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TITLE PAGE

Cohort study of occupational cosmic radiation dose and cancer mortality in German aircrew, 1960-2014.

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ABSTRACT

Objectives

To determine cancer mortality compared to the general population and to examine dose-response relationships between cumulative occupational radiation dose and specific cancer outcomes in the German aircrew cohort.

Methods

For a cohort of 26,846 aircrew personnel, standardized mortality ratios (SMR) were calculated. Dose-response analyses were carried out using Poisson regression to assess dose-related cancer risks for the period 1960-2014. Exposure assessment comprises recently available dose register data for all cohort members and newly estimated retrospective cabin crew doses for 1960-2003.

Results

SMR for all-cause, specific cancer groups and most individual cancers were reduced in all aircrew groups. The only increases were seen for brain cancer in pilots (n=23, SMR 2.01, 95% CI 1.15 to 3.28) and for malignant melanoma (n=10, SMR 1.88, 95% CI 0.78 to 3.85). Breast cancer mortality among female cabin crew was similar to the general population (n=71, SMR 1.06, 95% CI 0.77 to 1.44). Overall median cumulative effective dose was 34.2 mSv (max: 116 mSv) for 1960-2014. No dose-response associations were seen in any of the models. For brain cancer, relative risks were elevated across dose categories. An indicative negative trend with increasing dose category was seen for large intestine cancer in female cabin crew (n=23).

Conclusions

There was no evidence for significant dose-response patterns for the considered cancer types. Interpretation of results remains difficult as cumulative dose is closely related to age. Future work should focus on investigating radiation jointly with other risk factors that may contribute to risks for specific cancers among aircrew.

INTRODUCTION

Being exposed to ionizing radiation of cosmic origin, commercial aircrew is one of the occupational groups with the highest radiation exposure. Average annual effective doses in cockpit and cabin crew members registered in Germany ranged between 2 and 6 mSv in 2014 [1]. Lifetime occupational cumulative doses in both occupational groups may exceed 100 mSv [2 3]. Given the specific occupational exposure setting, several large studies have investigated mortality and cancer incidence among aircrew, and nine pooled/meta-analyses have been reported [4-14].

The largest mortality study of aircrew pooled cohorts from ten countries in total included 93,771 individuals (1,780,269 person-years) [11]. Overall mortality was significantly reduced in male cockpit and female cabin crew. Mortality from cancer was reduced or similar to the general population with some exceptions, in particular for malignant melanoma in male cockpit crew [11]. Pooled analysis of cancer incidence was only carried out in cohorts from the Nordic countries, which in total included 20,098 aircrew personnel (414,870 person-years) [5 10]. Slightly increased overall cancer incidence was reported for cabin crew only. Skin cancer incidence was strongly increased in both cockpit and cabin crew (SIR: 1.9-3.0). There was limited evidence for dose-related cancer risks for both occupational subgroups [5 10].

We here present new results on mortality in the German aircrew cohort after extending previous follow-ups by ten years. Exposure assessment was improved based on recent data from the Federal Radiation Protection Register (RPR) [15], including newly derived estimates for the earlier period (1960-2003) for cabin crew [16]. The aim of this study is to compare the cancer mortality in the cohort to the one of the German general population and furthermore to investigate dose-response relationships between cumulative radiation exposure and mortality from selected cancer entities for cockpit and cabin crew.

METHODS

Cohort and mortality follow-up

The cohort comprises cockpit and cabin crew first employed between 1960 and 1997 at Lufthansa German Airlines and LTU, later Air Berlin (now liquidated). Mortality follow-up was extended until December 31, 2014. Person-time started with the date of first employment (cockpit crew) or 6 months thereafter (cabin crew) or January 1st 1960, whichever occurred later. The individual follow-up ended with the date of last known vital status, date of emigration, date of death, or December 31, 2014, whichever occurred earlier. Details of the earlier follow-up are described in [17 18]. The latest follow-up was performed using information of the Federal Radiation Protection Register to which the cohort was linked: cohort members with dose records in December 2014 or who had at least one further record in 2015 were assumed to be alive as of December 31, 2014. For individuals without a register match, those whose dose records ended before the end of the study period and those already part of the previous follow-up, vital status was determined through enquires with the local population registries at the place of last known address. When individuals were reported deceased, copies of their death certificates were requested from the local public health offices at the places of death. Causes of death were coded according to the International Classification of Diseases revision in effect at the time of death using the same coding scheme in the cohort and in the general population data. Single and grouped causes of death were evaluated as in the previous cohort analyses [6 7 17 18]. Solid cancer was included as an additional group.

Exposure assessment

In addition to the exposure data for cockpit crew from previous analyses, the current analysis now uses recent RPR data for all crew members and new reconstructed historical data for cabin crew [16 18]. Effective radiation doses were partly obtained via data-linkage to the RPR, which systematically monitors all aircrew of airlines registered in Germany and holds data starting August 2003 [1 15]. Airlines are required by law to calculate individual doses for each flight and send accumulated monthly doses via the Federal Office of Civil Aeronautics to the RPR [15]. Data were retrieved for all active cohort members for the time period 2004-2015.

For this analysis, an improved assessment of exposure was possible, using a novel approach to estimate cabin crew doses for earlier periods [16]. In brief, based on dose register data for 2004-2015, cabin crew doses were first modeled as a function of age group, sex, solar activity, and corresponding pilots' doses. The fitted model was then applied to retrospectively estimate age-group- and sex-specific annual cumulative effective cabin crew dose for 1960-2003 based on JEM-based pilots' doses and historical solar activity data [16]. The sex-specific annual doses by 5-year age group were assigned to each cabin crew member and further corrected by their individual employment history available for 1960-2003.

Statistical analyses

Standardized mortality ratios (SMR) and corresponding 95% confidence intervals were calculated using sex, age-group, and calendar-period-specific German general population rates as reference. SMR were corrected to account for missing cause of death information by imputing the missing causes of death cases proportional to the frequency of known causes in the cohort [19].

Cumulative effective dose categories were set as 0<5, 5-<15, 15-<25, 25-<40, and ≥40 mSv to ensure approximately equal allocation of cases in each category while staying compatible with previous analyses. Only single entities and groups of causes of death with more than ten cases were included in the dose-response analyses. Here, results for all cancer, solid cancer, the group of "radiation-related cancer" (including oral, esophagus, stomach, colon, rectum, liver, pancreas, bone, non-melanoma, breast, ovary, bladder, CNS (brain), thyroid, and leukemia; based on [20]), CNS (brain), malignant melanoma, breast cancer, and large intestine cancer are reported.

Mortality rate ratios for cumulative effective dose categories were calculated by Poisson regression with the lowest category serving as reference group. Categories were represented by integers 0, 1, 2, 4 for trend analyses. To estimate relative mortality rates per 10 mSv cumulative effective dose, a log-linear Poisson model was fitted. In all analyses person-year-weighted age and calendar year were introduced as continuous covariates in addition to binary employment status. The main analysis used person-year-weighted mean cumulative dose lagged by 10-years to account for the assumed latency between radiation exposure and cancer mortality.

Sensitivity analyses

Sensitivity analyses were conducted using alternative assumptions on latency (2, 5, 15 years) for the Poisson models. Additionally, Cox-regression models were fitted based on individual-level data with time-varying covariates using all latencies including 10 years as in the main analyses. Hazard ratios were calculated for all cancer groups (all cancer, solid cancer, radiation-related cancer) for all occupational groups, and also individually for CNS cancer in male cockpit and for breast cancer in female cabin crew.

Data management and SMR analyses were performed in SAS version 9.3 [21]. Dose-response and sensitivity analyses were carried out using the R environment for statistical computing version 3.5.2 [22].

RESULTS

Cohort

The analytical sample consists of 26,846 individuals after excluding one duplicate record and 43 cohort members who had one of the following exclusion reasons: missing date of birth, employed <6 months, date of vital status or end of employment before study start (i.e., January 1, 1960). 21,688 (80.8%) individuals were still alive and 9,454 (35.2%) still active by the end of follow-up. 714 (2.7%) individuals were lost to follow-up and 2,852 (10.6%) emigrated. Mean follow-up duration was 28.0

years (752,456 person-years) and mean age at the end of follow-up was 53.2 years. 1,592 deaths were recorded until December 31, 2014 including 519 cancer deaths. For 223 cases (14%) cause of death information was not obtainable, mainly due to regulations about destruction of records at public health offices (**Table 1**).

Table 1 here

Exposure

Exposure data were unavailable for 11 male and 31 female pilots who were excluded for the dose-related analysis. 503,021 yearly effective doses were recorded for the period 1960-2014, of which 257,305 (51.1%) were based on retrospective cabin crew estimates for 1960-2003 (**Table 2**). For this period, median cumulative effective doses were 17.6 (IQR: 10.5-26.1, max: 73.2) and 27.2 mSv (IQR: 15.3-48.5, max: 86.6) in female and male cabin crew, respectively. For the study period 1960-2014, the median cumulative effective doses were 44.1 mSv (IQR: 30.5-54.1, max: 99.7), 25.1 mSv (IQR: 10.5-46.6, max: 96.7), and 49.7 mSv (IQR: 16.3-65.8, max: 116.0) for male cockpit (mean age: 59.8 years), and female (mean age: 50.9 years) and male cabin crew (mean age: 53.1 years), respectively (**Table 2**). 12 individuals (all male cabin crew), of whom 11 are still active at the end of follow-up, accumulated effective doses more than of 100 mSv. The correlation between effective dose and other co-variables, such as part-time adjusted employment duration was strong (Pearson's correlation [cockpit] =0.84, [cabin] =0.96).

Table 2 here

SMR Analysis

There was one single death (of "unspecified causes") among female pilots. Hence, further results for cockpit crew will only be reported for men.

Among male pilots, 701 deaths were reported (210 cancer deaths). Standardized mortality ratios (SMR) for all-cause, all cancer, solid cancer and radiation-related cancer were all significantly reduced (**Table 3**). SMR for most individual cancers were below one, many statistically significant (e.g., bronchial tree and lung: SMR 0.27, 95% CI 0.16 to 0.42). Cancer of the central nervous system including brain tumors was significantly increased (SMR 2.01, 95% CI 1.15 to 3.28), SMR for malignant melanoma was non-significantly increased (SMR 1.88, 95% CI 0.78 to 3.85) (**Table 3**). In female cabin crew, 530 deaths were recorded including 227 cancer cases. SMR for all cancer and solid cancer was below one, and mortality from radiation-related cancer was close to one (**Table 3**). Mortality from brain cancer (SMR 1.26, 95% CI 0.60 to 2.36) and large intestine cancer (SMR 1.57, 95% CI 0.89 to

2.59) was increased. A total of 71 female breast cancer cases was recorded (SMR 1.06, 95% CI 0.77 to 1.44). In male cabin crew, SMR for all-cause, all cancer and solid cancer were significantly below one. More cases than expected were observed for Non-Hodgkin's Lymphoma, but the estimate was imprecise (SMR 2.00, 95% CI 0.60 to 5.03) (**Table 3**).

Table 3 here

Dose-response Analysis

In male cockpit crew, the categorical Poisson regression showed no trend of mortality rate ratios (RR) with increasing dose category for any of the selected cancer types was observed. In general, RRs were not significantly different from one when compared to the reference category. For CNS cancer, RRs suggested an association with increased doses (RR between 2.74 and 5.65) (**Table 4**), but most estimates as well as the trend test were not statistically significant. In addition, for radiation-related cancer RR was significantly increased in dose category 15-25 mSv (RR 2.76, 95% CI 1.37 to 6.03). RRs among female cabin crew were not significantly different from the reference category but there was an indicative negative trend with increasing dose category for large intestine cancer (p=0.08) (**Table 4**). Using dose as a continuous variable, the RR per 10 mSv in male cockpit crew was 1.03 (95% CI 0.76 to 1.45) for brain cancer and 1.29 (95% CI 0.78 to 2.40) for malignant melanoma. Cabin crew had similar patterns for all cancer and solid cancer in these analyses, and no notable dose-related mortality increases were detected (**Table 4**). The sensitivity analyses indicated mostly very similar estimates in the categorical and continuous Poisson regression models for alternative lag periods (2, 5, 15 years) (data not shown). Similarly, using Cox regression, differences in the risk estimates were mostly very small but qualitatively not different compared to the Poisson regression (see Supplementary 1).

Table 4 here

DISCUSSION

The study examined cancer mortality risk associated with cumulative occupational radiation in one of the largest aircrew cohorts worldwide with up to 55 years of follow-up. Since the last follow-up, 671 additional deaths including 519 cancer deaths were observed and person-years increased substantially.

The extended follow-up period and the increase in observed deaths resulted in more reliable mortality rate estimates with narrower confidence intervals. Lower mortality than the general population was found for all-cause, all cancer, solid cancer, as well as for radiation and non-radiation-related cancer across all occupational groups. This confirms the findings of previous analyses of this cohort [17 18] and indicates a strong healthy worker effect. Cancer mortality patterns appear to be driven by low smoking-related cancer deaths (mainly lung cancer), in particular among cockpit crew. Also, alcohol-related cancer mortality (including oral cavity, pharynx, esophagus, liver and larynx) was below unity in all groups including male cabin crew (data not shown), for whom significantly elevated risks were found in the pooled Nordic incidence study [10]. Cumulative occupational radiation exposure substantially increased since the previous follow-up and exceeded 100 mSv in some individuals but lagged doses used in the dose-response and sensitivity analyses were lower (see Supplementary 2). All fitted models showed no significant dose-associated increases in mortality rates for all considered cancer types.

Increased brain cancer mortality has been observed in recent national and pooled studies [11 23], and was significantly associated with employment duration [17] and non-significantly with cumulative effective dose in the previous analyses of the German cockpit cohort [18]. In the present study, brain cancer deaths were elevated in male cockpit and female cabin crew. Mortality was markedly higher compared to the results of the pooled mortality cohort study [11]. In the PanAm cohort, significant risk increases with increasing radiation dose and for different lag periods (0, 5, 10 years) were reported among cockpit crew (hazard ratios: 2.17-2.37 per 10 mSv) [23]. The unlagged doses were of very similar range compared to the ten year lagged exposures in our study (PanAm: median: 31 mSv, range: 0.01-71 mSv; see Supplementary 2). In contrast, no significant associations with cumulative radiation dose were observed in the continuous analyses and in the sensitivity analyses. Some risk increases among cockpit crew were observed in the categorical analyses (RR: 2.74-5.65). These findings, however, need to be interpreted with caution in particular due to the small number of cases and the low cumulative effective doses involved. For instance, other occupational cohort studies such as INWORKS (nuclear workers) only observed increased risks for solid cancers from 70 mGy absorbed organ dose onwards and with more than eight million person-years of observation [24]. As there are only few known brain cancer risk factors beyond high-dose ionizing radiation [25], our findings are difficult to interpret, but the possibility remains that other risk factors associated with cosmic radiation may bias the observed associations. EMF has been hypothesized to be associated with brain cancer in aircrew but there is only one older study among US Air Force staff on this topic [26].

Malignant melanoma mortality reached levels comparable to other cohorts and further showed a moderate risk increase with dose. Findings from a recent meta-analysis of melanoma risk in airline crews were similar (SMR 1.83, 95% CI 1.27 to 2.63) [12], as was the result of the pooled cohort mortality analysis (SMR 1.57, 95% CI 1.06 to 2.25) [11]. Incidence studies from the Nordic countries, the

UK and more recently from Australia also reported increased risks. Results from the earlier studies suggest that the increased risks may be attributed at least partly to leisure time behavior including UV exposure rather than to occupational cosmic radiation, but this remains an open question [5 27-29]. Preventive measures such as UV protection and skin cancer screening during regular health check-ups may improve the current situation as overall prognosis after early detection is good [30 31].

The SMR for breast cancer was lower compared to the previous follow-up [17] and is comparable to the pooled cohort analysis [11]. Incidence of breast cancer was elevated in the pooled Nordic study (SIR 1.50; [10]) and in the PanAm cohort (SIR: 1.37; [32]). The excess in the PanAm cohort though may be explained by reproductive factors in the cohort [32]. A cross-sectional study on the prevalence of breast cancer risk factors in German cabin crew in part confirmed these results [33]. Cumulative effective doses in our cohort's female cabin crew were substantially higher compared to previously published studies [10 34]. No evidence for an association with cosmic radiation was found here[10], whereas in the PanAm cohort (with lower overall doses) a dose-response relationship was found in a small subset of high-parity women [34]. Large intestine cancer mortality in female cabin crew increased 1.8-fold compared to the previous study (SMR 1.57, 95% CI 0.89 to 2.59). Although this cancer is classified as radiogenic, an inverse association with cumulative effective dose was observed, which may be due to confounding or simply a chance finding. In male cabin crew, the number of Non-Hodgkin's Lymphoma deaths remained unchanged (n=6) since the last follow-up leading to a marked reduction in SMR [17]. This development is likely to be associated with the concurrent decrease in AIDS/HIV mortality in this cohort and in Germany overall.

The strengths of our study include the improved exposure assessment, as it was feasible to use dose register data for the first time for the full cohort. The register linkage provided high quality individual-level exposure data with nearly complete coverage of all aircrew registered in Germany between 2004 and 2014. With these we were able to estimate retrospective cabin crew doses for 1960-2003 and thus conduct a radiation exposure assessment for the entire cohort including cabin crew. This approach led to a 4.2-fold total increase in annual dose records available for 1960-2014 compared to the previous follow-up. Estimated doses were used for 1960-2003, whereas dose register data were used for 2004-2014.

The median annual doses in 2014 in our cohort were 1.85 mSv (IQR: 1.34-2.82, max: 4.69) in cockpit and 2.02 mSv (IQR: 1.50-2.56, max: 4.65) in cabin crew. These doses are slightly higher than the reported register doses for all currently active aircrew in Germany in 2014 (1.71 and 1.97 mSv, respectively) [1] and is probably due to higher mean age in this cohort. The observed cumulative effective doses of up to 116 mSv until 2014, and higher for those still active, highlight that lifetime occupational radiation exposure in fact exceeds 100 mSv for specific groups, and earlier assumptions about expected lifetime occupational doses may no longer hold true [2]. The observed radiation doses are well below occupational dose limits of 20 mSv/year as imposed by German radiation protection legislation [35].

For cabin crew, employment data for 1960-2003 was used to adjust mean radiation dose estimates to the individual work profile, which included interruptions linked to parental leave or other absences. Therefore, we assume that errors in retrospective radiation dose estimates are relatively small and did not substantially bias risk estimates. The register linkage further facilitated uninterrupted exposure assessment for those cohort members who may have worked for another German airline since the last follow-up. Overall, the register linkage significantly improved exposure assessment and further facilitated cohort retention.

This study also had limitations in that lifestyle (smoking, alcohol consumption, UV exposure) and reproductive factors, as well as information on socio-economic status and ethnicity were not available. Missing cause of death information remains an issue (n=223; 14%) and similar to previous studies was corrected for in the SMR analyses using a proportional approach [19]. This lack of information is due to short safe-keeping periods at local public health offices in some regions and is assumed to be non-differential with respect to cosmic radiation dose. The register data used for exposure assessment provide effective doses only, a poor surrogate for organ dose. In addition, the use of effective (and equivalent) dose is not optimal since these include a quality factor for different radiation components that contribute to overall cosmic radiation. There is discussion that effective and equivalent doses may potentially overestimate carcinogenic effects of cosmic radiation due to the strong contribution of high-linear-energy-transfer radiation with a radiation weighting factor of up to 20 [36]. This further limits the power to assess the risk of low-dose radiation exposure. In contrast to other cohorts [3 37 38], assessing the effects of circadian rhythm disruptions was not feasible due to missing individual data on flight routes and directions. A statistical limitation follows from the necessarily strong correlation between dose and age. Only older individuals with long employment duration have high exposures, in particular those who started in the 1970s with the beginning of the jet plane era. In regression models, such multicollinearity may reduce the precision of individual effect estimates without introducing bias. This is a general issue in most occupational cohort studies.

Overall, mortality was lower for most cancer types in this cohort compared with previous findings. As expected cumulative exposures substantially increased in parallel with ageing of the cohort; however, there was very little evidence for dose-response associations for the considered cancer types. Brain cancer and malignant melanoma mortality in male cockpit crew remain an issue. It is unclear whether skin cancer screening during regular health checks may have positive effects on melanoma mortality, but targeted UV protection advice for all staff should be considered. The inconclusive findings regarding brain cancer mortality and the inconsistent evidence on cumulative effective dose effects in the different cohorts should be evaluated in future large studies, ideally using both incidence and mortality data.

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Contributors

MB and HZ conceived the initial study. TS was responsible for data management and follow-up implementation. SD and GH were responsible for exposure data collection. SD and DW performed the statistical analyses, with assistance by GH. SD drafted the manuscript with DW and HZ. All coauthors critically reviewed and approved the final manuscript.

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Disclaimer

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Competing interests

None declared.

Provenance and peer review

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Ethics approval

The present study was approved by the Employee Representations of Lufthansa and Air Berlin. Ethical approval was obtained from Bremen Medical Council and University of Bielefeld’s institutional review board. In addition, authorization from the data protection representative of the Federal Office of Radiation Protection was obtained for linking the cohort with the Federal Radiation Register database to obtain exposure data. Individual informed consent was not required for this retrospective study.

TABLES

Tab. 1: Cohort characteristics: follow-up until the end of 2014

	Cockpit		Cabin		
	Male	Female	Male	Female	All
Cohort members	6,006	90	3,733	17,017	26,846
Vital status					
Alive	4,728	79	2,833	14,048	21,688
[Deaths until 1997	*255*	*0*	*170*	*141*	*566]*
[Deaths until 2004	*405*	*0*	*242*	*274*	*921]*
Deaths until 2014	701	1	360	530	1,592
Cancer deaths	*210*	*0*	*82*	*227*	*519*
Missing cause of death	*88*	*0*	*55*	*80*	*223*
Lost to follow-up	75	2	116	521	714
Emigrated	502	8	424	1,918	2,852
Follow-up					
Person-years	190,628	1,999	103,992	455,836	752,456
Mean duration of follow-up (in yrs.)	31.7	22.2	27.9	26.8	28
Mean age at the end of follow-up (in yrs.)	59.8	48.3	53.1	50.9	53.2
Employment status at the end of follow-up					
Still active	2,185	38	1,242	5,989	9,454
Not employed*	3,821	52	2,491	11,028	17,392

* Not employed anymore at one of the companies where the cohort was initially recruited from (this applies to those cohort members who stopped working until the end of the 2nd follow-up (2003/2004)).

Table 2: Estimated cumulative effective doses (mSv) by time period, 1960 - 2014 (based on 503,021 dose reports) - no lagged years

	1960 - 2003 (JEM; retrospective estimates)						**2004 - 2014 * (Federal Radiation Protection Register (RPR))**						**1960 - 2014 Total**					
	Cohort members	**Collective cumulative dose (Sv)**	**Average individual cumulative dose (mSv)**				**Cohort members**	**Collective cumulative dose (Sv)**	**Average individual cumulative dose (mSv)**				**Cohort members**	**Collective cumulative dose (Sv)**	**Average individual cumulative dose (mSv)**			
			Med	IQR		Max			Med	IQR		Max			Med	IQR		Max
All			n= 376,832						n=126,189						n= 503,021			
Total	26,804	637.7	21.3	12.1	32.1	86.6	13,119	272.2	20.8	13.4	28.5	50.0	26,804	909.9	34.2	13.1	51.5	116.0
Cockpit			n= 119,527						n= 31,394						n= 150,921			
Total	6,054	178.8	27.7	17.7	41.8	72.1	3,519	71.1	21.0	12.6	28.0	48.3	6,054	249.9	43.9	29.8	54.0	99.7
Male	5,995	178.4	27.9	18.1	41.9	72.1	3,466	70.3	21.1	12.6	28.1	48.3	5,995	248.7	44.1	30.5	54.1	99.7
Female	59	0.5	8.7	3.4	11.0	17.6	53	0.8	14.4	10.2	22.1	37.2	59	1.3	24.4	11.0	33.3	49.7
Cabin			n= 257,305						n= 94,795						n= 352,100			
Total	20,750	458.9	19.0	10.8	29.3	86.6	9,600	201.1	20.7	13.6	28.6	50.0	20,750	660.0	28.3	11.2	50.6	116.0
Male	3,733	119.6	27.2	15.3	48.5	86.6	1,723	43.7	27.3	18.3	33.8	47.8	3,733	163.3	49.7	16.3	65.8	116.0
Female	17,017	339.2	17.6	10.5	26.1	73.2	7,877	157.4	19.8	13.1	27.0	50.0	17,017	496.6	25.1	10.5	46.6	96.7

*Note: this is a partial cohort

Tab. 3: Standardized mortality ratios (SMR) - male cockpit and female and male cabin crew, 1960-2014

	Male Cockpit				Female Cabin				Male Cabin			
Cause of death	Cases	O_C	SMR_C	95% CI_C	Cases	O_C	SMR_C	95% CI_C	Cases	O_C	SMR_C	95% CI_C
All cause	701	701	0.48	0.45 to 0.52	530	530	0.70	0.64 to 0.76	360	360	0.76	0.69 to 0.85
All cancer	210	240.2	0.57	0.47 to 0.69	227	267.4	0.84	0.69 to 1.02	82	96.8	0.71	0.52 to 0.96
Solid cancer excl. leukemia and lymphoma	195	222.9	0.57	0.47 to 0.69	213	250.9	0.84	0.69 to 1.03	72	85.0	0.67	0.48 to 0.92
Radiation-related cancer[1]	113	129.2	0.66	0.51 to 0.84	164	193.2	0.95	0.76 to 1.18	44	51.9	0.79	0.52 to 1.17
Esophagus	4	3.4	0.29	0.06 to 0.85	4	4.7	1.39	0.29 to 4.10	7	8.3	1.40	0.47 to 3.32
Stomach	10	11.4	0.45	0.19 to 0.92	7	8.2	0.61	0.20 to 1.42	3	3.5	0.47	0.07 to 1.63
Large intestine	19	21.7	0.74	0.40 to 1.26	23	27.1	1.57	0.89 to 2.59	4	4.7	0.54	0.11 to 1.61
Rectum	4	4.6	0.26	0.06 to 0.76	6	7.1	0.81	0.24 to 2.00	5	5.9	1.05	0.27 to 2.83
Biliary tree/liver	12	13.7	0.72	0.33 to 1.40	2	2.4	0.24	0.02 to 1.04	4	4.7	0.76	0.16 to 2.26
Pancreas	20	22.9	0.92	0.51 to 1.56	13	15.3	0.99	0.46 to 1.89	9	10.6	1.27	0.49 to 2.74
Bronchial tree and lung	27	30.9	0.27	0.16 to 0.42	28	33.0	0.70	0.42 to 1.11	15	17.7	0.47	0.23 to 0.86
Malignant melanoma	10	11.4	1.88	0.78 to 3.85	5	5.9	1.02	0.27 to 2.72	2	2.4	0.99	0.08 to 4.28
Breast	0	-	-	-	71	83.6	1.06	0.77 to 1.44	1	1.2	5.71	0.07 to 38.60
Ovary	0	-	-	-	13	15.3	0.73	0.34 to 1.40	0	-	-	-
Prostate	24	27.5	0.93	0.54 to 1.51	0	-	-	-	6	7.1	1.04	0.31 to 2.62
Kidney	8	9.2	0.73	0.27 to 1.62	3	3.5	0.76	0.12 to 2.59	0	-	-	-
Bladder/other urinary tract	7	8.0	0.55	0.19 to 1.28	0	-	-	-	1	1.2	0.31	0.00 to 2.10
CNS (includes brain)	23	26.3	2.01	1.15 to 3.28	14	16.5	1.26	0.60 to 2.36	0	-	-	-
Non-Hodgkin's Lymphoma	8	9.2	0.91	0.33 to 2.00	6	7.1	1.08	0.32 to 2.67	6	7.1	2.00	0.60 to 5.03
All leukemia	7	8.0	0.53	0.21 to 1.09	5	5.9	0.58	0.15 to 1.55	4	4.7	1.04	0.22 to 3.10

[1] includes oral, esophagus, stomach, colon, rectum, liver, pancreas, bone, non-melanoma, breast, ovary, bladder, CNS (brain), thyroid, and leukemia

The subscripted *c* indicates the corrections based on the Becker and Rittgen approach as described in the methods section.

Table 4: Mortality rate ratios (RR) with 95% confidence intervals (CI) for selected cancer types in cockpit and cabin crew in Germany 1960-2014, for continuous and categorical estimated cumulative dose (mSv).

	All cancer			Solid cancer (excludes leukemia and lymphoma)			Radiation-related cancer[1]			CNS (includes brain)			Malignant melanoma			Breast			Large intestine		
Cumulative dose	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**
Male cockpit																					
Continuous per 10 mSv	210	0.95	0.85 to 1.05	195	0.93	0.83 to 1.04	113	0.94	0.81 to 1.08	23	1.03	0.76 to 1.45	10	1.29	0.78 to 2.40	0	-	-	19	0.79	0.57 to 1.09
Categorical																					
< 5 mSv	28	ref.	ref.	26	ref.	ref.	11	ref.	ref.	1	ref.	ref.	2	ref.	ref.	-	-	-	3	ref.	ref.
5-<15 mSv	37	1.10	0.66 to 1.85	34	1.07	0.63 to 1.84	21	1.67	0.80 to 3.70	3	4.05	0.79 to 30.69	2	1.20	0.15 to 9.97	-	-	-	5	1.29	0.29 to 5.71
15-<25 mSv	59	1.58	0.97 to 2.64	55	1.56	0.94 to 2.65	38	2.76	1.37 to 6.03	4	5.65	1.03 to 46.67	1	0.58	0.04 to 8.43	-	-	-	4	0.96	0.19 to 4.79
25-<40 mSv	51	1.04	0.62 to 1.80	50	1.07	0.63 to 1.88	23	1.18	0.54 to 2.75	6	3.34	0.56 to 30.33	0	0.00	0.00 to Inf	-	-	-	4	0.53	0.10 to 2.67
≥ 40 mSv	35	0.85	0.47 to 1.57	30	0.76	0.41 to 1.44	20	1.20	0.52 to 2.96	9	2.74	0.36 to 30.28	5	2.37	0.21 to 26.95	-	-	-	3	0.43	0.07 to 2.58
p-trend			0.50			0.39			0.68			0.75			0.61			-			0.18
Female cabin																					
Continuous per 10 mSv	227	1.04	0.95 to 1.14	213	1.04	0.94 to 1.14	164	0.96	0.85 to 1.07	14	0.83	0.48 to 1.31	5	-	-	71	0.95	0.78 to 1.15	23	0.79	0.54 to 1.06
Categorical																					
< 5 mSv	55	ref.	ref.	51	ref.	ref.	41	ref.	ref.	4	ref.	ref.	-	-	-	20	ref.	ref.	6	ref.	ref.
5-<15 mSv	71	0.84	0.58 to 1.21	67	0.83	0.57 to 1.22	55	0.85	0.56 to 1.31	3	0.74	0.17 to 3.18	-	-	-	24	0.90	0.48 to 1.71	11	0.86	0.32 to 2.52
15-<25 mSv	48	0.99	0.66 to 1.49	46	1.00	0.65 to 1.51	40	1.08	0.68 to 1.72	3	1.48	0.35 to 6.28	-	-	-	18	1.24	0.62 to 2.49	3	0.40	0.08 to 1.55
25-<40 mSv	31	1.53	0.95 to 2.43	28	1.45	0.88 to 2.35	17	1.10	0.59 to 1.95	4	0.68	0.07 to 6.90	-	-	-	6	1.05	0.37 to 2.62	1	0.32	0.02 to 1.88
≥ 40 mSv	22	0.92	0.53 to 1.57	21	0.90	0.51 to 1.55	11	0.60	0.28 to 1.18	0	0.00	-	-	-	-	3	0.48	0.48 to 0.11	2	0.39	0.06 to 1.18
p-trend			0.33			0.50			0.58			0.62			-			0.68			0.08
Male cabin																					
Continuous per 10 mSv	82	1.05	0.94 to 1.17	72	1.04	0.93 to 1.16	44	0.98	0.86 to 1.14	0	-	-	2	-	-	1	-	-	4	-	-
Categorical																					
< 5 mSv	12	ref.	ref.	9	ref.	ref.	7	ref.	ref.	-	-	-	-	-	-	-	-	-	-	-	-
5-<15 mSv	15	1.28	0.58 to 2.91	13	1.31	0.54 to 3.30	9	1.23	0.44 to 3.63	-	-	-	-	-	-	-	-	-	-	-	-
15-<25 mSv	9	1.47	0.57 to 3.68	8	1.52	0.54 to 4.20	5	1.30	0.36 to 4.37	-	-	-	-	-	-	-	-	-	-	-	-
25-<40 mSv	4	0.82	0.22 to 2.50	3	0.74	0.16 to 2.60	1	0.33	0.02 to 1.96	-	-	-	-	-	-	-	-	-	-	-	-
≥ 40 mSv	42	1.73	0.78 to 4.19	39	1.65	0.71 to 4.29	22	1.38	0.49 to 4.48	-	-	-	-	-	-	-	-	-	-	-	-
p-trend			0.26			0.37			0.78			-			-			-			-

Lag 10 years, adjusted for PY-weighted age and calendar year (continuous), and employment status (dichotomous: yes, no).

[1] includes oral, esophagus, stomach, colon, rectum, liver, pancreas, bone, non-melanoma, breast, ovary, bladder, CNS (brain), thyroid, and leukemia

Key messages

1. **What is already known about this subject?**

   Commercial aircrew personnel are occupationally exposed to ionizing radiation from cosmic origin as well as to other risk factors related to commercial aviation.

2. **What are the new findings?**

   As one of the largest aircrew cohorts this study accumulated up to 55 years of observation, and now includes high-quality radiation protection register data.

   Occupational cumulative effective doses exceed 100 mSv in few cohort members with lifetime doses reaching up to 116 mSv and higher.

   Lower mortality was found for all causes and all considered cancer groups across all occupational groups.

   Interestingly, several tumors related to life style were significantly reduced, while brain cancer and malignant melanoma mortality remained increased in male cockpit crew.

3. **How might this impact on policy or clinical practice in the foreseeable future?**

   It is unclear whether skin cancer screening during regular health checks may have positive effects on melanoma mortality, but targeted UV protection advice for all staff should be considered.

   The inconclusive findings regarding brain cancer mortality and the varying evidence with cumulative effective dose in the different cohorts should be evaluated in future large studies.

   The observed patterns in lifetime cumulative effective dose underscore the need for exposure monitoring for aircrew.

Online supplement tables
Supplementary 1:

Hazard ratios (HR) with 95% confidence intervals (CI) for selected cancer types in cockpit and cabin crew in Germany 1960-2014, for continuous estimated cumulative dose (mSv).

	All cancer			Solid cancer (excludes leukemia and lymphoma)			Radiation-related cancer[1]			CNS (includes brain)			Breast		
Cumulative dose	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI
Male cockpit															
Continuous per 10 mSv	210	0.88	0.77 to 1.01	195	0.86	0.75 to 0.98	113	0.97	0.80 to 1.17	23	1.05	0.65 to 1.29	0	-	-
Female cabin															
Continuous per 10 mSv	227	1.07	0.97 to 1.18	213	1.06	0.96 to 1.17	164	0.96	0.83 to 1.12	14	0.70	0.37 to 1.33	71	0.90	0.72 to 1.13
Male cabin															
Continuous per 10 mSv	82	1.05	0.93 to 1.18	72	1.03	0.92 to 1.17	44	0.96	0.85 to 1.09	0	-	-	1	-	-

Lag 10 years, time-varying covariates include cumulative dose, attained age, calendar year, and employment status.
[1] includes oral, esophagus, stomach, colon, rectum, liver, pancreas, bone, non-melanoma, breast, ovary, bladder, CNS (brain), thyroid, and leukemia

Supplementary 2:

Estimated cumulative effective doses (mSv), 1960 - 2014 by latency period

		2 years					**5 years**					**10 years**					**15 years**				
	Cohort members	**Collective cumulative dose (Sv)**	**Average individual cumulative dose (mSv)**				**Collective cumulative dose (Sv)**	**Average individual cumulative dose (mSv)**				**Collective cumulative dose (Sv)**	**Average individual cumulative dose (mSv)**				**Collective cumulative dose (Sv)**	**Average individual cumulative dose (mSv)**			
			Med	IQR		Max		Med	IQR		Max		Med	IQR		Max		Med	IQR		Max
All	26,804	869.5	32.5	13.1	48.6	107.7	798.5	29.1	13.1	43.2	95.5	661.6	22.2	12.6	33.6	86.8	532.5	16.7	8.22	26.2	83.6
Cockpit																					
Total	6,054	240.3	41.9	29.1	51.7	95.0	222.6	37.7	26.8	48.1	90.4	185.9	29.3	19.6	42.9	73.9	150.3	21.8	12.3	37.4	70.8
Male	5,995	239.1	42.1	29.5	51.8	95.0	221.7	37.9	27.4	48.2	90.4	185.4	29.4	19.9	43.0	73.9	150.1	21.9	13.0	37.6	70.8
Female	59	1.2	21.0	9.9	28.3	44.1	0.9	16.9	9.1	22.7	37.8	0.5	10.1	4.4	13.0	19.7	0.2	3.6	1.26	4.7	10.7
Cabin																					
Total	20,750	629.2	26.9	11.2	47.1	107.7	575.8	24.8	11.1	40.9	95.5	475.7	19.9	11.0	30.5	86.8	382.2	15.1	7.6	23.5	83.6
Male	3,733	157.0	46.4	16.3	63.5	107.7	145.8	40.1	16.3	58.7	95.5	123.5	28.5	16.0	49.7	86.8	102.2	20.1	9.65	43.4	83.6
Female	17,017	472.2	24.3	10.5	43.2	90.5	430.1	22.7	10.5	37.5	83.1	352.2	18.4	10.5	27.4	73.2	279.9	14.7	7.38	21.3	71.8