Cancer Incidence and Mortality Among Flight Personnel: A Meta-Analysis

TERRI BALLARD, DR.P.H., M.P.H., SUSANNA LAGORIO, M.D., GIOVANNI DE ANGELIS, D.SC., AND ARDUINO VERDECCHIA, D.SC.

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Background: Increased cancer risk among flight personnel have previously been noted, including breast cancer among flight attendants and acute myeloid leukemia among pilots. ***Hypothesis:*** Exposure to cosmic radiation and other physical or chemical agents may pose health risks for flight personnel. ***Methods:*** We performed an exhaustive search for published and unpublished cohort studies of flight personnel from 1986–98. We combined relative risks (RR) for selected causes from four mortality and/or incidence studies of pilots and two incidence studies of flight attendants, using standard meta-analytic methods. Heterogeneity among the combined studies was explored and adjustments were made for possible confounding by socioeconomic status (SES), where indicated, using correction factors from published studies. ***Results:*** SES-adjusted combined RRs were elevated (>1.2) among male pilots for mortality from melanoma [1.97 (95% CI: 1.02–3.82)] and brain cancer [1.49 (0.89–2.20)], and for cancer incidence of the prostate [1.65 (1.19–2.29)] and the brain [1.74 (0.87–3.30)]. Among female flight attendants, increases were seen for incidence of all cancers [1.29 (0.98–1.70)], melanoma [1.54 (0.83–2.87)], and breast cancer [1.35 (1.00–1.83)]. ***Conclusions:*** Flight personnel appear to be at increased risk for several types of cancer. Both occupational exposures and well-established non-occupational risk factors may contribute to this increased risk. To better control for confounding factors and to identify exposures potentially amenable to preventive measures, future studies should compare risks within cohorts by flight routes, work history, and exposure to cosmic and UV radiation, electromagnetic fields, and chemical substances.
Keywords: aviation, cancer incidence, mortality, occupation, review.

FLIGHT PERSONNEL, particularly those who fly longhaul flights at high altitudes, are exposed to levels of low-dose cosmic radiation that are higher than levels encountered at ground level (21,39) and may be at greater risk for certain health outcomes (22,34). In 1990, the International Commission on Radiological Protection recommended that in-flight natural background radiation exposure to jet aircrew should be specifically included as an occupational hazard (28). Health risks from low-dose exposures to ionizing radiation include cancer (8). According to a model of cancer risk, among 1000 cabin crew with 20 yr of flying between Minneapolis and New York, 220 would die from a non-occupational cancer (background rate) while 3 would die from cancer as a result of occupational exposure to radiation (excess mortality) (21). Besides cosmic radiation, flight personnel may also be exposed to electromagnetic fields (EMF) from cockpit instruments, ultraviolet radiation, cigarette smoke, pesticides, jet fuel and other volatile substances emanating from aircraft construction materials. Few epidemiologic studies of flight personnel have been published at present (6,7,25,30–32,43,48) and most lack the statistical power to identify an increased risk of acute leukemia, the type of cancer hypothesized to be most closely associated with exposure to ionizing radiation (44).

The main purposes of the current work are the following: a) to describe cancer risk observed in pilot and flight attendant cohort studies; b) to combine available estimates of cancer risk in order to increase the precision of the estimated association between occupation as pilot or flight attendant and selected cancer types; c) to analyze heterogeneity among combined studies; d) to compare the combined results with findings obtained from surveillance systems of occupational diseases and other population-based epidemiologic studies; and e) to comment on the available evidence with special regard to the desirable characteristics of further epidemiologic research.

METHODS

We performed a bibliographical search from 1986–98 for mortality and cancer incidence cohort studies of airline pilots and flight attendants. In addition, we solicited data from other flight crew studies not yet published at the time of the search.

In order to evaluate consistency of findings, to explore reasons for incoherence between studies, and to increase the precision of the relative risk estimates beyond that allowed by the size of any single study, we combined results from individual studies, based on the theoretical and statistical approaches used in the meta-analysis of environmental epidemiologic studies (10). For this purpose, we first classified the selected studies

From the Istituto Superiore di Sanità, Laboratorio di Igiene Ambientale, Rome, Italy.

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Address reprint requests to: Dr. Terri Ballard, who is an epidemiologist with the Istituto Superiore di Sanità, Laboratorio di Igiene Ambientale, Viale Regina Elena, 299, 00161 Rome, Italy; ballard@iss.it

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by outcome, occupation and study design, as follows: a) mortality and cancer incidence cohort studies of male pilots; and b) mortality and cancer incidence cohort studies of female flight attendants.

Only cohort studies of civilian pilots or flight attendants that compared their cancer mortality or incidence rates with those from a national reference population were included. Proportional morality studies were excluded as they do not measure the same effect as standardized mortality studies (47). Investigations of military pilots were also excluded because their occupational experience may be quite different from that of civilian pilots. We then combined results from cohort studies of civil aviation flight personnel separately by study outcome (mortality or incidence) for cause of death and cancer incidence sites showing an excess risk in at least one of the individual studies and for which there were at least five cases in total among eligible studies. We used a fixed effects model with inverse variance weighting of the log risk ratios to calculate combined relative risks (RRc) (27). Heterogeneity among studies was checked by the χ^2 test for heterogeneity. The DerSimonian and Laird method for random effects analysis was used to adjust for heterogeneity (defined as having a p-value ≤ 0.25) among combined studies (16).

For cancer sites with a known positive association with socioeconomic status (SES) (36,52), adjustments of the RRc were made using external estimates of confounding, as described by Greenland (27). We estimated the degree of confounding by SES in the following way. We considered flight personnel to belong to the highest social class. Using a publication of the International Agency for Research on Cancer (IARC) on socioeconomic differences in cancer incidence and mortality, we obtained the correction factor for SES confounding by taking an average of the listed RRs for social class I by cancer type (i.e., the ratio of cancer incidence/mortality rates of that social class to the rates of the standard population) derived from studies conducted in developed countries. The RRc and confidence limits of the SES-associated tumors in our analysis were then divided by the obtained correction factor for cancers of the colon, prostate, brain, and malignant melanoma. This adjustment was made on the fixed effects combined relative risk (RRc) when heterogeneity was not present, and on the random effects estimate otherwise.

For all causes and cancer sites we calculated either the attributable fraction for the exposed population—the proportion of exposed cases for whom the disease is attributable to the exposure (i.e., occupation)—or the prevented fraction, which is the proportion of the potential cases in the absence of exposure that were prevented by exposure (47). For these calculations we used the most adjusted risk ratio (i.e., random effects and/or SES-adjusted) as the base.

RESULTS

A Medline search yielded six published civilian flight personnel-specific cohort studies (6,7,30,32,43,48), one study of U.S. Air Force pilots (25), and one proportionate mortality study of pilots taken from a U.S. occupational mortality surveillance system (40). In addition, we received data from two additional flight personnel cohort studies in the process of publication at the time (Wartenberg D. Personal communication, 1998; 31). **Table IA** lists the 10 identified flight personnel studies and describes the study period, study and reference populations, number of observations, person-years at risk for cohort studies, and a designation of inclusion or not in the subsequent meta-analysis. Of the airline pilot studies, three were proportional mortality analyses (30,40,48), two were cohort studies of only mortality (31,32), two were cohort studies of both cancer incidence and mortality (6,7), and one a cohort study of cancer incidence only (25). The latter investigation followed U.S. Air Force pilots during active military service only, while all the others studied civilian pilots at least up to age 90. The three PMR studies and the military pilot investigation did not meet the inclusion criteria for the meta-analysis and were excluded. Of the two flight attendant incidence studies, one was national in scope (43) and the other followed a small group of retired flight attendants from one airline (Wartenberg D. Personal communication, 1998). Both were included in the meta-analysis.

Table II lists relative risks and numbers of observed cases for selected major causes of death or cancer incidence among airline pilots and female flight attendants for the studies included in the meta-analysis. Results provided in the original as multiples of 100 (31,54) were divided by 100 for reporting in Table II. Relative risks for several cancer sites not originally published were requested from authors but were not always available. Across the mortality studies of male pilots (Table IIA), deficits were seen for all causes mortality, all-sites cancer mortality, all leukemias, and for ischemic heart and respiratory diseases. Excess mortality (relative risks > 1.2) was seen in at least half of the studies with at least one case for cancers of the colon, prostate and brain, and for malignant melanoma of the skin. There were no observed cases for bone or thyroid cancer. All of the mortality studies found a higher risk of death among pilots from airline crashes compared to the general population, as might be expected given the hazards of the occupation. Cancer incidence relative risks among male pilots (Table IIB) showed high incidence (RR > 1.2) for melanoma and cancers of the prostate and brain, and a deficit for lung cancer. Both myeloid leukemia and acute myeloid leukemia were significantly elevated in the Band 1996 study (7). Among female flight attendants (Table IIC) both studies showed increased risks compared with standard populations for all-sites cancer, malignant tumors of the colon and breast, and melanoma. Increased risk for tumors of female pelvic reproductive organs and the thyroid were seen only among the U.S. retired flight attendants (Wartenberg D. Personal communication, 1998) and for bone and lung cancer and leukemia only among the Finnish flight attendants (43).

Table III lists the results of combined analyses of relative risk estimates for selected causes from four mortality and incidence studies of male pilots and from two cancer incidence studies of female flight attendants.

TABLE I. OCCUPATIONAL MORTALITY AND CANCER INCIDENCE STUDIES OF FLIGHT PERSONNEL.

Study Author	Study Description	Number Observed	Person-Years At Risk (Cohorts)	Inclusion in Combined Analysis
Band et al., 1990 (6)	Standardized cancer incidence and mortality: all male pilots of Canadian Pacific Airlines, Canada, 1950–1984. Reference population (ref pop): British Columbia males.	891*	18,060	yes
Salisbury et al., 1991 (48)	Proportional mortality: all deaths of male pilots from British Columbia, Canada, 1950–1984. Reference population: British Columbia males.	402†		no
Irvine and Davies, 1992 (30)	Proportional mortality: all male pilots from British Airways, Britain, 1966–1989. Reference population: male deaths—England and Wales.	446†		no
Kaji et al., 1993 (32)	Standardized mortality: all male cockpit crew members of Japan Airlines, 1952–1988. Reference population: Japanese males.	2327*	not reported	yes
Pukkala et al., 1995 (43)	Standardized cancer incidence: all airline flight attendants, Finnair (FA), Finland, 1967–1992. Reference population: Finnish males and females.	1577-females* 187-males*	21,974 2,496	yes no
Band et al., 1996 (7)	Standardized cancer incidence and mortality: all male pilots of Air Canada, Canada, 1950–1992. Reference population: Canadian males.	2680*	62,449	yes
Grayson & Lyons, 1996 (25)	Standardized cancer incidence: Air Force flight officers, USA, 1975–1989. Reference population: SEER.	59940*	532,981	no
Wartenberg and Stapleton, 1998 (¶)	Standardized cancer incidence: U.S. retired female FAs of one airline company. Reference population: SEER.	287*	unreported	yes
Irvine and Davies, 1999 (31)	Standardized cohort mortality (update of 1992 PMR study): all male pilots and flight engineers of British Airways, Britain, 1950–1992. Reference population: males—England and Wales.	6209-pilots* 1153-flight engineers	143,506 29,094	yes no
Nicholas et al. (39)	Proportionate mortality analysis: male pilots and navigators in 24 U.S. states, 1984–1991. Reference population: males, all occupations, combined from same states.	1538†		no

* Number of subjects followed.
† Number of deaths.
‡ Case/control total.
§ Pilot cases.
¶ D. Wartenberg 1998, personal communication, 1998.

We were not able to combine some causes that might have relevance to ionizing radiation, such as leukemia mortality, leukemia subtypes and multiple myeloma due to insufficient numbers of studies to include. Combined relative risks were calculated for all-sites cancer, seven specific cancer sites, ischemic heart disease and respiratory disease. For each combination category, the table reports the type and number of studies combined, the combined relative risk estimate (RRc) calculated by the fixed effect model along with its 95% confidence interval, the SES-corrected relative risks (RRc-ses) for those cancer sites known to have a positive association with social economic status, and the attributable risk or prevented fraction for the exposed population for all causes. Corrected relative risks for heterogeneity, where relevant, are reported in the text. The results of the analysis is described below by occupation.

Pilots

We included results from two to four individual airline pilot studies per subcategory in order to estimate the combined relative risks for nine causes of death or cancer incident sites. Deficits in mortality were seen for all cancers, lung cancer, all leukemias, ischemic heart disease and respiratory diseases. Malignant melanoma demonstrated excess mortality and incidence with no heterogeneity among studies. Relative risks were higher for melanoma mortality than for incidence, remaining after SES correction, with 49% of mortality and 7–20% of cancer incidence attributable to occupation as pilot. For prostate cancer, SES correction eliminated the excess risk for mortality but a moderate excess of approximately 65% remained for incidence with 40% of the incident cases attributable to occupation as pilot. Heterogeneity was

TABLE IIA. OCCUPATIONAL STUDIES OF FLIGHT PERSONNEL INCLUDED IN META-ANALYSIS PRINCIPAL FINDINGS (MORTALITY STUDIES OF MALE PILOTS).

Cause of Death	Band et al., 1990 (6) SMR (90% CI)	N	Kaji et al., 1993 (32) SMR (95% CI)	N	Band et al., 1996 (7) SMR (90% CI)	N	Irvine, Davies, 1999 (31) SMR (95% CI)	N
All causes	0.80 (0.60–1.00)	71		59	0.63 (0.56–0.70)	219	0.61 (0.56–0.66)	592
All-sites cancer	not reported	16	0.87 (0.53–1.35)	20	0.61 (0.48–0.76)	56	0.64 (0.55–0.74)	180
Esophagus cancer		0		0	0.86 (0.15–2.70)	2		
Stomach cancer		0		9	0.57 (0.15–1.47)	3		
Colon cancer	not reported	1		0	1.23 (0.67–2.09)	10	1.11 (0.68–1.71)	20
Rectal cancer	4.35 (1.20–11.2)	3		2		0		
Lung cancer	0.52 (0.10–1.40)	3		0	0.25 (0.12–0.45)	8	0.41 (0.30–0.56)	43
Bone cancer		0		0		0	(0–4.2)	0
Melanoma		0		0	1.49 (0.26–4.68)	2	3.33 (1.52–6.34)	9
Prostate cancer	not reported	1		0	1.52 (0.71–2.85)	7	1.11 (0.62–1.83)	15
Testicular cancer		0		0		0	(0–2.1)	0
Bladder cancer		0		1		0		0
Brain cancer	4.17 (1.40–9.50)	4		1	1.42 (0.56–2.98)	5	1.27 (0.66–2.28)	14
Endocrine cancer		0		0		0	(0–4.6)	0
Hodgkin's Disease	not reported	1		0	0.99 (0.01–5.50)*	1	1.39 (0.38–3.57)	4
Non-Hodgkin's lymphoma	2.95 (0.50–15.3)	2		1	0.62 (0.11–1.95)	2	1.00 (0.46–1.91)†	9
Multiple myeloma		0		0		0		0
All leukemias	not reported	1		0	0.86 (0.23–2.22)	3	0.51 (0.14–1.31)	4
Myeloid leukemia	not reported	1		0	1.32 (0.23–4.15)	2		
Acute myeloid leukemia	not reported	1		0				
Ischemic heart disease	0.60 (0.40–1.00)	13	0.27 (0.06–0.80)	3	0.57 (0.45–0.71)	56	0.39 (0.32–0.46)	126
Cerebrovascular accident	0.52 (0.10–1.64)	2	0.37 (0.10–0.94)	4	0.55 (0.27–0.99)	8		
Respiratory disease				0	0.28 (0.11–0.59)	5	0.21 (0.12–0.34)	17
Cirrhosis of the liver	0.59 (0.10–1.90)	2		0	0.30 (0.08–0.77)	3	1.46 (0.75–2.55)	12
Aircraft accidents	21.3 (14.6–30.2)	23	2.43 (1.63–3.50)	26	26.6 (19.3–35.9)	31	146.9 (111.9–189.5)	59

* Not reported in publication; personal communication with Band, 1998.
† Other lymphatic tissue malignancies.

noted for brain cancer incidence (p value = 0.25) and mortality (p value = 0.19) among pilot studies. Correcting for this heterogeneity yielded combined relative risks of 1.74 (0.90–3.35) for mortality and 2.09 (0.96–4.54) for incidence, both slightly higher than the non-corrected combined relative risks. With further correction for SES, the combined risk ratios remained moderately elevated, with an attributable risk for occupation as pilot of 31% for mortality and 43% for incidence.

Flight Attendants

Results from two flight attendant studies were combined for all-sites cancer, breast cancer and malignant melanoma of the skin. Excesses were seen for all sites

TABLE IIB. OCCUPATIONAL STUDIES OF FLIGHT PERSONNEL INCLUDED IN META-ANALYSIS PRINCIPAL FINDINGS (CANCER INCIDENCE STUDIES OF PILOTS).

Cancer Sites	Band et al., 1990 (6) SIR (90% CI) Male Pilots	N	Band et al., 1996 (7) SIR (90% CI) Male Pilots	N
All-sites	not reported	57	0.71 (0.61–0.82)	125
Esophagus		0	0.83 (0.14–2.61)	2
Stomach		0	0.70 (0.28–1.47)	5
Colon	not reported	1	0.87 (0.51–1.38)	13
Rectal	1.94 (0.70–3.00)	4	0.42 (0.14–0.96)	4
Lung	0.41 (0.10–1.20)	3	0.28 (0.16–0.46)	11
Bone		0		0
Melanoma	1.96 (0.50–5.10)	3	1.52 (0.76–2.74)	8
Prostate	1.54 (0.70–3.00)	6	1.87 (1.38–2.49)	34
Testicular	1.75 (0.30–5.50)	2	0.63 (0.11–1.98)	2
Bladder		0	0.36 (0.12–0.82)	4
Brain	3.45 (1.20–7.90)	4	1.53 (0.72–2.87)	7
Endocrine		0		0
Hodgkin's Disease	4.54 (1.20–11.70)	3		0
Non-Hodgkin's lymphoma	1.18 (0.20–3.70)	2	0.52 (0.18–1.19)	4
Multiple myeloma		0		0
All leukemias	not reported	2	1.65 (0.86–2.88)	9
Myeloid leukemia	not reported	1	2.93 (1.37–5.50)	7
Acute myeloid leukemia	not reported	1	4.72 (2.05–9.31)	6

TABLE IIC. OCCUPATIONAL STUDIES OF FLIGHT PERSONNEL INCLUDED IN META-ANALYSIS PRINCIPAL FINDINGS (CANCER INCIDENCE STUDIES OF FEMALE FLIGHT ATTENDANTS).

Cancer Sites	Pukkala et al., 1995 (43) SIR (95% CI)	N	Wartenberg et al., 1998¶ SIR (95% CI)	N
All-sites	1.23 (0.86–1.71)	35	1.4 (0.9–2.3)	17
Stomach	1.04 (0.03–5.78)	1	(0–61.5)	0
Colon	1.32 (0.16–4.75)	2	2.0 (0.3–14.4)	1
Rectal	included in colon		included in colon	0
Lung	1.61 (0.04–8.95)	1	(0.–6.0)	0
Bone	15.1 (1.82–54.4)	2	(0.–92.2)	0
Melanoma	2.11 (0.43–6.15)	3	3.4 (0.8–13.4)	2
Breast	1.87 (1.15–2.23)	20	2.0 (1.0–4.3)	7
Cervix uteri	(0–3.7)	0	5.2 (1.7–16.2)	3
Uterus	(0–3.1)	0	121.0 (17.0–859)	1
Ovary	0.47 (0.0–2.61)	1	2.1 (0.3–14.6)	1
Brain	0.51 (0.01–2.86)‡	1	(0–15.4)‡	0
Thyroid	0.62 (0.02–3.42)	1	4.3 (1.1–17.1)	2
Lymphoma	0.91 (0.23–5.06)§	1	(0–8.0)	0
All leukemias	3.57 (0.43–12.9)	2	(0–13.6)	0

§ All lymphomas.
¶ Personal communication, D. Wartenberg, 1998.

with the strongest finding for melanoma (RRc of 2.31). Correcting the single cancers for SES, the combined relative risks remained elevated. These findings suggest that more than 22% of all cancers, 35% of melanomas and 26% of breast cancers may be attributable to occupation as flight attendant.

DISCUSSION

A meta-analysis of six cohort studies of flight personnel for a series of causes of death or cancer sites demonstrated small elevated risks for tumors of the prostate and brain among male pilots, for tumors of the breast

TABLE III. COMBINED RELATIVE RISKS FOR SELECTED CAUSES OF MORTALITY AND CANCER INCIDENCE-FLIGHT PERSONNEL.

Cause of Death/Cancer Site	Type Study	Number of Studies	References	Fixed Effects Model RRc*	Fixed Effects Model 95% CIc*	SES Correction RRc-ses*†	SES Correction 95% CIc*	Attributable Risk (Prevented Fraction)
Male Pilots								
All-sites cancer								
Mortality	flight crew SMR	3	7,31,32	0.64	(0.58–0.71)			(0.36)
Colon								
Mortality	flight crew SMR	2	7,31	1.15	(0.78–1.68)	1.05	(0.71–1.53)	0.05
Lung								
Mortality	flight crew SMR	3	6,7,31	0.39	(0.29–0.52)			(0.61)
Incidence	flight crew SIR	2	6,7	0.78	(0.45–1.36)			(0.22)
Melanoma (skin)								
Mortality	flight crew SMR	2	7,31	2.96	(1.53–5.73)	1.97	(1.02–3.82)	0.49
Incidence	flight crew SIR	2	6,7	1.61	(0.82–3.15)	1.07	(0.55–2.10)	0.07
Prostate								
Mortality	flight crew SMR	2	7,31	1.22	(0.77–1.92)	1.11	(0.70–1.75)	0.10
Incidence	flight crew SIR	2	6,7	1.82	(1.31–2.52)	1.65	(1.19–2.29)	0.39
Brain								
Mortality	flight crew SMR	3	6,7,31	1.60	(0.99–2.59)	1.45‡	(0.75–2.80)	0.31‡
Incidence	flight crew SIR	2	6,7	2.03	(1.04–3.96)	1.74‡	(0.87–3.30)	0.43‡
All leukemias								
Mortality	flight crew SMR	2	7,31	0.63	(0.27–1.49)			(0.37)
Ischemic Heart Disease								
Mortality	flight crew SMR	4	6,7,31,32	0.44	(0.38–0.50)			(0.56)
Respiratory Disease								
Mortality	flight crew SMR	2	7,31	0.22	(0.14–0.35)			(0.78)
Female Flight Attendants								
All-sites cancer								
Incidence	flight crew SIR	2	43,§	1.29	(0.98–1.70)			0.22
Melanoma (skin)								
Incidence	flight crew SIR	2	43,§	2.31	(1.24–4.30)	1.54	(0.83–2.87)	0.35
Breast cancer								
Incidence	flight crew SIR	2	43,§	1.89	(1.40–2.56)	1.35	(1.00–1.83)	0.26

* RR_c = combined relative risk based on a fixed effect model (Greenland, 1987). $RR_{c\text{-}ses}$ = combined RR corrected for social-economic status (SES).
† SES correction factor (colon 1.10; breast 1.40; melanoma 1.50; prostate 1.1; brain 1.20).
‡ Performed on random effects RR_c*.
§ Personal communication, D. Wartenberg, 1998.

cancer among female flight attendants, and for malignant melanoma in both groups. The present quantitative review of epidemiologic studies of flight personnel is affected by several limitations. Due to few studies in each category, the resulting combined relative risk estimates cannot be interpreted as summary measures of effect across studies. Our purpose, instead, was to synthesize the evidence from the small number of available flight crew studies as a background rationale for further research. Bias in the combined estimates of effect for several cancers may have occurred due to missing data. We requested the expected numbers for cancer sites with zero observed cases from all authors and the unreported relative risks for sites with 1–2 observed cases in the 1990 study of Band et al., (6) but these data were not always available. Some of the combinations for specific sites were incomplete, therefore, due to these problems. Another limitation is that we were unable to control for confounding factors other than SES. The major confounders that might be desirable to control for include diet, tobacco and alcohol use, reproductive factors and family history of certain cancers.

Heterogeneity among studies was observed only for brain cancer. It may be of value to investigate possible sources of this heterogeneity. Examination of the individual studies reveals that the earlier Band et al. study of pilots from one Canadian airline (6) reported relative risks for both brain cancer mortality and incidence that were much higher than those in the later study of pilots working for another Canadian airline (7). The lower RR of the 1996 study is in line with the results of the British Airways study for brain cancer mortality (31). The incidence density rate (number of cases per person-years of followup) for brain cancer mortality was almost three times as high in the 1990 study with respect to the 1996 study. It may be either that the large number of cases was found by chance, or that the 1990 cohort had more non-occupational risk factors for brain cancer than the 1996 cohort. The effect of this heterogeneity was small as correction increased the RR by only 9% for mortality and by 3% for incidence.

Several of the excess cancers highlighted by this analysis may be explained by factors other than occupational exposures, such as high socioeconomic status. Flight personnel, particularly pilots, fall into upper income levels and enjoy the advantages of healthy lifestyles and access to health care that the general population may not. They are also subject to frequent medical check-ups. Early detection of tumors may result in higher rates of cancer incidence at lower stages of tumor development but would not likewise increase mortality rates (9,13). This type of detection bias could explain at least in part the excess incidence with respect to the general population for malignant melanoma of the skin and cancers of the prostate and breast cancer among flight personnel. One study attempted to control for the differences in SES level and access to health care by comparing cancer incidence between flying U.S. Air Force officers and non-flying officers, comparisons groups that by definition should be similar in most respects other than flying status (25). No excess of melanoma was found among flying officers compared with non-flying military officers of similar ranks, whereas the standardized rate ratio was elevated among pilots compared with the general population. This suggests that confounding by SES and other factors may have been present.

Certain occupational exposures may explain in part the excess cancer seen among flight personnel. The effects of occupational exposure to ionizing radiation on developing leukemia and malignant melanoma, in particular, have been studied primarily among cohorts of nuclear industry workers. A pooled analysis of seven cancer mortality studies of nuclear workers from three countries was published by the International Agency for Research on Cancer (IARC) in 1995, with 2.12 million person-years of follow-up and cumulative dose exposure data on all subjects (14). The study demonstrated an increased risk ratio of 1.22 for leukemia excluding chronic lymphatic leukemia for a cumulative protracted dose of 100 mSv compared with 0 mSv. Elevated risks for prostate cancer seen in two of the studies included in the pooled analysis were felt to be due to exposure to specific radionuclides (14,46). Melanoma has also been associated with occupation as nuclear worker. An update of an earlier study of workers at the U.S. Lawrence Livermore National Laboratory continued to show higher incidence of malignant cutaneous melanoma among workers exposed to ionizing radiation compared to non-exposed workers (odds ratio = 3.7) (3,4). Excesses of melanoma in this population have been confirmed by an independent re-analysis of the original study (50). However, studies of nuclear workers in many other settings have not found increased mortality from malignant melanoma either from low dose ionizing radiation or other job-related exposures (56). Excess brain cancer has not been noted among nuclear workers exposed to ionizing radiation (15).

Nuclear workers may not be a logical reference group for occupational radiation effects for flight personnel exposed to cosmic ionizing radiation as they do not comprise a group of workers with uniform activities or exposures to radiation [see Table I of Cardis et al., 1995 (14)]. Furthermore, exposure to cosmic radiation is qualitatively different from exposure to ionizing radiation or radionuclides from industrial use (58). Flight crewmembers represent the largest population of persons exposed to high energy neutrons and the only population exposed to high energy protons (59). The relative biological effectiveness (RBE) of these types of radiation, which characterizes their ability to produce a specific disorder such as cancer, is 20 times greater than the RBE of gamma radiation for a given unit of gray (the amount of energy absorbed in matter as a result of radiation interaction) (12). A flight deck crewmember may receive an annual dose of cosmic radiation of from 0.2 to 9.1 mSv (21). Measurements of cosmic radiation on Concorde flights, modeled to estimate annual doses, found that no flight deck crewmember exceeded 6 mSv · yr (5). These estimates represent an exposure of less than one-half the proposed new occupational annual dose limit of of 20 mSv as an annual average over 5 yr (29). However, a 20 yr flying career at an estimated

annual dose of 6 mSv would yield a cumulative lifetime dose of 120 mSv, greater than that received by the nuclear workers for whom an excess of leukemia was demonstrated with a cumulative lifetime dose of 100 mSv (14). If cosmic radiation has a high biological effectiveness for provoking cancers, one would expect to find a real excess of radiation-related cancers, especially leukemia, among aircrew members. Only one of the pilot cohort studies found an increased risk of myeloid and acute myeloid leukemia (7), therefore we were unable to explore these sub-types in the meta-analysis. But even if we could have, the statistical power would most likely have been inadequate to highlight a small excess risk.

Supporting evidence of a positive association between occupation as pilot and brain cancer comes from an occupational case-control study in New Zealand that found an odds ratio of 1.7 (95% CI:0.6–5.0) for airline pilots (42). It has been hypothesized that exposure to extremely low frequency (30–300 Hz) electric and magnetic fields (ELF-EMFs) may be a risk factor for brain cancer (49). A recent meta-analysis found a small increased risk of brain cancer, in particular for gliomas, for a broad group of workers exposed to ELF-EMFs (33). In a nested case-control study from a cohort of U.S. Air Force personnel, Grayson and Lyons (26) investigated the association of radiation exposure and brain tumor risk among workers potentially exposed to extremely low frequency and radio frequency/microwave EMFs and ionizing radiation (pilots were not listed among the "exposed"). Exposures were measured from a job title-time-exposure matrix for ELF-EMFs and personal dosimetry data for ionizing radiation; single and joint effects of these exposures were examined. Only a small increased risk was found for occupational exposure to extremely low frequency and radio frequency/microwave EMFs, and no increased risk for exposure to ionizing radiation was seen, while the strongest risk factor was SES as measured by military rank.

The major risk factors for malignant melanoma of the skin are non-occupational and include upper social economic status, intermittent sun exposure, sunburn at early age, and host factors related to skin color and nevi (1). This tumor is known to be associated with ultraviolet radiation (UVR), which may be also an occupational exposure. However, exposure to solar UVR during commercial flights does not seem to be a problem since the materials used in aircraft windshields and side windows should offer complete protection from solar radiation, and personal and flight deck measurements of UVR reveal only minimal exposure at high cruise altitudes—far less than that received by outdoor and occupationally exposed indoor workers (17,57). The role of ionizing radiation as an occupational risk factor for melanoma among aircrew members cannot be excluded given epidemiological and experimental evidence of a causal role (4,45). Positive associations between occupation as pilot and melanoma have also been seen in two occupational cancer studies. A case-control analysis of cancer registry data in Los Angeles County, CA, found an elevated relative risk for airline pilots [RR = 1.6 (95% CI: 0.8–3.2)] (24). From a study combining tumor registry data in Sweden and in England and Wales, airline pilots had the highest relative risk of all occupations [RR = 2.73 (95% CI: 1.18–5.38)] (54). It was hypothesized by the authors of this last study that flight personnel perhaps have more opportunity than those of other occupations for non-occupational sun exposure.

There are well-established non-occupational risk factors for breast cancer such as age at first birth, nulliparity, higher family income and family history. These factors may account for up to one-half of all female breast cancer cases (37) and are likely to be associated with occupation as flight attendant. To control for these factors in the meta-analysis, we used a correction factor for SES but we cannot be sure that this adequately controlled for SES or reproductive factors associated with SES in the case of breast cancer. Environmental or occupational etiology of female breast cancer must be seriously considered given that the cause for 50% of incident breast cancers is unknown (23). Increased risk of breast cancer among flight attendants has been found as well as in Denmark where the RR for Danish female flight attendants with respect to all working women was 1.61 (0.9–2.7), higher than the RR for all women in social class I (1.40) (36). The breast is a known radiosensitive organ and elevated rates of breast cancer have been demonstrated among atomic bomb survivors (greatest among women exposed before age 20) and among women receiving radiation therapy for various medical reasons (12). Another hypothesized risk factor for breast cancer is exposure to organochlorine pesticides (60), pertinent to flight attendants who in past decades have been exposed to mandatory spraying of the aircraft cabin on arrival in certain countries. Wartenberg and Stapleton used a self-reported number of flights on which pesticides were sprayed to evaluate risk of breast cancer, finding an OR of 2.2 (95% CI: 1.04–10.9) for flight attendants with higher than the median number of "exposed" flights (55). Another possible risk factor for breast cancer among flight attendants arises from the disruption of circadian rhythms due to flying across time zones. Melatonin may have a protective effect against cancer development, especially in hormone-dependent tumors (53), and disruptions in sleep-waking cycles may lead to an increase in cancer risk by suppressing melatonin secretion (38). An epidemiologic study of totally blind and severely visually impaired persons found reduced cancer incidence for breast and prostate among the totally blind compared with a standard population, but not among the partially blind, suggesting that only the total absence of light results in a free-running melatonin cycle, and thus protects against cancer (20). According to some researchers, EMF exposure might increase risk of breast cancer by causing alterations in normal pineal function (53), although there is no direct evidence of this. Several epidemiologic studies have found small increases in breast cancer risk among women with occupational or environmental EMF exposures (19,35).

A record linkage study that examined occupation and prostate cancer risk in Sweden demonstrated ex-

cess incidence for airline pilots [RR of 2.2 (95% CI 0.8–4.8)] (Hsing A. Personal communication, 1998.). The consistent excess of prostate cancer among pilots is more difficult to relate to possible occupational factors. As mentioned earlier, exposure to specific radionuclides have been shown to be associated with prostatic tumors in nuclear workers (46), but this is not applicable to pilots. An occupational association for tumors of the prostate has been found with exposure to liquid fuel combustion products (2) but a mortality and cancer incidence study of military workers exposed to aircraft fuel failed to find an association with this exposure and any malignancy including prostate tumors (51).

The data used in our meta-analysis came from comparisons of flight personnel with standard populations, and did not take into account specific occupational hazards. While the increased cancer risks found here may be explained by well-known risk factors, they may also be due to unmeasured occupational exposures specific to flight personnel. Several of the studies included in this review have attempted to compare cancer risk within the cohorts by occupational factors. The mortality study by Irvine and Davies categorized pilots and flight engineers by proxies of exposure intensity using as the measure "longhaul" or "shorthaul" to reflect the most common types of routes flown during a flying career (31). They found several small increases in cancer mortality among pilots habitually flying short haul routes [all causes RR = 1.22 (95% CI: 1.03–1.45); all cancer RR = 1.10 (95% CI 0.81–1.49); brain and CNS cancer RR = 1.37 (95% CI: 0.49–3.90)]. Only lymphatic and hemotopoietic tissue cancers showed a deficit [RR = 0.69 (95% CI:0.28–1.74)] among shorthaul pilots compared to those mainly flying longhaul routes whose exposure to cosmic radiation would be greater. Wartenberg used number of flights flown as a proxy for cosmic radiation when analyzing the risk of breast cancer among flight attendants and found a small deficit of breast cancer by an increasing number of flights (55). Future studies that compare cancer risk by work history (for example, flight hours, duration of employment, routes flown, levels of exposure to cosmic radiation), that take into account cancer characteristics (for example, subtypes of leukemia, tumor latency and diagnosis by age or time periods) and that adequately control for confounding variables, will do a great service toward identifying workplace risk factors that are potentially amenable to preventive measures. It is of importance both to flight personnel and to frequent flyers to determine if their risk of cancer is elevated from the potentially harmful effects of ionizing radiation in the form of cosmic rays and whether current occupational standards provide sufficient protection. To address these issues, a European multi-center retrospective cohort study of cancer risk among flight personnel is underway that will estimate exposure to cosmic radiation and other potential carcinogens for individual cohort members and will assess cancer risk by levels of the various exposures over time with sufficient power to detect small excesses (11).

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