The Independent Medical Expert Group (IMEG) 5th Report

Report and recommendations on medical and scientific aspects of the Armed Forces Compensation Scheme

February 2020

Topic 6 - Cutaneous Malignant Melanoma (CMM) in Air Crew

Key Points

1. The 2017 IMEG report considered skin melanoma as a recognised disease and concluded that the evidence available then did not support a doubling of risk from any service exposure or factor and so the criterion for presumption of service causal connection was not met.

2. Attention has recently been drawn to the significant literature concerning the risk of Cutaneous Malignant Melanoma (CMM) in commercial air crew. While mortality and incidence of most common cancers is lower in this group than in the general community, the evidence suggests overall that incidence and mortality for CMM is higher than in the age and sex adjusted general population.

3. Risk factor studies have focused on occupational Ultraviolet Radiation (UVR) and cosmic radiation. On this topic many of the studies are small, reliant on self-report for diagnosis, and work conditions such as aircraft types, flight durations, shift patterns etc are very different from today. Controls are often matched only for age and sex, not skin colour and type, presence of naevi and family history.

4. A 2005 study looked at UVR transmittance through aircraft windshields. This study found raised CMM incidence both in pilots and cabin crew and also in Air Traffic Controllers (ATCOs). Neither cabin crew nor ATCOs are at risk of occupational UVR exposure, suggesting other factors must be involved. The study did not measure cosmic radiation dose but from other studies, average annual exposure of cabin crew is low, in the range 2-6 mSv. Most international expert bodies do not consider CMM radiogenic.

5. Considering the literature, findings are often inconsistent, and studies are almost entirely based in the Northern hemisphere. The one Southern hemisphere (Australia) 2019 study of commercial pilots followed-up from 2001-2016 for a total of 91370 person-years found 114 CMM tumours, 5 invasive and 63 in situ. When age-specific incidence rates (SIR) were compared with the corresponding general population rates there was a slightly increased rate of melanoma in situ but no increase in invasive melanoma compared with the general population.

6. Studies of military aircrew are limited. One 2017 US study showed an increase in CMM diagnoses over time, but diagnoses were clinical, not all histologically proven. Principal service occupations were assessed only at a single point in time and despite average short service duration, follow-up finished at service termination. Overall, the evidence in commercial aircrew, with some heterogeneity, does suggest a raised risk of CMM in pilots and aircrew but does not identify mechanisms.

7. This review had to conclude that UVR exposure might well be non-occupational and even pre-date employment. We also recognise the very different aircraft, flight duties, speeds and heights, work patterns and flight durations for military aircrew compared with commercial flying.

8. We will continue to monitor the literature and recommend that claim determinations for CMM from pilots and flight crew should routinely have medical input and be based on individual case facts.

Introduction and Background

1. The 2017 Fourth IMEG report contained a section considering Ultraviolet Light and Skin cancers, including Cutaneous Malignant Melanoma (CMM), as recognised diseases. Based on the published peer-reviewed evidence, IMEG concluded that CMM could not at that date be considered a recognised disease i.e. presumed to have service causal connection, but that each claim to AFCS should be considered on its facts.

2. Since publication of the Fourth report, attention has been drawn to the significant body of evidence, spanning many years, on the risk of CMM in airline pilots and aircrew. With high socioeconomic status and regular medical examinations, commercial airline pilots, the subject of most studies, are a selected population, fitter physically and mentally than the age and sex adjusted general population. Overall mortality and incidence rates of most common cancers and cardiovascular disorders in these groups are low (1). An apparent exception is CMM. The published literature on overall mortality, cancer incidence and mortality include case studies, meta-analyses and systematic reviews, and provides the strong impression that the rate of skin cancers, particularly CMM incidence, is significantly higher in pilots and aircrew than in the age and sex adjusted general population (2). CMM mortality rates have been less studied, with inconsistent results, but in some studies, death rates are increased in both pilots and aircrew, men more than women (3).

Findings:

3. Studies have considered risk factors, most frequently occupation-related solar Ultraviolet Radiation (UVR) exposure. UVR is part of the continuous spectrum of electromagnetic radiation that is sunlight. This is divided arbitrarily into UVA (315-400nm), UVB (280-315nm) and UVC (315-400nm). In terms of CMM, UVC is not relevant as it is absorbed by the earth's atmosphere but the longer wavelength UVB (1-10% of UVR reaching the earth's surface) and UVA of which 90-99% might reach the skin are important. UVA can penetrate deep into the skin. Once thought to be innocuous, UVA is now considered key in carcinogenesis, where exposure is prolonged and excessive. UVA causes tanning and skin ageing and leads to indirect damage to DNA, through the formation of reactive oxygen species. In turn these cause breaks in DNA, mutations and then cancer. UVB penetrates the upper layers of the epidermis and can cause sunburn, tanning, skin ageing and skin cancer much more effectively through direct damage to DNA. UVA and UVB are classified by the International Agency for Research into Cancer (IARC) as group 1 carcinogens (4). An issue for occupation-related personal injury schemes, as discussed in the 2017 IMEG report, is that occupational UVR exposure is inevitably accompanied by recreational exposure, and there is no robust basis on which to apportion the two. It is also relevant in CMM that many experts believe sunburn in late childhood or adolescence to be the key aetiological factor in melanoma.

4. Occupational UVR exposure for pilots and aircrew is mainly through aircraft windshields. The evidence confirms that transmittance of UVB by both glass and plastic windscreens is low (less than 1%) while for the higher wavelength UVA (320-380 nm) a more varied transmittance pattern is seen, ranging from less than 1% to over 50%, with plastic attenuating UVA more effectively than glass. As well as for pilots, the incidence of melanoma is raised in cabin crew and air traffic controllers (ATCOs) (5). Neither cabin crew nor ATCOs are at risk of occupational UVR exposure and so other risk factors are likely to be implicated. The overall evidence acknowledges that despite limitations in individual study size, cancer risks e.g. breast, prostate and acute myeloid leukaemia, have been reported as raised in flight and cabin crew (6)(7)(8). Most consistent is CMM, with a large pooled study confirming the risk for CMM, but not for the other sites (9). Additional occupational hazards listed for flight crew are cosmic ionising radiation and potentially relevant personal characteristics, skin type and susceptibility to sunburn, ethnicity, cigarette smoking and recreational UVR exposure. The dos Santos study (5) referenced above, attempted to distinguish occupational and lifestyle exposures and compared site specific cancer risk between in flight crew and air traffic control officers (ATCOs). Overall cancer incidence was lower in both sets of occupations compared to the general population, mainly owing to low rates of smoking and so smoking-related cancers, but CMM incidence was raised in both flight crew and ATCOS. In flight crew, rates increased with hours flying, suggesting a connection with occupational exposure. However, the CMM incidence rates were similar in both occupational groups suggesting that the risk is not driven by occupation-related UV or cosmic radiation (neutron and gamma), neither of which is a potential hazard for ATCOs. The strongest risk predictors in both groups were personal and lifestyle factors, skin that burns easily and sunbathing to get a tan. Both groups have access to discounted air travel. The study had some limitations including lack of cosmic radiation dose estimates.

5. Other studies of commercial aircrew have looked at cosmic radiation with dose estimates for cabin crew of 2-6 mSv per year (10) i.e. about twice UK average annual dose from background or background and medical sources. This exposure is much lower than annual background in some UK locations, dependent on underlying geology and, based on current understanding, even over many years would be associated with low risk of adverse health effects including cancers, cataract, cardiovascular disease and importantly, CMM which is not accepted by international authorities e.g. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) as radiogenic (11). Pilot and aircrew cosmic radiation dose was estimated in the studies, using a variety of approaches, information on flying hours, employment duration, types of flight undertaken and job exposure matrices of year specific aircraft type annual dose rates. Recent and contemporary dose rates are likely to be lower reflecting time directives and industry standards on flying hours. The relation between hours worked or estimated dose in the various studies of pilots and flight attendants to CMM incidence is inconsistent with some studies suggesting raised incidence of CMM (12) but not others (13). Other issues include whether there was flying was long or short haul, or a mixture, whether it included return trips and number of daylight hours flying.

6. Most studies are retrospective cohort. Limitations in the published evidence include small study size, with only a few cases of melanoma, often identified by self-report. Particularly in respect of AFCS compensation, relevance to contemporary conditions are important. Some publications date from the 1970s and include data from the 1940s with the majority of studies analysing data now 30-40 years old. Controls are commonly matched only for age and sex but not for other potential confounders such as skin colour, type and presence of naevi or multiple naevi and family history. Few studies are based on histologically confirmed melanoma with subsequent risk of misclassification and ascertainment bias. Three mortality studies, with analyses based on national registers, found a rise in male pilots, (3)(7)(14), but this was not correlated with any assessment of cosmic radiation dose (15). By contrast no such rise in mortality from CMM was found in cabin crew (3) and as before there was no link to cosmic radiation dose (16). No study took account of recreational UVR exposure, the changing societal habits of sun exposure with inexpensive available recreational flying, use of sun beds, holidays in the sun etc., over the last fifty years; i.e. when the incidence of documented melanoma in the general community rose rapidly. Most studies finding raised incidence of melanoma are from the northern hemisphere, often Scandinavia or US.

7. A contemporary 2019 Australian cohort study of commercial pilots followed up histologically confirmed malignant melanoma from 2001-2016 (17). Observed for 91370 person-years (PYs), 114 tumours were detected, 51 invasive and 63 in situ. When age specific incidence rates (SIR) were compared with corresponding general population rates, SIR was 1.20 (0.9-1.78) for invasive melanoma and 1.39 (1.08-1.78) for melanoma in situ; i.e. there is slightly raised risk of melanoma in situ, but no elevation of invasive melanoma compared with the general population. The highest proportion of cases came from Queensland, which also has the highest average UVR exposure of all Australian states and territories. As in the rest of Australia and in many of the studies considered in this short paper, the body site distribution of melanoma showed no excess in head and neck or upper limb, as might be expected if UVR exposure was causal. A factor may be the strong public health messages that Australia has run about prevention of sun exposure for now almost 50 years.

8. Studies of military aircrew are limited. A 2017 study of malignant melanoma rates in different US occupational military groups over 2001-2015 found 2333 incident diagnoses of malignant melanoma (18). Rates were highest in fixed wing pilot aircrew, lowest in the infantry, special operations and combat engineers and intermediate in health care providers. Overall rates increased exponentially over the time period. Rates tended to be low during the first years of service and then increased rapidly. At least some of these findings are likely to reflect different ages in the groups (e.g. health care workers tend to be on average older than infantry soldiers), and ascertainment bias may be an issue, especially with healthcare staffs. There are some obvious limitations. Diagnoses were clinical not histological and may have included "suspected" or "rule out" diagnoses. Principal service occupations were assessed at a single point in time. Exposure to UVR and other potential risk factors are likely to have varied over time with perhaps change in role /speciality and reflecting the very different shape and variety of tasks of military employment compared with most civilian employment, e.g. outdoor activities such as training, field operations, deployments interspersed with spells of indoor work, classroom-based training etc. No account was taken in the study of off-duty exposures. In military studies the long latent period for clinical presentation of many disorders compared with the relatively short average service duration means that for completeness there should be ongoing post-service follow-up. We are unaware of any such published study in the international literature.

Conclusion:

i. Strength of association: Those exposed to the relevant agent as compared to those not exposed (risk ratio); e.g. lung cancer in asbestos workers (20).

ii. Consistency: The finding has been repeatedly observed by different researchers at different times in different populations.

iii. Specificity: The association is limited to specific people and types and sites of disease.

iv. Temporality: The cause should always come before the effect.

v. Biological gradient: There is an exposure response; i.e. the greater the level of exposure the greater the risk of the disease.

vi. Plausibility: The finding accords with the current understanding of pathophysiology.

vii. Coherence: The finding is coherent with contemporary understanding of the natural history and biology of the disease.

viii. Experiment: There is a reduction in the incidence of the disorder when the factor is reduced or limited; e.g. by reduction or elimination of the exposure.

10. From his initial lecture at the Royal Society of Medicine, Bradford Hill made it clear that the listed factors were not rigid or a checklist but were guidelines to inform epidemiological investigation. Of the nine viewpoints, temporality is the only one which is inarguable. Bradford Hill also reminded us of the play of chance and the utility of a test of statistical significance to prevent hasty conclusions on the generalisability of a finding in a single study. Over fifty years on, the Bradford Hill viewpoints remain the foundation of causal inference in medicine and are relevant to this paper (21).

11. Overall the evidence, with some heterogeneity, suggests a raised risk (in some studies doubling) of CMM in pilots and aircrew, but does not identify mechanism or causal factors. We have discussed some study limitations and now consider the evidence against the Bradford Hill viewpoints. Some of the viewpoints are met; e.g. temporality, strength of association, dose response, but others not so e.g. specificity, and raised incidence are also seen in the general population. This means in the occupational personal injury context that exposure to the causal exposure may be non-occupational and pre-date employment. Most importantly the underlying casual connection and its basis remain elusive.

12. Present evidence does not allow recognition of a general presumed occupational causal connection between military aircrew duties and raised risk of CMM. In the AFCS context almost all the evidence reflects circumstances long pre-dating 2005 and the introduction of the AFCS, and relates to commercial flying, which is very different in terms of aircraft types, height, speed and duration of flights, terms and conditions of flight crew service and working patterns**.**

Recommendation:

13. We will continue to monitor the literature and recommend that claim determinations for CMM from pilots and flight crew should routinely have medical input and be based on individual case facts

References:

1. Nicholas, J. S.et al. Mortality among US commercial pilots and navigators. J. Occup. Env. Med.1998; 40:980-5.

2. Miura, K. et al. Do airline pilots and cabin crew have raised risk of melanoma and other skin cancers? Systematic review and meta -analysis. Brit. J. Derm. 2019; 181 :55-64.

3. Hammer, G.P. et al. Mortality from cancer and other causes in commercial airline crews: a joint analysis of cohorts from 10 countries. Occ. Environ. Med. 2014; 71:313-322.

4. World Health Organisation (WHO). International Agency for Research on Cancer. (IARC). IARC monographs on the evaluation of carcinogenic risk to humans. vol 100D Radiation. Lyon France IARC 2012.

5. dos Santos, I et al. Cancer incidence in professional flight crew and air traffic control officers: disentangling the effect of occupational versus lifestyle exposures. Int. J. Cancer.2013; 132(2):374-384.

6. Reynolds, P. et al. Cancer incidence in California flight attendants (United States). Cancer Causes Control. 2002; 13:317-324.

7. Band, P.R. et al. Cohort study of Air Canada pilots: mortality, cancer incidence and leukaemia risk. Am. J. Epidemiol.1996; 143:137-43.

8. Gundestrop M. et al. Radiation induced acute myeloid leukaemia and other cancers in commercial jet cockpit crew: a population-based cohort study. Lancet.1999;354:2029-2031.

9. Zeeb, H. et al. Mortality from cancer and other causes among airline cabin attendants in Europe; a collaborative cohort study in eight countries. Am. J. Epidemiol.2003; 158:35-46.

10. Bartlett, D.T. et al. Radiation protection aspects of the cosmic radiation exposure to aircraft crew. Health Phys. 2004; 109:349-55.

11. Parkin, D.P. et al. Cancers in 2010 attributable to ionising radiation exposure in the UK. Br. J. Cancer. 2011; 105(Suppl. 2): S57-65.

12. Haldorsen, T. et al. Cancer incidence among Norwegian airline pilots. Scan. J. of Work, Environment and Health. 2000; 26(2):106-111.

13. Pukkala, E.et al. Cancer incidence among Nordic airline cabin crew. Int. J. Cancer. 2012; 131:2886-97.

14. Irvine, D. et al. British Airways flight deck mortality study 1950-92. Aviat. Space Environ. Med. 1999; 70:548-555.

15. Yong, L.C. et al. Mortality among a cohort of commercial airline cockpit crew. Am. J. Ind. Med.2014; 57:906-14.

16. Pinkerton, L. E. et al. Cause specific mortality among a cohort of US flight attendants. Am. J. Ind. Med. 2012; 20,55:25-36.

17. Olsen, C.M. et al. Melanoma incidence in Australian commercial pilots, 2011-2016. Occup. Environ. Med. 2019;76: 462-466.

18. Brundage, J.F. et al. Incidence rates of malignant melanoma in relation to years of military service, overall and in selected military occupational groups, active component, USAF 2001-2015. MSMR 2017; v2 no2.

19. Bradford Hill, A. The environment and disease: association or causation? J.R.Soc.Med.1965; 108(1):32-37.

20. Doll, R. et al. Asbestos: effects on health of exposure to asbestos. HSE Books. London 1985.

21. Fedak, K. et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg. Themes Epidemiol. 2015; 12,14. doi:10.1186/s12982-015-0037-4.