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ORIGINAL PAPER

Cancer mortality among German aircrew: second follow-up

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Abstract Aircrew members are exposed to cosmic radiation and other specific occupational factors. In a previous analysis of a large cohort of German aircrew, no increase in cancer mortality or dose-related effects was observed. In the present study, the follow-up of this cohort of 6,017 cockpit and 20,757 cabin crew members was extended by 6 years to 2003. Among male cockpit crew, the resulting all-cancer standardized mortality ratio (SMR) ($n = 127$) is 0.6 (95% CI 0.5–0.8), while for brain tumors it is 2.1 (95% CI 1.0–3.9). The cancer risk is significantly raised (RR = 2.2, 95% CI 1.2–4.1) among cockpit crew members employed 30 years or more compared to those employed less than 10 years. Among both female and male cabin crew, the all-cancer SMR and that for most individual cancers are close to 1. The SMR for breast cancer among female crew is 1.2 (95% CI 0.8–1.8). Non-Hodgkin's Lymphoma among male cabin crew is increased (SMR 4.2; 95% CI 1.3–10.8). However, cancers associated with radiation exposure are not raised in the cohort. It is concluded that among cockpit crew cancer mortality is low, particularly for lung cancer. The positive trend of all cancer with duration of employment persists. The increased brain cancer SMR among cockpit crew requires replication in other cohorts. For cabin crew, cancer mortality is generally close to population rates. Cosmic radiation dose estimates will allow more detailed assessments, as will a pooling of updated aircrew studies currently in planning.

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Introduction

About 20 years ago, the first results from epidemiologic studies on mortality and cancer incidence among aircrew were published (Band et al. 1990; Irvine and Davies 1992; Salisbury et al. 1991). This was done to learn about the mortality and disease incidence in this selected occupational group, and with particular emphasis on whether exposure to ionizing radiation of cosmic origin would increase the risk of cancers and other diseases. The radiation exposure of aircrew was found to be similar to that of other occupational groups such as nuclear plant workers, with lifetime cumulative ionizing radiation doses generally well below about 100 mSv and with individual variations depending on the detailed occupational history. Data from the German Federal Radiation Registry indicate that individual annual effective doses for cockpit and cabin crew range from 0–5.4 mSv, with slightly higher median doses for cabin crew and age- and sex-dependent patterns of exposure (Stegemann et al. 2005)

Detailed cohort studies were launched in the 1990s, mainly in Europe and North America. Data from European cohort studies were pooled and allowed the analysis of both cancer incidence (Pukkala et al. 2002) and mortality (Blettner et al. 2003; Langner et al. 2004; Zeeb et al. 2003a). While attempts were made to assess individual occupational radiation doses in a majority of the studies, scarce information on other health risk factors was available from these retrospectively conducted cohort studies. Factors of interest include exposure to ultraviolet radiation, smoking, reproductive factors, measures of circadian rhythm changes and others.

Most findings to date point to a comparatively low overall mortality of aircrew (Sigurdson and Ron 2004), indicating a strong healthy worker effect particularly regarding cardiovascular deaths, and reflecting the high socioeconomic status of cockpit crew. In terms of cancer, standardized mortality analyses pointed to increases of malignant melanoma mortality in male aircrew, as well as slight increases in breast cancer mortality among female cabin crew. Deaths from AIDS among male cabin crew and from aircraft crashes were found to be markedly raised. Cancer incidence analyses indicated elevated risks for breast cancer and few other cancer sites when compared to those of reference populations. So far, no strong evidence for risk increases with increasing radiation dose has emerged. However, even the pooled studies had low statistical power to assess this question, as exposure levels and numbers of incident cancers and deaths were comparatively low.

One of the largest cohorts of aircrew was established in Germany. All flight personnel from Lufthansa German Airlines (DLH) and LTU International Airways actively flying between 1960 and 1997 constitute the cohort, and results for the first follow-up until end of 1997 were published several years ago (Blettner et al. 2002; Zeeb et al. 2003b, 2002). The present study represents a further follow-up of the cohort and presents updated epidemiologic results. The main reasons for performing the cohort update relatively soon after the first follow-up were that (1) some German population registers keep death certificates only for a few years and (2) airline companies keep personnel data on detailed flight records usually only for a time span up to 7 years. The report follows guidelines of the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" initiative (Vandenbroucke et al. 2007; von Elm et al. 2007).

Materials and methods

Cohort

The German aircrew study is a retrospective occupational cohort study. The study material and methods have been described previously (Blettner et al. 2002; Zeeb et al. 2003b, 2002). The existing cohort of cockpit and cabin crew, including more than 27,000 individuals, was now followed up until December 31, 2003, extending the previous follow-up by 6 years. No new cohort members were included. Cohort data were intensively checked prior to performing the mortality follow-up via population registries, especially for those cohort members for whom no previous follow-up was done before because they were known to have been active until December 31, 1997. Personnel files of collaborating airlines were also checked to establish (a) whether cohort members were still registered as active in the company by end of 2003 and (b) whether basic cohort data such as date of birth and gender were identical to our existing study database. If active employment was confirmed, the vital status was taken as alive. For all others, the vital status was actively researched through written information requests to the population registry at the last known place of residence. Migrants during the period 1998–2003 were censored at the last date of registration in Germany. For deceased cohort members, the cause of death was obtained from the copy of the original death certificate. This is usually held by the local public health office at the place of death. Where this certificate could not be obtained or necessary information about date or place of death was missing, additional sources were scrutinized including files at the registrar's office, city archives, further personnel files or administrative data held by collaborating airlines.

For each individual, the period of follow-up thus ended with the last known date of vital status, the date of death, or the December 31, 2003, whichever was earlier. Loss to follow-up occurred for 69 cockpit crew (1.0%), 96 (2.6%) male cabin crew and 345 (2.7%) female cabin crew members. In addition, 352, 302 and 1,339 cockpit, male and female cabin crew members emigrated and thus had to be censored (5.0, 8.1 and 7.9%, respectively; Table 1).

Table 1 Characteristics of the German cohort: follow-up to end of 2003

	Cockpit		Cabin		Total
	Male	Female	Male	Female	
Persons	6,017	90	3,735	17,022	26,864
Deaths until 1997	255	0	170	141	566
Deaths until 2003	385	0	232	266	883
Cancer deaths	127	0	45	103	275
Lost to follow-up	67	2	96	453	618
Emigrated	345	7	302	1,339	1,993
Person-years	136,413	1,125	71,374	296,563	505,475
Mean follow-up (years)	22.7	12.5	19.1	17.4	18.8

Exposure

In previous analyses, the job-exposure matrix approach was used to estimate occupational radiation exposure, including an estimation of individual annual effective radiation dose computed with specific software (Hammer et al. 2000). For the current analysis, only duration of employment in jobs involving active flight duties could be used; more detailed information on individual flight history is currently being collected. For each individual, the date of first and last employment with the respective airline company was abstracted. We summarized individual periods if individuals had several employment episodes. No information was available on employment at other companies prior to or after having left employment at one of the included airlines (DLH, LTU).

In a previous validation study, a high correlation between different measures of exposure, including employment duration and estimated effective dose of ionizing radiation was found (Hammer et al. 2000). Therefore, in the present study, duration of employment is regarded as a reasonable dose proxy.

Statistical analyses

All cause of death information was coded according to the International Classification of Diseases revision in use at the date of death. For analytic purposes, we formed a group of radiation-associated cancers that include cancers of the esophagus, stomach, large intestine, breast, ovary, bladder/urinary tract, thyroid gland as well as leukemia.

Using German population rates as a reference, standardized mortality ratios (SMR) and corresponding exact 95% confidence intervals (CI) were computed, using 5-year age and calendar time intervals for person-year and mortality rate computations. To correct for missing causes of death, an approach described by Rittgen and Becker (Rittgen and Becker 2000) was used whereby the proportions of known causes among all deaths are used to interpolate missing causes. In analyses stratified by time period or by duration of exposure, this correction was done stratum-specific, such that different correction factors apply to different strata. By doing so, the more complete cause of death information of more recent periods can be adequately reflected.

For internal analyses that were carried out to investigate effects by duration of employment as a proxy for occupational radiation exposure, Poisson regression modeling was used, with age in 5-year groups and duration of employment in the categories 0–<10, 10–<20, 20–<30 and 30+ years, respectively. Linear trends were tested using a chi-square statistic, with scores 1–4 assigned to the respective categories.

Results

The analysis cohort comprises a total of 26,864 persons. This number has changed slightly in comparison with our earlier analyses, since additional information on some individuals emerged during the second follow-up: duplicate entries for 237 persons were removed. Gender could be assigned to 34 persons of previously unknown sex. The gender of 872 cohort members (869 cabin crew and 3 cockpit crew members) was corrected. Overall, 883 deaths occurred in the analyzed cohort (Table 1). Mean employment duration among those retired was 20.2, 13.8 and 8.7 years for male cockpit, male cabin and female cabin crew members, respectively.

Cockpit crew

No deaths were observed in female cockpit crew members ($n = 90$). Among the 6,017 male cockpit crew members (136,413 person-years), there were 385 deaths, 127 of which were due to cancer. The SMR was 0.49 (95% CI 0.45–0.55) for all causes, and 0.64 (95% CI 0.51–0.81) for cancer deaths (Table 2). Most SMR for individual cancer causes were non-significant with point estimates below one, while a marked SMR reduction of almost 70% was seen for lung cancer. An elevated SMR for cancer of the central nervous system (SMR 2.13, 95% CI 1.03-3.93) was found based on 14 cases (5 astrocytoma, 8 glioma and 1 unspecified

Table 2 Standardized mortality ratios (SMR)—cockpit crew, 1960–2003; O = observed number of cases; CI = confidence interval

Cause of death	Cockpit crew, men		
	O[a]	SMR	95% CI
All causes	385	0.49	0.45–0.55
All cancers	127	0.64	0.51–0.81
Stomach	10	0.68	0.28–1.39
Large intestine	12	0.85	0.38–1.64
Rectum	4	0.50	0.11–1.45
Pancreas	13	1.28	0.60–2.41
Lung/bronchial tree	18	0.33	0.17–0.57
Malignant melanoma	3	0.98	0.15–3.29
Prostate	11	0.96	0.42–1.91
Central nervous system (inc. brain)	14	2.13	1.03–3.93
Kidney	5	0.79	0.21–2.10
Non-Hodgkin's lymphoma	6	1.27	0.39–3.12
All leukemia	4	0.61	0.13–1.79
Radiation-associated cancers[b]	32	0.64	0.40–0.98

[a] only where two or more cases were observed

[b] includes: esophagus, stomach, large intestine, breast, ovary, bladder/urinary tract, thyroid gland, leukemia

brain tumor). For radiation-associated cancers (as defined in (Boice, Jr. 2006) and described in the "Statistical analyses" section), the SMR was 0.64 (95% CI 0.40–0.98).

Cause of death information was unavailable for 6.3% of all cockpit crew members. In particular, early years of follow-up proved problematic, as old death certificates were no longer kept in some public health offices.

Duration of employment was associated with all-cancer mortality (*P* for trend <0.01), with an RR of 2.2 (95% CI 1.19–4.08) in the highest duration category compared to the reference 0-<10 years. Brain cancers showed similar patterns, but the numbers were small (Table 3).

Cabin crew

There were 266 deaths among 17,022 female cabin crew members (296,563 person-years; Table 1). 103 cancer deaths resulted in an SMR of 0.95 (95% CI 0.72–1.26; Table 4). The cause of death was missing for 14.3% of all cases. For individual cancers, the SMR estimates were generally close to unity. There were 36 breast cancer deaths (SMR 1.17, 95% CI 0.74-1.80). The observed number of radiation-associated cancers in cabin crew was close to expected numbers calculated from population rates. No trends by duration of employment were found in the regression analyses (Table 5).

Among male cabin crew, there were only 45 cancer deaths (SMR 0.89, 95% CI 0.59–1.33), out of a total number of 232 deaths (71,374 person-years) driven by a high AIDS-related mortality. For 12.9% of deaths, no cause was available. The large majority of individual cancer sites had SMRs close to unity or differed non-significantly from unity. Deaths from Non-Hodgkin's Lymphoma ($n = 6$) were increased (SMR 4.24, 95% CI 1.26–10.76). As among female cabin crew, the regression analyses did not indicate significant risk differences according to duration of employment (Table 5).

Discussion

We present results of the second follow-up of one of the large civilian flight crew cohorts, adding a further 6 years of follow-up. Note that this analysis is not independent of

Table 3 Relative risks (RR) by duration of employment—male cockpit crew, 1960–2003

Cause of death	Cockpit crew				
	Duration of employment	O	RR[a]	95% CI	*P* (Trend)
All causes	0–9.99[b]	86	1.00		0.02
	10–19.99	125	0.85	0.64–1.13	
	20–29.99	127	0.73	0.55–0.97	
	30+	47	0.71	0.50–1.02	
All cancers	0–9.99[b]	16	1.00		<0.01
	10–19.99	27	0.90	0.47–1.69	
	20–29.99	51	1.44	0.81–2.56	
	30+	29	2.20	1.19–4.08	
Lung/bronchial tree	0–9.99[b]	4	1.00		0.57
	10–19.99	3	0.34	0.07–1.61	
	20–29.99	7	0.71	0.20–2.48	
	30+	4	1.15	0.29–4.60	
Central nervous system (includes brain)	0–9.99	0	0.00	−0.73	0.0002
	10–19.99[b]	4	1.00		
	20–29.99	7	2.49	0.73–8.52	
	30+	3	3.56	0.80–15.90	
Prostate	0–9.99[b]	1	1.00		0.47
	10–19.99	4	1.27	0.14–11.82	
	20–29.99	4	1.40	0.16–12.54	
	30+	2	2.55	0.22–29.04	
Radiation-associated cancers	0–9.99[b]	4	1.00		0.35
	10–19.99	7	0.96	0.27–3.42	
	20–29.99	12	1.40	0.44–4.47	
	30+	5	1.55	0.41–5.87	

[a] RR adjusted for age

[b] reference category

Table 4 Standardized mortality ratios (SMR)—cabin crew, 1960–2003; O = observed number of cases; CI = confidence interval

Cause of death	Cabin crew, men			Cabin crew, women		
	O	SMR	95% CI	O	SMR	95% CI
All causes	232	1.03	0.90–1.17	266	0.83	0.73–0.93
All cancers	45	0.89	0.59–1.33	103	0.95	0.72–1.26
Buccal cavity/pharynx	5	1.41	0.36–3.87	0	–	–
Stomach	1	0.31	0.00–2.15	5	0.91	0.23–2.48
Large intestine	2	0.63	0.05–2.72	7	1.18	0.39–2.82
Rectum	2	1.02	0.08–4.45	3	1.09	0.16–3.78
Pancreas	4	1.53	0.32–4.63	4	1.17	0.24–3.51
Lung/bronchial tree	10	0.74	0.30–1.56	11	1.07	0.46–2.19
Breast	0	–	–	36	1.17	0.74–1.80
Prostate	2	1.42	0.11–6.18	–	–	–
Central nervous system (incl. brain)	0	–	–	6	1.18	0.35–2.99
Non-Hodgkin's lymphoma	6	4.24	1.26–10.76	3	1.19	0.18–4.12
All leukemia	3	1.55	0.23–5.38	4	0.88	0.18–2.66
Radiation-associated cancers	9	0.76	0.29–1.65	61	1.08	0.75–1.53

Table 5 Relative risks (RR) by duration of employment—German cabin crew, 1960–2003; O = observed number of cases; CI = confidence interval

Cause of death	Duration of employment	Cabin crew, men			*P* (Trend)	Cabin crew, women			*P* (Trend)
		O	RR[a]	95% CI		O	RR[a]	95% CI	
All causes	0–9.99[b]	88	1.00	–	0.44	174	1.00	–	0.93
	10–19.99	73	1.60	1.17–2.19		55	0.82	0.61–1.11	
	20–29.99	61	1.18	0.81–1.72		28	1.07	0.71–1.61	
	30+	10	0.41	0.20–0.83		9	1.31	0.65–2.62	
All cancers	0–9.99[b]	16	1.00	–	0.23	59	1.00	–	0.56
	10–19.99	6	0.64	0.25–1.65		22	0.96	0.59–1.56	
	20–29.99	17	1.06	0.52–2.19		13	1.17	0.64–2.15	
	30+	3	0.30	0.08–1.08		5	1.30	0.51–3.33	
Lung/bronchial tree	0–9.99[b]	1	1.00	–	0.33	6	1.00	–	0.38
	10–19.99	2	3.40	0.31–37.60		1	0.47	0.06–3.95	
	20–29.99	5	4.82	0.53–43.81		3	2.46	0.61–9.86	
	30+	2	2.97	0.23–37.72		1	1.48	0.17–12.89	
Breast	0–9.99[b]					23	1.00	–	
	10–19.99					8	0.89	0.40–1.99	0.88
	20–29.99					4	1.02	0.35–3.02	
	30+					1	0.86	0.11–6.66	
Radiation-associated cancers	0–9.99[b]	3	1.00	–	0.15	35	1.00	–	0.91
	10–19.99	1	0.52	0.05–5.11		13	0.96	0.51–1.81	
	20–29.99	2	0.54	0.09–3.31		7	1.05	0.46–2.38	
	30+	0	–	–		2	0.83	0.19–3.58	

[a] RR adjusted for age

[b] reference category

our previous analyses. The number of deaths and of person-years increased by some 50% since the first follow-up. The main results are essentially unchanged compared to our earlier evaluations and were not affected by the corrections concerning the gender assignment (see "Results" section). A more pronounced risk increase and an association pattern with longer duration of employment are now seen for cancers of the central nervous system among male cockpit crew.

Results of the current analyses are in line with findings from other cohort studies. Regular health monitoring and certain requirements in terms of fitness, body weight and size as well as an occupational non-smoking environment may contribute to the low overall and cancer mortality predominant in the cohort, particularly among cockpit crew. While no direct assessment of smoking in the cohort is available, low lung cancer rates among the cockpit crew provide a clear indication of low smoking rates at least in this sub-cohort.

Duration of employment is the only exposure proxy available at the current state of analysis. For all cancers, a positive association with duration of employment among pilots is seen both in the first and the updated analysis. Although the analyses are adjusted for age in 5-year bands, some residual confounding by age may be present. However, this should not play a major role since any residual age differences would have to be differentially distributed in the duration strata to markedly change effect estimates, which is unlikely. An explanation for the observed pattern may be a decreasing healthy hire effect. However, other components of the healthy worker phenomenon such as the healthy survivor effect may partially counteract this influence. In addition, healthy worker effects are generally described to be less extensive in cancer mortality as opposed to overall mortality (Checkoway et al. 2004), but since there are very strong selection forces at work in aircrew cohorts, this may be different here.

In terms of radiation-associated cancers, no elevated risks are seen in external and internal analyses using duration of employment as a proxy for radiation exposure. Leukemia—which could not be well classified into subgroups from the information on the investigated death certificates—was not remarkable in any way, with only small numbers observed and expected. Incidence studies among cockpit crew in Nordic countries have provided most information on this issue, and no statistically significant risk increases were observed in these analyses (Pukkala et al. 2002).

The more than twofold risk increase for CNS tumors among cockpit crew is higher than that observed in our earlier follow-up, which was somewhat increased but not statistically significant. There are now 14 cases compared to seven cases in the earlier analysis. The SMR estimates in the different employment-duration strata beyond 10 years range from 2.3 to 2.9, and the internal analyses provide evidence of a significant trend with increasing duration of employment. Some earlier studies among aircrew also indicated toward somewhat elevated brain cancer risks (Band et al. 1996; Irvine and Davies 1992), but in the joint European mortality evaluation, the SMR was not significantly raised (SMR 1.2; 95% CI 0.87-1.67).

Note that, beyond the excess risks for brain cancer reported from the study of atomic bomb survivors (Preston et al. 2002), so far, only therapeutic radiation has been linked to increased brain cancer risk in epidemiological studies (UNSCEAR 2008). In contrast, the excess relative risk per Sievert was not significantly different from zero, for brain cancer among nuclear power workers in the 15-countries study (Cardis et al. 2007). In line with these findings, a recent explorative study of medical exposures to ionizing radiation performed in the framework of the INTERPHONE study on mobile phones showed slight risk elevations for meningioma and acoustic neuroma associated with head and neck radiotherapy and not with low-level diagnostic irradiation (Blettner et al. 2007). Risk factors for CNS tumors are generally poorly understood. The extent to which specific occupational exposures might influence brain cancer risk remains unclear, but putative agents including pesticides (Provost et al. 2007; Samanic et al. 2008) and occupations such as fire fighters (Kang et al. 2008) continue to be studied. The association of socioeconomic status and brain cancer risk also remains unclear, with inconsistent results in recent population-based studies (Chakrabarti et al. 2005; Lawlor et al. 2006).

An increased melanoma incidence and mortality have been found in pooled incidence and mortality analyses (Blettner et al. 2003; Pukkala et al. 2002; Zeeb et al. 2003a). Our new results show a melanoma SMR close to one for cockpit crew, but case numbers are small. In terms of risk factors, no information on UV exposure is available for German aircrew.

The breast cancer risk of female cabin crew has raised concern in the past (Pukkala et al. 1995; Reynolds et al. 2002). The results of our extended German mortality analysis remain essentially unchanged to the earlier result, with a slight but non-significant SMR elevation and with no association with duration of employment. The excess incidence among cabin crew noted in other studies (Tokumaru et al. 2006) seems to be more strongly elevated than the excess mortality. One interpretation is that cabin crew breast cancer cases may have a slightly more favorable therapeutic outcome than cases in the overall population, perhaps because they are diagnosed particularly early. To shed some further light on risk factor distributions among cabin crew in Germany, we are currently conducting a cross-sectional study among female cabin crew members, but the absence of incidence data continues to be a limitation of our study.

In the male cabin crew, the increases in NHL mortality may be associated with the clearly elevated frequency of AIDS-related deaths in this group, as documented in earlier analyses of the cohort (Zeeb et al. 2003a). NHL may have been assigned as the cause of death by the certifying physician without also including information on an underlying AIDS diagnosis.

The follow-up of a highly mobile cohort such as aircrew members continues to pose challenges. We chose not to wait too long before performing a second follow-up, in order to minimize losses to follow-up and avoid loss of exposure data that might otherwise not be retained in the airlines′ files. Intense follow-up activities allowed the clarification of several uncertain data issues. However, there continues to be a relatively high proportion of death cases for which information on the underlying cause could not be obtained. This situation is unfortunate for retrospective studies such as the present one, and establishment of a national death index could help to reduce such problems in the future. As in previous analyses, a correction method was used here to deal with missing causes of death, and while this allows a somewhat more realistic assessment, assumptions concerning for example the distribution of missing causes may not always hold.

Conclusion

In summary, results of the second follow-up of German aircrew presented here remain in line with initial findings from both the German and the joint European cohort. We are currently working on the calculation of radiation dose estimates for cockpit crew using retrospective flight information available for this group. When these data become available, a more specific assessment concerning radiation dose will be possible. The inclusion of our data into a new international pooled mortality analysis is also under way. The positive associations for all cancer and CNS tumors with duration of employment in German cockpit crew need to be carefully discussed and reviewed in the light of upcoming analyses of cohort data from other countries.

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