Incidence and Mortality of Prostate Cancer in Commercial Airline Cockpit Crew: Systematic Review and Meta-Analysis

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Abstract

Commercial airline cockpit crew (CCC) are potentially exposed to occupational risk factors that may have detrimental health effects. However, available literature on prostate cancer (PCa) as a health outcome is conflicted. Therefore, this review of cohort studies aims to evaluate the incidence of and mortality from PCa in CCC based on studies published to date. PubMed, Medline, EMBASE and SCOPUS were searched from 1946 to April 2021. Cohort studies reporting standardized incidence ratios (SIR) and/or standardized mortality ratios (SMR) of PCa in CCC were included. Military, cabin crew and service personnel data were excluded. Independent data extraction was conducted, and study quality assessed. Standardized ratios were pooled using a fixed effects model and expressed with 95% confidence intervals. 75 studies were assessed for eligibility from which 6 involving 129 374 licensed CCC were included in the final analysis: Two reported incidence only, 1 incidence and mortality and 3 reported mortalities only. The pooled SIR for PCa in CCC was 1.41 (95% CI 1.17 to 1.71) with moderate heterogeneity (I^2 = 53%) however, the pooled SMR was not statistically significant (1.08; 95% CI 0.94 to 1.24) also with moderate heterogeneity (I^2 = 70%). The available evidence shows that CCC are at a higher risk of developing PCa but there is no evidence to suggest a similarly higher risk of death from the disease. The effect of early detection through PSA testing in this cohort is unclear. Occupational exposure to radiation and sleep disturbance may play a role, but clear evidence of additional risk is lacking. Our review indicates that most evidence is dated and to confidently assess contemporary health outcomes of CCC, further research is required.

Introduction

Commercial airline cockpit crew (CCC) usually includes captains (pilot in command), co-pilots (first officer) and flight engineers with variations in number depending on type of aircraft and route[1]. This is an occupational cohort who undergo strict medical surveillance and are often regarded as healthier than the general population[2]. Although a healthy worker effect exists among pilots[3,4], their unique work environment exposes them to several risk factors including exposure to electromagnetic fields, ionizing radiation of cosmic origin, disruptions of circadian rhythm, and noise pollution[5], ultimately raising their risk of poorer outcomes in several physical and mental health parameters[6–8,9].

Key Words

Prostate cancer, commercial airline pilots, incidence, mortality

Competing Interests

None declared.

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Abbreviations

CCC commercial airline cockpit crew
PCa prostate cancer
PSA prostate specific antigen
SIR standardized incidence ratio
SMR standardized mortality ratio

In 1990, The International Commission on Radiological Protection recommended that natural background radiation exposure be included as an occupational hazard for aircrew[10], and since then, various reports[5,9,11–21] have described the incidence and mortality risks of cancer in pilot cohorts. In summary, decreased mortality from cardiovascular and respiratory diseases was reported in some cohorts[5,11,13,14] as well as all cancer deaths[13,15,16,18,20,21] when compared with mortality in the general population. Malignant melanoma has been consistently associated with high incidence[12,13,22–26] and mortality ratios[5,13,14].

Prostate cancer ranks second in incidence after lung cancer and fifth in mortality rates in males globally[27]. To our knowledge, no studies have exclusively investigated PCa in CCC. However, data on prostate cancer risks have been reported in studies documenting outcomes from multiple disease types that report conflicting results associated with incidence and mortality rates of PCa. From these, 6 studies have reported increased incidence[12,13,25–29], 2 reported no significant association[23,26] and one[30] reported a lower incidence of PCa compared with background population rates. Similar contradictory evidence is available in mortality studies, with data reporting lower[9], unchanged[14,16,17,21,31,32], and higher[5,13,33] mortality rates of PCa in CCC relative to population statistics.

Several commentaries[7], meta-analyses[34,35], and reviews[36] have reported cancer risks in flight personnel, with data for cockpit crew, flight attendants, and military personnel generally analyzed separately. These studies report for all cancer types, except one study[37] that focused exclusively on PCa in pilots. Raslau et al. in the review and meta-analysis reported a higher incidence of PCa (RR 1.20; 95% CI 1.08 to 1.33) in pilots compared with the general population, but mortality was not significantly elevated (RR 1.20; 95% CI 0.91 to 1.60). After initial retraction[38], the revised version[37] was criticised[39] for omission of eligible studies[5,9,12,21] and re-inclusion of military data[40].

Given the inconclusive nature of literature in this area and the previously retracted and criticised review, a new analysis is required. This study, therefore, in addition to correcting past errors, aimed to provide a systematic review and meta-analysis of data exclusively focusing on PCa in CCC.

Materials and Methods

This systematic review and meta-analysis was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations[41]. Two independent investigators (H.F. and H.K.) conducted the literature search, study selection, and data extraction, and resolved any discrepancies through discussion.

Selection criteria

Studies that fit the following criteria were included in the meta-analysis: (1) published studies only, (2) original population data, (3) cohort study design, (4) investigating CCC only, (5) PCa as either one of the outcomes or the only outcome reported, (6) reporting in terms of standardized incidence ratios (SIR) or standardized mortality ratios (SMR) and their 95% confidence intervals (CI) only or studies containing sufficient data for calculation of these parameters, (7) reporting 2 or more cases of prostate cancer in either incidence or mortality occurrences and (8) written in any language. All studies that investigated military, cabin crew, flight attendants and other personnel not designated as an occupation undertaken inside the cockpit were excluded. Latest studies that were investigative extensions of previous data cohorts were selected to avoid data duplication.

Literature search and data sources

Eligible cohort studies in any language published on PubMed, Medline, EMBASE and SCOPUS from inception up to April 2021 were searched using the search strategies outlined in Appendix 1. Commercial aircraft pilot, navigator, and flight engineer data were included as CCC, and military and helicopter pilots, flight/cabin attendant and service personnel data were excluded. Flight attendant cohorts that reported cancer incidence[24,42] and mortality[43,44] collectively analyzed 5 times as many females as males; most of the population were younger than 50 years, and they had a much shorter work period than pilots. They were therefore excluded. Military and helicopter pilots fly different routes and at different altitudes[29] from commercial cockpit crew and so were also excluded from the analysis.

The titles and abstracts of all identified articles were reviewed by 2 investigators independently, and disagreements and ambiguities resolved by discussion. The reference lists of identified studies and previous systematic reviews were manually examined for additional stud-

ies of interest. Reports in which the data were duplicated were identified, and only the most recent cohorts were included. The abbreviation "CCC" and the words "pilots" and "cockpit crew" are used interchangeably throughout the paper.

Data extraction and quality assessment

A standardized data extraction form was used by 2 independent researchers. The following relevant information was extracted from each study: author, year of publication, study outcome (incidence, mortality, or both), title of paper, country, population size of cohort, duration of study, mean age at conclusion, Newcastle–Ottawa Scale (NOS)[45] score, risk factors assessed (years of employment, cumulative radiation dose in μSv or mSv, cumulative block hours and high altitude long-haul or short-haul flights), observed and expected number of PCa cases, SIR or SMR, and 95% confidence intervals.

The quality of the papers included in the review was assessed using the Newcastle–Ottawa Scale (NOS) developed by Wells et al.[45]. The NOS is tailored to the design type and allows assessment the validity of results in the presence of selection, reporting, and confounding biases. It uses 3 domains for assessment: selection, comparability, and outcome. Stars were added in each domain, with the totals signifying "good," "fair," or "poor" quality. Details of each item can be found on the website (www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Data synthesis and statistical analysis

The outcomes of interest were standardized incidence ratios (SIR) and standardized mortality ratios (SMR). For each study, the observed and expected numbers were extracted. This allowed the calculation of the standardized ratios (SR) and corresponding confidence intervals to be consistent across studies. The SR was calculated as observed/expected and then log-transformed. The standard error of the log(SR) was calculated using 1/sqrt(observed) and confidence intervals constructed on the log-scale and exponentiated. This ensured that all estimates would be positive.

A fixed effects meta-analysis was used to calculate the pooled standardized ratios across studies. The I^2 statistic was calculated to investigate the extent of heterogeneity across studies. Heterogeneity was considered low for I^2 values between 25% and 50%, moderate for 50% to 75%, and high for >75%. R software (version 4.0.2) was used for computation of the estimates and construction of forest plots packages, with packages meta[46] and metaphor[47]. Publication bias could not be assessed as the study included fewer than 10 studies[48].

Results

Literature search and study selection

Figure 1 shows the literature search and study selection process. We identified 3100 records by key word search, and hand searching elicited 17 further studies. After screening, 75 remaining full-text articles were assessed for eligibility of which 6 were included in the review: 2 studies reported incidence only, 3 reported mortality only, and 1 reported both for PCa. From the large number of studies excluded, 30 were tabulated with reasons for exclusion and selected data characteristics (0- and Supplementary Table S1B).

Methodological evaluation of studies: identification of systematic bias

The NOS components and total scores are shown against each study in Table 1. The 1996 study by Band et al.[13] was assessed for incidence and mortality outcomes separately. The median total score was 6, and only 2 studies scored a total of 7, indicating an overall good quality of studies and no manuscripts with a high risk of bias. Total scores and thus quality of the studies tended to be less prone to bias if they were published more recently.

Incidence of prostate cancer among CCC: meta-analysis results

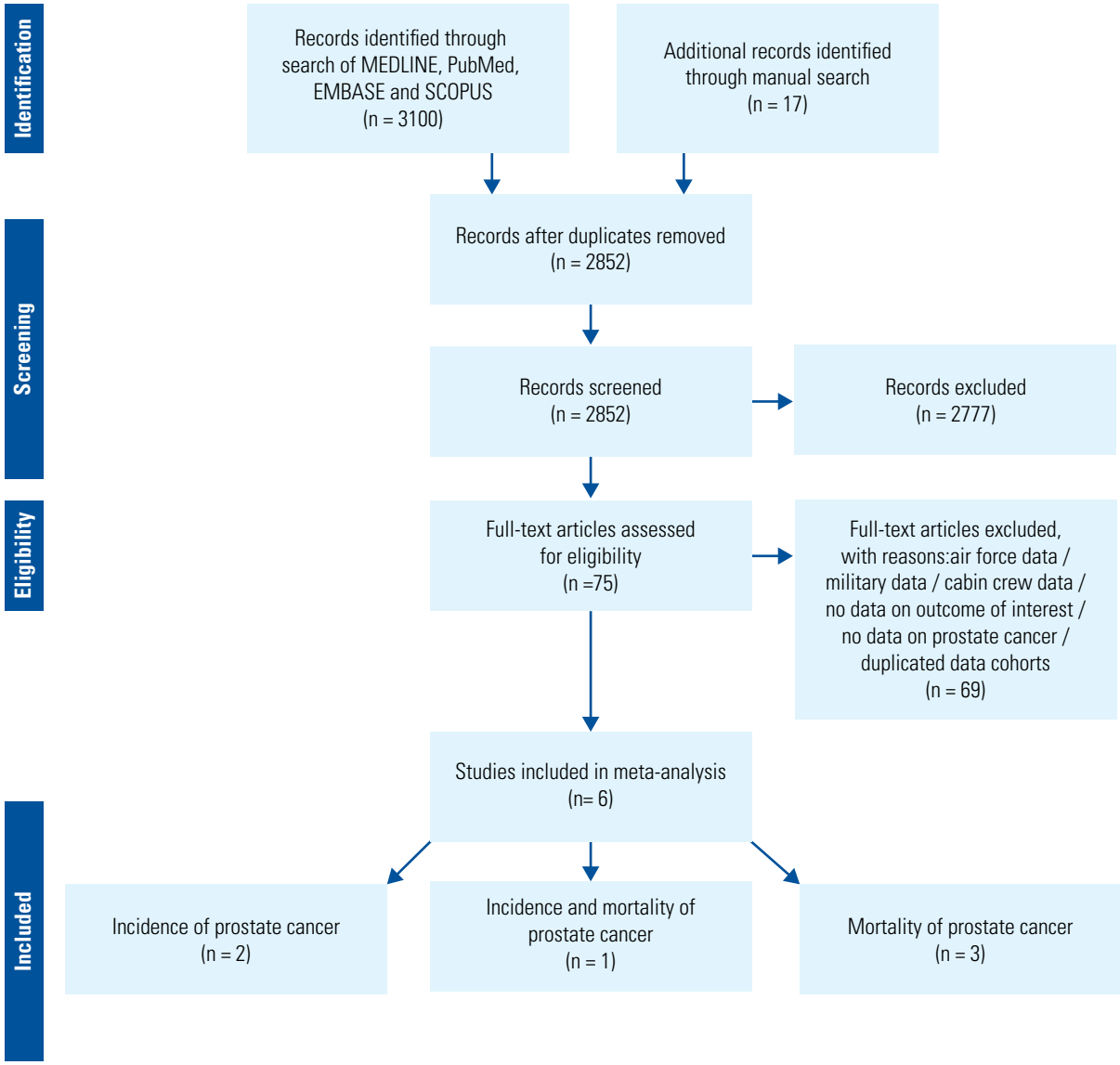
Table 2 and Figure 2 summarize the results of the meta-analysis of 3 studies reporting incidence of PCa. The pooled analysis resulted in a pSIR of 1.41 (95% CI 1.17 to 1.71) suggesting that observed rates were significantly higher than expected. The pooled results were of moderate heterogeneity (I^2= 53%). An exploration of sources and subsequently a pooled analysis of subgroups and risk factors was not possible because of heterogeneity and lack of sufficient and consistent data in individual cohorts. Studies by Band et al.[12,13] did not include a risk factor analysis, leaving only one[25] from the included incidence studies attempting to analyze cosmic radiation and circadian disruptions as risk factors of PCa by calculating relative risk estimates. They did so by approximating radiation exposure with block hours on short-haul flights and hormone disturbances with block hours on long-haul flights.

Mortality of prostate cancer among CCC: meta-analysis results

The summary of results of the meta-analysis of the 4 mortality studies are shown in Table 3 and Figure 3. The analysis resulted a pSMR of 1.08 (95% CI 0.94 to 1.24), suggesting that observed mortality rates were not significantly different to the rate expected in the general population with moderate heterogeneity (I^2=70%). The 1990[12] study by Band et al. was excluded from the mortality analysis because only 1 death from PCa

FIGURE 1.

Flow diagram of literature search and study selection for meta-analysis of prostate cancer in commercial airline cockpit crew/pilots.



was observed. From the included studies, only 2[5,21] reported a risk factor analysis (discussed below); however, it is noteworthy that Yong et al.[21] reported standardized rate ratios of duration of employment and cumulative cosmic radiation dose with mortality, but no data on PCa were available. Lack of risk factor analysis from other included studies prevented a multivariable analysis with mortality data as well.

Discussion

This systematic review and meta-analysis summarizes available literature pertaining to incidence and mortality rates of PCa in CCC. These results may support the hypothesis that prostate cancer risks in CCC reflect a combination of screening, sociodemographic, and environmental factors that increase the risk of diagnosis but have no effect on the risk of death from prostate cancer. However, because of substantial heterogeneity among studies and an overall small sample size, we believe these results should be interpreted with caution.

The most plausible drivers of the observed increased incidence of PCa in CCC appear to be occupational risk factors discussed in detail below. However, it is also worth noting that over the last 2 decades the rise of prostate specific antigen (PSA) testing in many developed countries has led to dramatic increases in the incidence rates of PCa via diagnosis of sub-clinical disease[49]. Although in most developed countries, PSA testing is

not mandated as part of the medical certification process for CCC[50–52], CCC are more likely to be tested for PSA upon inquiry of reported lower urinary tract symptoms as they undergo more regularly scheduled and concentrated medical surveillance[2] than males in the general population. The results of this meta-analysis are likely also affected by increased use of PSA testing in CCC, which results in the detection of more localised PCa compared to the general population. CCC typically have higher incomes and PSA testing with subsequent follow-up of abnormal results is performed more frequently in men with higher incomes[53].

Despite increased incidence, mortality from PCa was unchanged as compared with the general population. Higher socioeconomic status and better baseline health could be factors in this observation, especially given the general long life expectancy of men diagnosed with PCa. The data related to the impact of PSA testing and early diagnosis of PCa is controversial, with current literature suggesting it does not affect overall mortality[54], which would be consistent with these results.

Exposure to ionizing radiation of cosmic origin

PCa is not frequently included in the list of neoplasms attributable to ionizing radiation[55], largely due to the lack of sensitivity of the prostate to ionizing radiation, but also due to the latency period of radiation induced solid tumours being decades[56] and PCa being among the slower growing solid tumours. Supporting this theory, studies investigating radiologists and other medical radiation workers have shown no increase in incidence[57] or mortality[58] rates of PCa. In contrast to this, studies after the 1986 Chernobyl incident show an increase in the incidence of PCa in regions surrounding the area of the accident[56,59]. The large release of radioactive material from the incident[60] makes it less relevant to pilots; however, findings of radiation induced incidence rates of PCa in pilots show similarly conflicting results.

The study of Nordic pilots[25] quantified cumulative radiation exposure by converting aircraft specific block hours to effective doses. Block hours are industry-standard measure of aircraft use and are defined as the time elapsed between closure of aircraft doors before departure and opening of these doors at the arrival gate following landing of the aircraft. The same study used the number of block hours on long-haul aircrafts to estimate circadian hormonal disruption among pilots as well. A statistically significant increase of PCa was observed in exposure category ≥ 20 mSv, RR 9.13; 95% CI 1.11 to 74.9 in men age < 60 years as compared with older ages in the same category of exposure (RR 1.08; 95% CI 0.55 to 2.12). Similarly, Gudmundsdóttir et al.[26] reported a statistically significant risk ratio of 2.57 (95% CI 1.18 to 5.56) in Icelandic pilots exposed to > 25mSv of ionizing radiation of cosmic origin compared with pilots who were not. These values could possibly be related to greater levels of UV radiation at the poles than at the equator. The association between prostate cancer and radiation exposure remains uncertain. According to available literature it seems unlikely that development of prostate cancer at an early age would be associated with ionizing radiation as no studies have been able to establish a causal link between the two[25]. Adding to this evidence is the 20-year-old Norwegian study[23] that reported an inconsistent trend in SIR values as ionizing radiation exposure increased from 0mSv to >20mSv with a statistically non-significant elevated SIR of 1.8 (95% CI 0.7 to 4.0) for pilots exposed to >20mSv of ionizing radiation.

Overall mortality data show moderate but higher heterogeneity than incidence data, but information on measurement of risk factors is less conflicted, with the majority of studies showing no significant difference, although with heterogeneity in measurement methodology. A mortality analysis of PCa cases exposed to >25 mSv cumulative effective dose of cosmic radiation reported in a German publication[32] reported low and non-significant mortality and risk ratios (SMR 0.92; 95% CI 0.00 to 37.69, RR 0.94; 95% CI, 0.18 to 4.79). A large European cohort study (ESCAPE)[61] attempted a risk factor analysis of cosmic radiation and mortality rates in pilots. PCa was placed in the category of non-radiation related neoplasms[62,63] but SMRs of PCa with increasing doses of radiation were not reported individually. Mortality studies that quantify years of employment[16,31] or number of block hours since attaining a license[15] as proxies for radiation exposure have reported no statistically significant mortality ratios of PCa. An extension[5] of the ESCAPE[61] study cohort with addition of pilots from Greece and United Kingdom, analyzed years of employment as proxy for cumulative radiation exposure. This large study, included in this review, also reported no consistent change in SMRs in proportion to increasing years of employment. It is important to keep in mind that this study was an extension of previously reported cohorts hence similar results were to be expected. Further research into occupations frequently exposed to radiation is warranted for clarification of the relationship between radiation and prostate cancer.

Exposure to electromagnetic fields and disruption of circadian rhythm

Although not fully understood, the incidence of PCa has been suspected to be linked with exposure to magnetic fields, which, it has been suggested, may lead to alteration in pineal function, subsequently causing reduction in levels of the pineal hormone, melatonin[33]. Melatonin is associated with the sleep–wake cycle and maintenance

TABLE 1.

Characteristics of six studies included in the meta-analysis of prostate cancer among pilots

Study author (Year)	Sample size	Study period	Country/ region	Observed	Expected	SIR (95% CI)	
Band et al. (1990)	891	1950–1988	Canada	6	3.9	1.54 (0.69–3.43)	
Band et al. (1996)	2680	1950–1992	Canada	34	18.2	1.87 (1.34–2.62)	
Pukkala et al. (2003)	10 051	1946–1997 (Denmark from 1946, Finland up to 1996, Iceland from 1937, Norway 1946–1994, Sweden 1957–1994)	Nordic countries	64	52.9	1.21 (0.93–1.54)	
Band et al. (1996)	2680	1950–1992	Canada	7	4.62	1.52 (0.72–3.19)	
Cashman et al. (2007)	72 972	1980–2002	United States	4	10.9	0.37 (0.10–0.94)	
Yong et al. (2014)	5964	1953–2008	United States (PanAm)	77	Not available	0.90 (0.71–1.12)	
Hammer et al. (2014)	36 816	1957–1999 (Denmark 1960–1996, Finland 1971–1997, Germany, Greece, Iceland 1960–1997, Italy 1965–1996, Norway 1962–1994, Sweden 1957–1994, United Kingdom 1989–1999)	Europe / United States†	114	119.99	1.23 (1.03–1.47)	

**Assessed by the Newcastle-Ottawa Scale45*

†United States was part of the cohort but data on pilots was not available or analysed (cabin crew data analysed only)

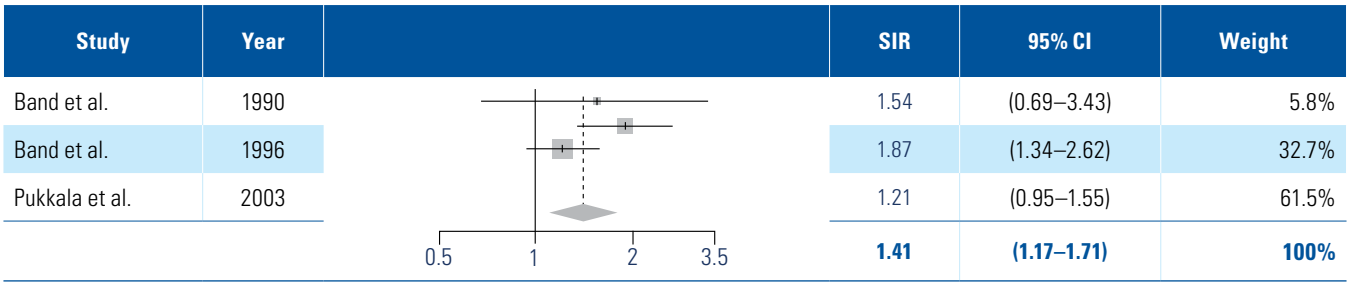
	Mean age at conclusion	Risk factors considered	Quality score categories			Total quality score*
			Selection	Comparability	Outcome	
	49.9	Not available	★	★	★★★	6 Fair
	50.5	Not available	★★	★	★★★	6 Fair
	Not available	Cumulative block hours, Cumulative radiation dose	★★★	★★	★★	7 Good
	50.5	Not available	★★	★	★★★	6 Fair
	43.09	Not available	★★	★	★★★	6 Fair
	Not available	Duration of employment, Cumulative radiation dose	★★★	★	★★	6 Good
	53.3	Duration of employment as proxy for radiation exposure	★★★	★	★★★	7 Good

TABLE 2.

Included incidence studies with observed and expected number of prostate cancer cases, individual and calculated SIR, weightage, and calculated heterogeneity. SIR, standardised incidence ratio

Study author (Year)	Observed	Expected	SIR (95% CI)	Weight, %
Band et al. (1990)	6	3.9	1.5400 (0.6919–3.4279)	5.8
Band et al. (1996)	34	18.16	1.8700 (1.3362–2.6171)	32.7
Pukkala et al (2003)	64	52.9	1.2100 (0.9471–1.5459)	61.5
Overall I^2 = 53%			1.4146 [1.1673–1.7144]	100.0

FIGURE 2.



of circadian rhythm, and it may have a protective effect against prostate cancer[64]. Magnetic field exposure in commercial aircraft has been measured in a prior study[65] and was concluded to be substantially higher than that of a home or a typical office environment. Most studies used block hours as approximate values for amount of magnetic field exposure and hormonal disruption[21,25]. The Nordic study[25] reported increased risk associated with a greater number of long-haul hours in men > 60 years of age as the strongest flying-related variable studied in the context of prostate cancer. The possibility that circadian disruptions have a role in causing hormone-related neoplasms cannot therefore be entirely excluded. However, a precise association or disassociation between jet lag and development of hormone-related cancers could not be established. Gudmundsdóttir et al.[26] observed similar results of higher incidence rates of PCa in pilots with >10 000 cumulative air hours (RR 2.61; 95% CI 1.22 to 5.60). In contrast, however, an incidence study[29] not included in the meta-analysis (**Supplementary Table S1A** and **Supplementary Table S1B**) reported no significant increase in the incidence of PCa in relation to block hours (SIR 1.28; 95% CI 0.73 to 2.08 for >10 000 block hours). Similarly, the Norwegian pilot cohort[23] reported a statistically non-significant SIR of 1.1 (95% CI 0.6 to 1.9) among pilots who flew >10 000 block hours. The same year, in their study on Icelandic pilots, Raffnson et al.[28] attempted to evaluate the possible association between cancer risk and circadian rhythm disturbance but reported only incidence rates of malignant melanoma and all-cancer risk. An extension of this cohort[26] could not differentiate between pilots who had flown to North America and those who had flown within Europe, as all Icelandic pilots had flown both ways and so were unable to report cases of PCa in pilots on long-haul versus short-haul flights.

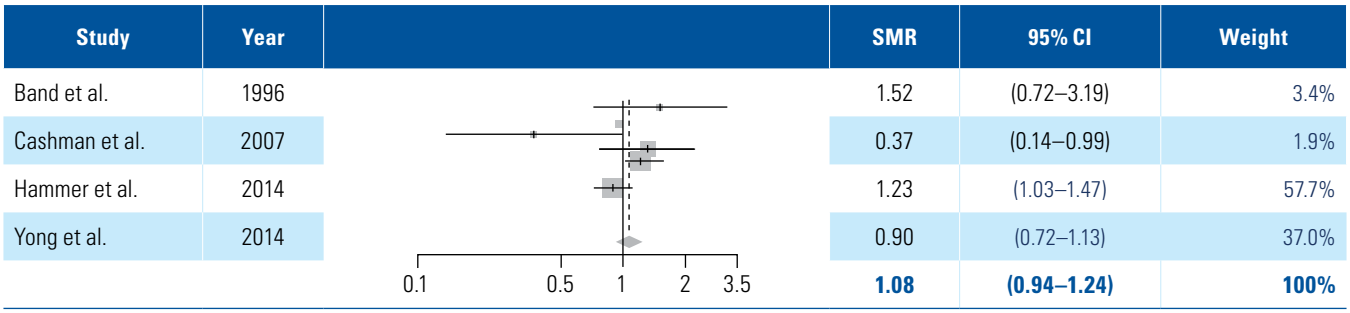
Although long-haul flights suppress melatonin and, as hypothesized, might be expected to be associated with higher incidence rates of PCa, a study of British Airways pilots[14] (excluded from the review because of inclusion of helicopter crew data) reported a statistically non-significant relative risk of PCa (RR 2.47; 95% CI 0.83 to 7.65) for short-haul compared with long-haul flights. In an attempt to resolve ambiguities in this area, a recent review[66] reported that neither short sleep (RR 0.99; 95% CI 0.91 to 1.07) nor long sleep (RR 0.88; 95% CI 0.75 to 1.04) was associated with PCa in the general population, and long sleep may have a protective effect on PCa; however, specific pilot cohorts were not investigated. Available evidence has again proven to be inconsistent in arriving at a conclusion on the association of circadian abnormalities and PCa necessitating deeper investigation into the subject.

TABLE 3.

Included mortality studies with observed and expected number of deaths due to prostate cancer, individual and calculated SMR, weightage and calculated heterogeneity. SMR, standardised mortality ratio

Study author (Year)	Observed	Expected	SMR (95% CI)	Weight, %
Band et al. (1996)	7	4.62	1.5200 [0.7246–3.1884]	3.4
Cashman et al. (2007)	4	10.9	0.3700 [0.1389–0.9858]	1.9
Hammer et al.(2014)	114	119.99	1.2300 [1.0285–1.4710]	57.7
Yong et al. (2014)	77	not available	0.9000 [0.7198–1.1252]	37.0
Overall I^2 = 70%			1.0783 [0.9413–1.2353]	100

FIGURE 3.



Other considerations

The pilot population investigated to date has reported a mean age at conclusion of 41.7 to 50.5 years in incidence and 43.1 to 53.3 years in mortality studies. It is important to note that the Japanese study[11] recorded a mean age of 45.9±13.6 years at conclusion of follow-up, indicating PCa cases contributing to the reported all-cancer mortality could possibly be non-existent because of the very low incidence of prostate cancer in younger men[67]. As older age is a well-established risk factor for PCa, it can be deduced that studies on CCC reflecting the mean age group mentioned above may be reporting an underestimation of true risk of the disease.

The strengths of this review lie in its exhaustive search and strict selection criteria for accurate representation of disease outcome and the inclusion of only CCC. Including data related to military pilots and cabin crew can often be misleading, especially when risk factors such as ionizing radiation exposure and circadian rhythm are being explored concomitantly, because of the differences in aircraft and route selection and flight altitudes between the 2 categories of pilot[29]. Although a sub-group analysis was not performed because of heterogenous exposure assessments in different studies, a streamlined sample approach aims to increase the credibility of this review.

An important limitation of our review was the inability of search terms to produce important studies that were instead discovered by manual searching of references by both researchers. The large North American study[9] eligible for the meta-analysis, as well as some that were later excluded, were not initially identified via the online database search. It is noteworthy that the recent review by Raslau et al.[37] did not include this study, perhaps due to the same reason.

Quality assessment of each study was conducted by both researchers independently, using the NOS[45] that has proven to be useful in multiple similar systematic reviews[68,69]. The quality of 2 out of 3 incidence studies was "fair," only one was "good" and none were "poor." It was noted that studies with lower population samples were of 'fair' quality and also reported higher incidence rates than the 'good' quality study. This phenomenon of likelihood of publishing studies with lower sample sizes and positive associations has been previously described by researchers[70]. Additionally, studies with fair quality were also older (published in the 1990s) than the 'good' quality study (published in 2003)[25].

In comparison to incidence cohorts, half of the mortality studies were of "fair" quality, and the other half were of "good" quality (none were of "poor" quality). It is noteworthy that the study with the largest sample

of pilots (n = 72 972)[9] scored a total of 6 on the NOS and was of "fair" quality. It also reported a markedly decreased mortality rate of PCa among pilots, the lowest among all mortality studies, as well as in comparison to the pooled SMR (1.08; 95% CI 0.94 to 1.24). Although risk of potential bias is known to decrease with a higher sample size, this study is not only an exception but is also outnumbered by other included studies in this review that support results of low or unchanged mortality rates among pilots in comparison to the general population. The 1996 publication by Band et al.[13] favours the theory of increased risk of bias associated with a smaller sample size and positive associations as it reported the highest mortality rate among all studies.

We are aware of the latest 2017 study by Gudmundsdóttir et al.[26]. However, after consideration by the authors, it was concluded that this study should be excluded for a number of reasons. Firstly, the 2003 study by Pukkala et al. was a multinational cohort[25], inclusion of which would allow examination of a larger sample size, whereas the 2017[26] study by Gudmundsdóttir et al. investigated only Icelandic pilots. Secondly, the latter study added only 47 new pilots to the initial Icelandic sample in the Pukkala et al. study, resulting in 83.6% data duplication (n = 239[25] and n = 286[26]). Furthermore, it cannot be confirmed that differences in observed cases of PCa from the 2003 study were in fact, observed cases in the added number of pilots. To demonstrate that results remain unchanged even with inclusion of this study, an analysis was performed with adjustment of sample sizes between the 2 studies to prevent data duplication (**Supplementary Figure S1A**). **Supplementary Figure S1B** shows pooled SIR results (meta-SIR 1.39; 95% CI 1.16 to 1.67 with I^2 = 35.9%). It is evident that results remain largely unchanged.

Conclusions

This systematic review of all available evidence suggests that compared with the general population, commercial airline cockpit crew have an increased risk of developing PCa; however, there was no evidence of elevated risk of death from this disease. Caution is suggested in interpretation of results, as most evidence is dated, results are inconclusive, and because of significant data duplication, the sample size for assessment of outcomes is ultimately small. The risk of developing PCa as a result of exposure to ionizing radiation and circadian disruptions needs to be investigated further for accurate estimates of the associated burden of disease. This work supports previous calls for national registries for commercial airline cockpit crew to track incidence and mortality rates of PCa and for better understanding of health outcomes in this population.

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SUPPLEMENTARY TABLE S1A.

Incidence studies excluded during eligibility assessment for the final meta-analysis, with characteristics and reasons for exclusion

	Study	Sample size	Study duration	Observed	
Prostate cancer Incidence data: Standardized Incidence Ratio (SIR)					
1	Haldorsen et al. (2000)	3701	1946–1994	25	
2	Gudmundsdottir et al. (2017)	286	1955–2015	15	
3	Rafnsson et al. (2000)	265	1955–1997	4	
4	Hammar et al. (2002)	1490	1961–1997	18	
5	Dos Santos De Silva et al. (2013)	15 867	1989–1999	Not reported	
6	Gundestrup et al. (1999)	3790	1921–1995	3 (jet) 3 (non-jet)	
7	Milanov et al. (1999)	34	1964–1994	Not reported	
8	Nicholas et al. (2001)	6533	1970–1998	65	
9	Pukkala et al. (2002)	10 032	1946–1997 (Denmark from 1946, Finland up to 1996, Norway 1946–1994, Sweden 1957–1994 Iceland 1955–1997	64	
10	Pukkala et al. (2012)	1559	1947–1997 (Finland 1947–1993, Iceland 1947–1997, Norway 1950–1994, Sweden 1957–1994)	24	
11	Rogers et al. (2011)	106 418	1987–2008	Not reported	

	Expected	Standardized ratio	Mean age at conclusion	Country/ region	Reason(s) for exclusion
	25	1.00 (0.68–1.48)	Not reported	Norway	Duplicated data cohort in Pukkala et al. (2003)
	11.8	1.27 (0.71– 2.10)	Not reported	Iceland	Duplicated data cohort in Pukkala et al. (2003)
	2.84	1.41 (0.53– 3.76)	Not reported	Iceland	Duplicated data cohort in Pukkala et al. (2003)
	14.5	1.24 (0.78–1.97)	Not reported	Sweden	Duplicated data cohort in Pukkala et al. (2003)
	Not reported	1.10 (0.96–1.26)	Not reported	United Kingdom	Duplicated data cohort in Hammer et al. (2014)
	3.97 (jet) 3.59 (non-jet)	0.8 (0.2–2.2) for both	41.65 years	Denmark	Duplicated data cohort in Pukkala et al. (2002)
	Not reported	Not reported	Not reported	Republic of Bulgaria	No statistical data on prostate cancer reported
	Not reported	0.7 (0.59–0.84)	Not reported	United States, Canada	Investigated cancer incidence by questionnaire (self-reported disease outcomes)–different methodology could give inconsistent results
	52.9	1.21 (0.93–1.54)	Not reported	Nordic countries	Duplicate data cohort in Pukkala et al. (2003)
	21.7	1.11 (0.71–1.65)	Not reported	Finland, Iceland, Norway, Sweden	Cabin crew data
	Not reported	Not reported	Mean age at diagnosis ~ 50 years	United States	Exclusively Air force / military data, comparative study, calculates hazard ratio

SUPPLEMENTARY TABLE S1B.

Mortality studies excluded during eligibility assessment for the final meta-analysis, with characteristics and reasons for exclusion

	Study	Sample size	Study duration	Observed	
1	Salisbury et al. (1991)	402	1950–1984	Not reported	
2	Irvine & Davies (1992)	411	1966–1989	Not reported	
3	Kaji et al. (1993)	2327	1952–1988	Not reported	
4	Nicholas et al. (1998)	1538	1984–1991	38	
5	Haldorsen et al. (2002)	3707	1946–1994	Not reported	
6	Irvine & Davies (1999)	6209	1950–1992	15	
7	Ballard et al. (2002)	3022	1965–1996	4	
8	Zeeb et al. (2002) (cockpit crew)	6061	1953–1997	8.7	
9	Zeeb et al. (2003) (cabin crew/ att -endants)	11 079	1946–1997 (Denmark 1947–1996) (Finland 1947–1992) (Germany 1953–1997) (Greece 1946–1997) (Iceland 1955–1997) (Italy 1965–1995) (Norway 1950–1994) (Sweden 1957–1994)	5.2	
10	Zeeb et al. (2010) (cockpit crew)	6017	1953–2003	11	
11	Blettner et al. (2003)	27 797	1921–1997 (Denmark 1946–1996) (Finland 1921–1997) (Germany 1953–1997) (Greece 1946–1997) (Iceland 1935–1997) (Italy 1965–1995) (Norway1946–1994) (Sweden 1957–1994) (United Kingdom 1950–1997)	54	
12	Hammer et al. (2012)	6006	1960–2004	11.9*	
13	Dreger et al. (2020)	6006	1960–2014	24	
14	Langner et al. (2004)	19 184 (ESCAPE)	1921–1997	Not reported	
15	Stavola et al. (2012)	15 881	1989–1999	Not reported	
16	Krstev et al. (1998)	60 878	1984–1993	Not reported	
17	Linnersjö et al. (2011)	1478	1957–1994	Not reported	
18	Blettner et al. (2002)	4185	1953–1997	Not reported	
19	Paridou et al. (2003)	2678	1960–1997	Not reported	

	Expected	Standardized ratio	Mean age at conclusion	Country/ region	Reason(s) for exclusion
	Not reported	Not reported	Not reported	Canada	Discusses proportional mortality rates, unable to pool in to standardized mortality data
	Not reported	Not reported	Not reported	United Kingdom	Helicopter pilots included and discusses proportional mortality rates, unable to pool in to standardized mortality data
	Not reported	Not reported	45.9 ± 13.6 years	Japan	No statistical data on prostate cancer
	27.56	1.38 (1.00–1.90)	Not reported	USA	Discusses proportional mortality rates, unable to pool in to standardized mortality data
	Not reported	Not reported	Not reported	Norway	Helicopter pilots included, duplicated data cohort in Hammer et al. (2014) and no statistical data on prostate cancer.
	13.48	111.3 (62.3–183.5)	Not reported	United Kingdom	Includes helicopter pilot data as well
	3.76	1.06 (0.40–2.82)	Not reported	Italy	Duplicated data cohort in Hammer et al. (2014)
	6.9	1.26 (0.53–2.59)	Not reported	Germany	Duplicated data cohort in Blettner et al. (2003)
	4.8	1.09 (0.35–2.68)	Not reported	Europe	Cabin crew data, no mention of separate data for pilots/cockpit crew
	Not reported	0.96 (0.42–1.91)	Not reported	Germany	Extended (+6 years) follow up after 2003 study – no new cohort members added hence duplicated data cohort in Blettner et al. (2003)
	60.1	0.94 (0.72–1.23)	Not reported	Europe	Duplicated data cohort in Hammer et al. (2014)
	12.4	0.96 (0.36–2.53)	51.5 years	Germany	Duplicated data cohort in Hammer et al. (2014)
	27.5	0.93 (0.54–1.51)	59.8 years	Germany	Only German data and extended follow-up (to 2014) of the same cohort from Hammer et al. 2014. Cumulative SMR of all countries only in 2014 study
	Not reported	Not reported	Not reported	Europe	Duplicated data cohort in Hammer et al. (2014) and no statistical data on prostate cancer
	Not reported	Not reported	Not reported	United Kingdom	Duplicated data cohort in Dos Santos de Silva et al. (2013) and no statistical data on prostate cancer
	Not reported	Not reported	Not reported	United States	Discusses mortality odds ratio—unable to pool in to standardized mortality data, case–control study
	Not reported	Not reported	Not reported	Sweden	No statistical data on prostate cancer
	Not reported	Not reported	Not reported	Germany	Cabin crew / attendant data
	Not reported	Not reported	Not reported	Greece	No statistical data on prostate cancer

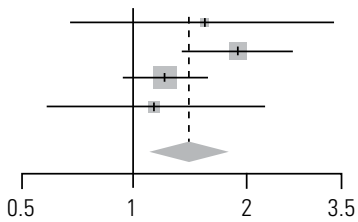
SUPPLEMENTARY FIGURE S1A.

Adjustmentof sample size between 2 studies

Study	Original totals	Number overlapping	Number deducted
Pukkala et al.			
Total	10032	239	120
Observed	64		0.77
Expected	52.9		0.63
Gudmundsdóttir et al.			
Total	286	239	119
Observed	15		6.24
Expected	11.8		4.91

SUPPLEMENTARY FIGURE S1B.

Pooled SIR results with inclusion of latest study

Study	Year		OR	95% CI	Weight
Band et al.	1990		1.54	(0.69–3.43)	5.4%
Band et al.	1996		1.87	(1.34–2.62)	30.4%
Pukkala et al.	2003		1.21	(0.95–1.55)	56.5%
GGudmundsdóttir et al.	2017		1.12	(0.58–2.17)	7.8%
I^2 = 35.9%			**1.39**	**(1.16–1.67)**	**100%**