usually associated with HIV infection and AIDS, was elevated in studies of male flight attendants from California [Reynolds et al., 2002] and Sweden [Linnersjö et al., 2003]. Mortality from non-Hodgkin's lymphoma was elevated among men but not women and may be related to HIV-related disease not coded as such on death certificates. The lack of an observed exposure–response relationship with the four metrics of exposure is consistent with this hypothesis. Mortality from non-Hodgkin's lymphoma was also elevated among men but not women in the collaborative European study of flight attendants [Zeeb et al., 2003]. Some of the deaths in the other causes category were also due to causes of death that may be related to HIV-related disease. Prior to 1987, HIV-related deaths were classified to deficiency of cell-mediated immunity, pneumocystosis, malignant neoplasms including neoplasms of the lymphatic and hematopoietic tissues, and to a number of other causes [NCHS Definitions, n.d.].

Among female flight attendants, we observed an increase in mortality from alcoholism, (accidental) drowning, and intentional self-harm. A threefold increase in mortality from suicide, based on six observed deaths, was observed among female Italian flight attendants [Ballard et al., 2002], but no increase in mortality from suicide was observed among female German flight attendants [Blettner et al., 2002]. When data from the Italian and German study were pooled with other data in a large, collaborative study of eight European countries, a non-significant 19% increase in mortality from suicide among female flight attendants was observed [Zeeb et al., 2003]. In a study of Swedish flight attendants, an increase in alcohol-related mortality (i.e., mortality from alcoholism, alcoholic

TABLE III. SMRs for Female Breast Cancer, Melanoma, and Brain Cancer in Men and SRRs for Female Breast Cancer Stratified by Quartiles of Estimated Cumulative Exposure (Employment Duration, Radiation Dose, Time Zones Crossed, and Work During the Standard Sleep Interval)[a]

Exposure variable	Female breast cancer					Melanoma			Brain cancer in men		
Exposure quartile[b]	OBS	SMR	95% CI	SRR	95% CI	OBS	SMR	95% CI	OBS	SMR	95% CI
Employment duration (years)											
<2.5	21	1.16	0.72, 1.77	1.00	Referent	1	0.62	0.02, 3.45	1	3.71	0.09, 20.65
2.5–<5.9	17	0.89	0.52, 1.43	0.81	0.42, 1.57	2	1.12	0.14, 4.04	0	0.00	0.00, 9.27
5.9–<13	22	1.19	0.75, 1.81	0.93	0.50, 1.75	2	1.03	0.12, 3.70	0	0.00	0.00, 4.56
13+	18	0.83	0.49, 1.31	0.65	0.34, 1.23	2	0.81	0.10, 2.94	5	3.20[c]	1.04, 7.47
Cumulative radiation dose (mSv)											
<5.7	22	1.22	0.76, 1.84	1.00	Referent	1	0.63	0.02, 3.52	1	3.26	0.08, 18.16
5.7–<12.7	16	1.04	0.59, 1.68	0.99	0.51, 1.91	1	0.67	0.02, 3.74	0	0.00	0.00, 8.73
12.7–<29.4	18	1.14	0.68, 1.80	0.89	0.46, 1.74	1	0.61	0.02, 3.41	1	1.57	0.04, 8.74
29.4+	20	1.04	0.63, 1.60	0.83	0.44, 1.55	3	1.52	0.31, 4.43	3	3.08	0.63, 9.00
Cumulative number of time zones crossed											
<1,100	23	1.17	0.74, 1.76	1.00	Referent	1	0.58	0.01, 3.24	1	3.28	0.08, 18.26
1,100–<2,500	15	1.02	0.57, 1.68	0.90	0.46, 1.78	1	0.68	0.02, 3.80	0	0.00	0.00, 8.18
2,500–<5,600	17	1.12	0.65, 1.79	0.80	0.40, 1.58	1	0.62	0.02, 3.46	1	1.50	0.04, 8.37
5,600+	21	1.10	0.68, 1.69	0.86	0.47, 1.59	3	1.59	0.33, 4.64	3	3.26	0.67, 9.53
Cumulative time spent working in the standard sleep interval (hr)											
<410	19	1.04	0.63, 1.63	1.00	Referent	2	1.24	0.15, 4.48	1	5.12	0.13, 28.50
410–<1,000	14	0.95	0.52, 1.60	0.89	0.44, 1.82	0	0.00	0.00, 2.68	0	0.00	0.00, 10.97
1,000–<2,300	22	1.31	0.82, 1.99	1.17	0.61, 2.23	1	0.61	0.02, 3.39	0	0.00	0.00, 6.85
2,300+	21	1.11	0.69, 1.69	1.01	0.52, 1.93	3	1.46	0.30, 4.27	4	3.15	0.86, 8.06

OBS, observed deaths; SMR, standardized mortality ratio; CI, confidence interval; SRR, standardized rate ratio.
[a]SMRs and SRRs were obtained by standard life-table analysis using LTAS.NET.
[b]Quartiles of cumulative exposure were based on all flight attendants in the cohort for employment duration (n = 11,311) and all flight attendants in the exposure subcohort for the other metrics (n = 10,155).
[c]95% CI excludes 1.0.

polyneuropathy, alcoholic gastritis, and chronic liver disease and cirrhosis) was observed among men but not women [Linnersjö et al., 2011]. Findings for alcoholism and drowning have not been reported in other mortality studies of flight attendants [Ballard et al., 2002; Blettner et al., 2002; Paridou et al., 2003; Zeeb et al., 2003]. In our study, mortality from alcoholism was associated with a metric of circadian rhythm disruption. Data exist suggesting that a causal relationship is plausible. Alcohol may be used as a sleep aid [Patrick et al., 2011] due to sleep disruption resulting from circadian rhythm disruption. Although the data are inconsistent, several studies suggest that work schedules may influence alcohol use [Bushnell et al., 2010]. In addition, researchers have reported an increased risk of relapse in recovering alcoholics with sleep disturbances [Brower and Perron, 2010].

Many of the deaths from intentional self-harm in our study occurred among women who no longer worked for Pan Am. However, we do not know how many were subsequently employed by other airlines. Ballard et al. [2004, 2006] explored the role of work-related factors on psychological distress to follow-up on the increase in suicide mortality among female Italian flight attendants. In a small qualitative study [Ballard et al., 2004], they found that poor mental health of female Italian flight attendants was a problem due, in part, to job stressors such as isolation when travelling, limited time and energy to fulfill their roles outside of work, dealing with difficult passengers, and lack of institutional support. In a subsequent, larger study [Ballard et al., 2006], they found psychological distress among currently employed female flight attendants was related to low job satisfaction, sexual harassment by superiors or colleagues and passengers, and frequent tension with their partner over child care. Almost 40% of both current and former female flight attendants reported a history of serious depression; over 10% reported using alcohol to relieve stress and sadness. Similarly, MacDonald et al. [2003] found that job stressors including mental demands, psychological job demands, imbalance between job demands and obligations outside of work, and low supervisor support were predictive of psychological distress in a sample of 73 currently

TABLE IV. Adjusted Rate Ratios[a] for Mortality From Female Breast Cancer by Estimated Cumulative Exposure (Employment Duration, Radiation Dose, Time Zones Crossed, and Work During the Standard Sleep Interval)

Exposure variable	Female subcohort[c]		Female breast cancer[d]		
Exposure sextile[b]	N (%)	PYAR	OBS	RR	95% CI
Employment duration (years)					
<1.8	1,610 (17%)	55,769	13	1.00	Referent
1.8–<3.2	1,651 (17%)	54,313	12	0.94	0.43, 2.07
3.2–<6.1	1,865 (19%)	66,026	14	0.86	0.41, 1.84
6.1–<10	1,445 (15%)	51,201	13	0.97	0.45, 2.11
10–<17	1,643 (17%)	48,363	12	0.89	0.41, 1.96
17+	1,396 (15%)	30,549	14	0.90	0.42, 1.94
				Trend P-value = 0.86[e]	
Cumulative radiation dose (mSv)					
<3.2	879 (10%)	31,863	13	1.00	Referent
3.2–<7.3	2,147 (24%)	70,614	12	0.52	0.24, 1.14
7.3–<13	1,412 (16%)	47,564	13	0.83	0.39, 1.80
13–<24	1,537 (18%)	53,712	13	0.76	0.35, 1.64
24–<38	1,259 (15%)	36,428	13	1.03	0.47, 2.27
38+	1,444 (17%)	32,918	12	0.59	0.27, 1.29
				Trend P-value = 0.71	
Cumulative number of time zones crossed					
<550	660 (8%)	26,607	13	1.00	Referent
550–<1,300	2,107 (24%)	71,087	12	0.44[f]	0.20, 0.96
1,300–<2,500	1,741 (20%)	56,544	13	0.62	0.29, 1.35
2,500–<5,100	1,778 (20%)	59,574	12	0.57	0.25, 1.26
5,100–<7,000	963 (11%)	26,195	14	1.26	0.58, 2.74
7,000+	1,429 (16%)	33,093	12	0.51	0.23, 1.13
				Trend P-value = 0.97	
Cumulative time spent working in the standard sleep interval (hr)					
<240	1,291 (15%)	47,404	12	1.00	Referent
240–<620	2,101 (24%)	68,140	13	0.79	0.36, 1.73
620–<1,200	1,529 (18%)	50,925	13	1.00	0.45, 2.21
1,200–<1,800	923 (11%)	31,677	13	1.54	0.70, 3.41
1,800–<3,000	1,645 (19%)	46,386	13	0.91	0.41, 2.00
3,000+	1,189 (14%)	28,568	12	0.80	0.35, 1.81
				Trend P-value = 0.68	

N, number of flight attendants; PYAR, total person-years-at-risk; OBS, observed deaths; RR, rate ratio; CI, confidence interval.
[a]RRs for female breast cancer adjusted for race (non-white vs. white), time since first exposure (20+ years vs. <20 years), and age and year of birth using natural regression splines (i.e., restricted cubic splines with $k = 3$ knots at the 10th, 50th, and 90th percentiles).
[b]Sextiles of cumulative exposure were based on the exposure distribution among the female breast cancer cases.
[c]For employment duration analysis, N = 9,610; for cumulative radiation, time zones crossed, and standard sleep interval travel analyses, N = 8,678.
[d]For employment duration analysis, OBS = 78 breast cancer cases; for cumulative radiation, time zones crossed, and standard sleep interval travel analyses, OBS = 76 breast cancer cases.
[e]The trend test P-value was obtained by treating cumulative exposure group as a continuous variable in the Poisson regression model where the weight assigned to each group was equal to the PYAR-weighted mean exposure level for the group.
[f]95% CI excludes 1.0.

employed U.S. female flight attendants. U.S. flight attendants and other flight attendants probably experience many of the same job stressors but some work-related stressors may differ due to the competitive nature and instability of the U.S. airline industry. Several major U.S. airlines, including Pan Am, have declared bankruptcy and/or ceased operations. Many of the flight attendants in this study were laid off when Pan Am downsized and subsequently ceased operations in 1991. However, in a separate study of mortality among Pan Am employees, we found no evidence of increased mortality from suicide among employees who were laid off [Steenland and Pinkerton, 2008].

We observed an almost twofold increase in brain cancer mortality among men based on six observed deaths. An increase in brain cancer has been observed in some studies of male pilots [Sigurdson and Ron, 2004; Zeeb et al., 2010] and one study of cancer incidence among male flight attendants based on three observed cases [Haldorsen et al., 2001] but brain cancer mortality was not elevated (SMR 0.94) among male flight attendants in the collaborative European study [Zeeb et al., 2003]. All of the observed deaths occurred in men with 20 or more years since first employment, and five of the six deaths occurred in men in the highest quartile of employment duration. However, there was not a clear exposure–response relationship and similar findings were not observed among women.

In contrast to several studies of cancer incidence [Sigurdson and Ron, 2004; Buja et al., 2006; Tokumaru et al., 2006], we found no evidence of an increase in breast cancer. In the collaborative European study of flight attendants, breast cancer mortality among women was slightly elevated (SMR 1.11) but not significantly (95% CI 0.82 to 1.48) [Zeeb et al., 2003]. Breast cancer mortality was also elevated (SMR = 1.17) but not significantly (95% CI 0.74–1.80) in a recent cohort mortality update of German flight attendants [Zeeb et al., 2010]. There are limitations, however, in using mortality data to evaluate the risk of breast cancer. In the United States, the overall 5-year relative survival rate for breast cancer ranged from 74.8% to 89.9% between 1975 and 2006 [Altekruse et al., 2010]. We are currently conducting a study of the incidence of breast cancer and other cancers among women in this cohort to address this limitation. Data collected from cohort members or their next-of-kin will be used to evaluate the role of occupational versus non-occupational factors in the breast cancer risk.

We did not observe an increase in mortality from melanoma, and there was not a clear exposure–response relation between melanoma and metrics of exposure. Melanoma has been elevated in a number of cancer incidence studies among flight attendants and cockpit crew [Sigurdson and Ron, 2004; Buja et al., 2005; Buja et al., 2006]. In the large collaborative European studies of mortality among cockpit crew [Blettner et al., 2003] and flight attendants [Zeeb et al., 2003], melanoma mortality was elevated among male cockpit crew and male flight attendants but not among female flight attendants. However, mortality is also an insensitive outcome measure for melanoma. In the United States, the overall 5-year relative survival rate for melanoma ranged from 82.6% to 93.0% between 1975 and 2006 [Altekruse et al., 2010].

Other limitations of the current study include the relatively young age of the cohort and the limited power to detect a significant increase in melanoma mortality. The power to detect an association of melanoma or breast cancer with cosmic radiation dose was also limited by the low cumulative radiation doses and the narrow dose range observed for this cohort with relatively short durations of employment. In addition, many of the flight attendants in the study may have also worked as a flight attendant for other airlines, especially during the last 16 years of the study period. However, the results of the sensitivity analysis suggest that the impact of underestimating duration of employment for some cohort members on the study findings is minimal. There are also limitations to our estimation of exposures [Waters et al., 2009]. Our exposure estimates account for variability between domiciles and over time but do not account for the variability among flight attendants based at the same domicile during the same period. In addition, estimates of cosmic radiation dose were highly correlated to circadian rhythm disruption due to travel across time zones. Better separation may be possible in other studies depending on the routes. Grajewski et al. [2002] found these two exposures can be separated by including a study population flying predominantly north–south flights. Nonetheless, a strength of the study is the estimation of cosmic radiation dose and metrics for circadian rhythm disruption. Radiation dose has been estimated in several cancer studies of pilots [Haldorsen et al., 2000; Rafnsson et al., 2000; Pukkala et al., 2002; Zeeb et al., 2002; Langner et al., 2004], but has only been estimated in one cancer study of flight attendants—a nested case–control study of breast cancer [Kojo et al., 2005]. Only two studies of flight crew have evaluated the association of cancer risk with surrogates of circadian rhythm disruption. In the nested case–control study of breast cancer among flight attendants, self-reported data on disruption of sleep and menstrual cycles were evaluated [Kojo et al., 2005]. Sleep disruption was positively associated and menstrual cycle disruption was negatively associated with breast cancer risk, but these associations were not statistically significant; breast cancer risk was not associated with cumulative radiation exposure. Rafnsson et al. [2000] observed higher melanoma incidence among pilots who had flown over five time zones than among pilots who had never flown over five time zones (standardized incidence ratio (SIR) 25.0; 95% CI 6.73, 64.0 versus SIR 9.09; 95% CI 0.12, 50.58), but the findings were based on a small number of observed melanomas and the CIs were wide.

In conclusion, we found no evidence that flight attendants in this cohort are at increased risk of breast cancer or melanoma. This may be related to the fact that mortality is a poor outcome measure for these outcomes and the limited power resulting from few melanoma deaths and low cumulative radiation doses due to relatively short employment durations. Overall mortality was low among female flight attendants. However, we found a marked increase in HIV-related disease among male flight attendants and an increase in alcoholism and intentional self-harm among female flight attendants. Some data on job stressors among female flight attendants are available [MacDonald et al., 2003; Ballard et al., 2006]; targeted efforts to reduce these job stressors and to enhance social support may improve the well being and satisfaction of currently employed flight attendants [MacDonald et al., 2003]. If the findings related to alcoholism and intentional self-harm are corroborated in studies of currently employed flight attendants, additional research could be conducted to further evaluate the role of circadian rhythm disruption and specific job stressors and to guide prevention efforts.

ACKNOWLEDGMENTS

This study was funded, in part, by the Office of Women's Health of the U.S. Department of Health and Human Services. We would like to thank the many people who obtained records, abstracted and edited data to construct the cohort, and abstracted and edited data from flight schedules to develop exposure estimates for this study. We would also like to thank Dr. Wallace Friedberg and Mr. Kyle Copeland of the FAA for providing the CARI program. We gratefully acknowledge the support of the U.S. states and the National Death Index in providing death certificate information for this study.

APPENDIX

Additional Details on Sensitivity Analysis

A sensitivity analysis of the life table results was performed to evaluate the impact of underestimating duration of employment for the following two groups of cohort members: (1) cohort members who transferred to two other U.S. airlines when routes were sold to these airlines in 1986 and 1991 (n = 2,178), according to the company personnel records, and (2) cohort members who were still employed when Pan Am ceased operations (n = 1,180), many of whom may have sought employment as a flight attendant at other airlines. Self-reported work history information was available for approximately half of these cohort members from a separate study. Workers who transferred to other airlines or were still employed when Pan Am ceased operations were assumed to have worked until the self- or proxy- reported date last employed as a flight attendant, if available, age 65 years (unless the self- or proxy- reported date last employed occurred after age 65), the date last observed in the United States, or the study end date, whichever came first. Under this alternative scenario, the employment duration category changed for 1,396 (12.3%) of the 11,311 workers in the analysis.

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