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# Occupational cosmic radiation exposure and cancer in airline cabin crew

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Säteilyturvakeskus
Strålsäkerhetscentralen
Radiation and Nuclear Safety Authority

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**STRÅLSÄKERHETSCENTRALEN**
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# Academic dissertation

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## Occupational cosmic radiation exposure and cancer in airline cabin crew

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**Keywords:** Cabin crew, epidemiology, cosmic radiation, exposure assessment, occupational exposure, neoplasms

# Abstract

Cosmic radiation dose rates are considerably higher at cruising altitudes of airplanes than at ground level. Previous studies have found increased risk of certain cancers among aircraft cabin crew, but the results are not consistent across different studies. Despite individual cosmic radiation exposure assessment is important for evaluating the relation between cosmic radiation exposure and cancer risk, only few previous studies have tried to develop an exposure assessment method. The evidence for adverse health effects in aircrews due to ionizing radiation is inconclusive because quantitative dose estimates have not been used. No information on possible confounders has been collected. For an occupational group with an increased risk of certain cancers it is very important to assess if the risk is related to occupational exposure.

The goal of this thesis was to develop two separate retrospective exposure assessment methods for occupational exposure to cosmic radiation. The methods included the assessment based on survey on flight histories and based on company flight timetables. Another goal was to describe the cancer incidence among aircraft cabin crew with a large cohort in four Nordic countries, i.e., Finland, Iceland, Norway, and Sweden. Also the contribution of occupational as well as non-occupational factors to breast and skin cancer risk among the cabin crew was studied with case-control studies.

Using the survey method of cosmic radiation exposure assessment, the median annual radiation dose of Finnish airline cabin crew was 0.6 milliSievert (mSv) in the 1960s, 3.3 mSv in the 1970s, and 3.6 mSv in the 1980s. With the flight timetable method, the annual radiation dose increased with time being 0.7 mSv in the 1960 and 2.1 mSv in the 1995. With the survey method, the median career dose was 27.9 mSv and with the timetable method 20.8 mSv. These methods provide improved means for individual cosmic radiation exposure assessment compared to studies where cruder indicators, such as number of work years for occupational exposure, were used. When selecting the approach for further studies, the feasibility issues of the study affect the decision, i.e.,

can the flight history data of the cabin crew be collected by a survey or are the historical flight timetables available from the flight company.

In the follow-up of more than 10,000 Nordic cabin crew members, the standardized incidence ratio (SIR) of all cancers was 1.16 (95% confidence interval (CI): 1.06–1.25) for women and 1.39 (95% CI: 1.17–1.62) for men. These results confirm the evidence for an elevated overall cancer risk among cabin crew compared to the general population. Of specific cancer types, the significant risks were observed for breast cancer, cutaneous malignant melanoma, non-melanoma skin cancer, leukaemia, Kaposi sarcoma, laryngeal and pharyngeal cancer.

This thesis cannot not provide an explanation for the elevated breast or skin cancer risk among aircraft cabin crew. Breast cancer is previously known to be strongly related to reproductive and hormonal factors – including endogenous hormone levels and exogenous hormone use. Thus, these factors may present the plausible explanation for the increased risk of breast cancer also among cabin crew. Exposure to ultraviolet radiation (UVR) is the most likely explanation for the increased risk of skin cancers, but there was no evidence on cabin crew excess exposure to UVR compared to general population in this work.

Finding a cause for the increased incidence of cancer among cabin crew warrants further studies. This work found no relation between estimated occupational cosmic radiation exposure and cancer risk. The current exposure limitations of radiation to cabin crew need not be altered.

*KOJO Katja. Työperäinen kosminen säteilyaltistus ja syöpä lentokoneen matkustamohenkilöstöllä. STUK-A257. Helsinki 2013, 83 s. + liitteet 42 s.*

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# Tiivistelmä

Lentokoneessa työskentelevät altistuvat kosmiselle säteilylle, jonka annosnopeus on lentokorkeuksissa huomattavasti korkeampi kuin maan pinnalla. Aikaisemmissa epidemiologisissa tutkimuksissa on havaittu viitteitä lentokoneessa työskentelevän matkustamohenkilöstön lisääntyneestä syöpäriskistä, mutta tulokset eivät ole olleet aivan johdonmukaisia. Kosmisen säteilyn ja syöpäriskin välisen yhteyden selvittämiseksi kosmisen säteilyn yksilöllisen annosarviointimenetelmän kehittäminen olisi tärkeää, mutta aikaisemmissa tutkimuksissa yritystä tähän ei juuri ole ollut. Puuttuvan annosarvioinnin vuoksi, kosmisen säteilyn haitallisesta vaikutuksesta lentohenkilöstön terveyteen ei ole näyttöä. Lisäksi tietoa muista mahdollisista riskitekijöistä ei ole kerätty. Ammattiryhmällä, jolla on havaittu suurentunut syöpävaaraa, on tärkeä selvittää johtuuko riski työperäisestä altistumisesta.

Tämän väitöskirjatyön tavoitteena oli kehittää kaksi kosmisen säteilyn historiallista annosarviointimenetelmää. Toisessa menetelmässä annosarvio tehtiin kyselytietojen perusteella ja toisessa käytettiin tietoja lentoaikatauluista. Lisäksi tavoitteena oli kuvata syöpäilmaantuvuutta lentokoneessa työskentelevällä matkustamohenkilöstöllä hyödyntäen neljän pohjoismaan (Suomi, Islanti, Norja ja Ruotsi) ilmaantuvuustietoja. Lisäksi selvitettiin syytekijöitä matkustamohenkilöstön suurentuneeseen rinta- ja ihosyöpäriskiin.

Kyselytietoihin perustuvalla kosmisen säteilyn annosarviointimenetelmällä suomalaisen matkustamohenkilöstön vuosiannoksen mediaaniksi saatiin 0,6 millisieverttiä (mSv) 1960-luvulla, 3,3 mSv 1970-luvulla ja 3,6 mSv 1980-luvulla. Lentoaikataulumenetelmällä vuosittainen annos kasvoi ajan myötä ollen 0,7 mSv vuonna 1960 ja 2,1 mSv vuonna 1995. Kyselytietoihin perustuvalla menetelmällä koko uran annokseksi laskettiin 27,9 mSv (mediaani) ja aikataulumenetelmällä 20,8 mSv. Aikaisemmissa tutkimuksissa kosmisen säteilyn annosarviointiin on käytetty karkeampia indikaattoreita kuten työvuosien määrää. Tässä tutkimuksessa kehitetyt menetelmät tarjoavat tarkemman keinon yksilökohtaiseen annosarviointiin. Käytettävät toteuttamismahdollisuudet tulevissa tutkimuksissa määräävät, kumpaa kehitettyä menetelmää

voidaan soveltaa; voiko kyselytietoja kerätä ja onko historiallisia lentoaikatauluja saatavilla.

Yli 10 000 pohjoismaisen (Suomi, Islanti, Norja ja Ruotsi) matkustamossa työskentelevän henkilön seurantatutkimuksessa vakioitu ilmaantuvuussuhde kaikille syöville oli 1,16 (95% luottamusväli (confidence interval (CI): 1,06–1,25) naisilla ja 1,39 (95% CI: 1,17–1,62) miehillä. Nämä tulokset vahvistavat lisääntyneen syöpäriskin matkustamohenkilöstöllä verrattuna muuhun väestöön. Yksittäisistä syöpätyypeistä merkittävimmät riskit havaittiin rintasyövän, ihomelanooman, muiden ihosyöpien, leukemian, Kaposin sarkooman, kurkunpään ja nielun syöpien kohdalla.

Tässä väitöskirjatyössä etsittiin syytekijöitä kohonneeseen rinta- ja ihosyöpäriskiin tapaus-verrokkitutkimuksilla mutta tuloksissa ei ilmennyt selkeää syytä näihin riskeihin. Aikaisemmat tutkimukset ovat osoittaneet rintasyövän olevan vahvasti yhteydessä reproduktiotekijöihin sekä hormoneihin – sekä sisäsyntyisiin että hormonivalmisteiden käyttöön – ja täten nämä seikat ovat mahdollisesti syytekijöinä myös matkustamohenkilöstön lisääntyneeseen riskiin. Altistuminen ultraviolettisäteilylle (ultraviolet radiation, UVR) taas on todennäköisin selitys kohonneeseen ihosyöpäriskiin. Tässä väitöskirjatyössä ei kuitenkaan havaittu näyttöä siitä, että matkustamohenkilöstö altistuisi muuta väestöä enemmän UVR:lle.

Matkustamohenkilöstön syöpävaaran selvittämiseksi lisätutkimukset ovat tarpeen. Tämä tutkimus ei osoittanut yhteyttä kosmisen säteilyaltistumisen ja syöpävaaran välillä. Jo voimassa olevia matkustamohenkilöstön säteilyannosrajoituksia ei ole tarpeen muuttaa.

# Contents

# List of original communications

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals, I–V.

I Kojo K, Aspholm R, Auvinen A (2004): Occupational radiation dose estimation for Finnish aircraft cabin attendants. Scandinavian Journal of Work, Environment & Health 30: 157–163.

II Kojo K, Pukkala E, Auvinen A (2005): Breast cancer risk among Finnish cabin attendants: a nested case-control study. Occupational and Environmental Medicine 62: 488–493.

III Kojo K, Helminen M, Leuthold G, Aspholm R, Auvinen A (2007): Estimating the cosmic radiation dose for a cabin crew with flight timetables. Journal of Occupational and Environmental Medicine 49: 540–545.

IV Kojo K, Helminen M, Pukkala E, Auvinen A (2013): Risk factors for skin cancer among Finnish airline cabin crew. Annals of Occupational Hygiene, doi: 10.1093/annhyg/mes106. [Epub ahead of print, electronic publication available only on the publisher's website: *http://annhyg.oxfordjournals.org/content/early/2013/01/11/annhyg.mes106*]

V Pukkala E, Helminen M, Haldorsen T, Hammar N, Kojo K, Linnersjö A, Rafnsson V, Tulinius H, Tveten U, Auvinen A (2012): Cancer incidence among Nordic airline cabin crew. International Journal of Cancer 131: 288–296.

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# Abbreviations

| | |
|---|---|
| BCC | Basal cell carcinoma |
| CI | Confidence interval |
| CMM | Cutaneous malignant melanoma |
| D | Absorbed dose |
| DDT | Dichloro-biphenyl-trichloroethane |
| eV | Electron volt |
| E | Effective dose |
| EAR | Excess absolute risk |
| ERR | Excess relative risk |
| Ft | Feet, 1 foot = 0.305 m |
| Gy | Gray, the unit of absorbed radiation dose |
| H*(10) | Equivalent dose |
| HR | Hazard ratio |
| IARC | International Agency for Research on Cancer |
| ICRP | International Commission for Radiological Protection |
| LET | Linear-energy-transfer |
| LSS | The Life Span Study cohort of Japanese atomic bomb survivors |
| NMSC | Non-melanoma skin cancers, most common are SCC and BCC |
| OR | Odds ratio |
| p | Statistical significance |
| Pan Am | Pan American World Airways |
| PCB | Polychlorinated biphenyl |
| PI | Posterior interval |
| PIC | Personal identification number |
| RR | Relative risk |
| $R^2$ | Coefficient of determination |
| SAS | Scandinavian Airlines |
| SCC | Squamous cell carcinoma |
| s.e. | Standard error |
| SES | Socioeconomical status |
| SHS | Second hand smoking |
| SIR | Standardized incidence ratio |
| SLSY | Finnish Cabin Crew Union |
| SMR | Standardized mortality ratio |
| Sv | Sievert |
| TEPC | Tissue equivalent proportional counter |
| UNSCEAR | United Nations Scientific Committee on the Effects of Atomic Radiation |

| | |
|---|---|
| UVR | Ultraviolet radiation |
| WHO | World Health Organization |
| µT | microTesla |


Figure: *http://gallery.finnair.com*

# 1 Introduction

Aircraft cabin personnel have unique working conditions. Their work is often shift work with a possibility of flights over different time zones which can cause circadian disruption. Aircraft cabin is pressurized when flying at cruising heights with a probability to hypoxia. In addition, the cabin has a very low relative humidity. Cosmic radiation dose rates are considerably higher at cruising altitudes than at ground level. Therefore, The International Commission on Radiation Protection (ICRP) has recommended that aircrew should be classified as radiation workers (International Commission on Radiological Protection. 1991). Despite the importance of individual cosmic radiation exposure assessment in epidemiological studies, few previous studies have tried to develop an exposure assessment method.

A number of previous studies have evaluated the relation between cancer and occupational exposure to prolonged low-doses of ionizing radiation. Necessary evidence is available for evaluating the risks and for setting occupational radiation protection standards. However, the dose-response pattern of low dose ionizing radiation and cancer is not yet fully understood (Gilbert 2009). The Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation has summarized that, at present, the evidence for adverse health effects for aircrews due to ionizing radiation is inconclusive because dose estimates have not been used (National Research Council . Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation 2006). Considering an occupational group with increased risk of certain cancers, it is very important to assess whether the increased risk is related to occupational exposure. If this is the case, guidance and work protection standards are important intervention strategies.

Worldwide, airline cabin crew profession provides employment for hundreds of thousands of persons. Alone in Finland, Iceland, Norway and Sweden there has been approximately 10 200 cabin crew personnel members from the 1940s onwards. Finnair is a Finnish airline company established in 1923. It is one of the oldest still operating airline companies in the world. Finnair and its subsidiaries have approximately 1 800 cabin crew members (*www.finnairgroup.com*).

# 2 Review of the literature

## 2.1 Occupational exposures of the airline cabin crew

### 2.1.1 Cosmic radiation

#### 2.1.1.1 Ionizing radiation

Radiation is energy that moves through the space in a high speed. When passing through a solid material, radiation releases energy to it. If the energy is high enough, ionization occurs. This means that ions are produced, i.e., electrons are released from atoms. Energy of the radiation is expressed as electron volts (eV). The higher the frequency of the radiation wave is, the greater the energy.

The density of ionizations along the path the radiation is travelling through matter is described with Linear Energy Transfer (LET). Radiation types that cause dense ionization along their track (such as neutrons and alpha particles) are high-LET radiation. Low-LET radiation types (such as gamma radiation and x-rays) release their energy only sparsely along their way (Figure 1). Thus, high-LET radiation is more destructive to biological material than low-LET radiation because at the same dose the low-LET radiation induces the same number of ionization more sparsely in a material, whereas the high-LET radiation releases most of its energy to a small region of the cell. The localized DNA damage is more complex to repair than the disperse DNA damage (National Research Council . Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation 2006).

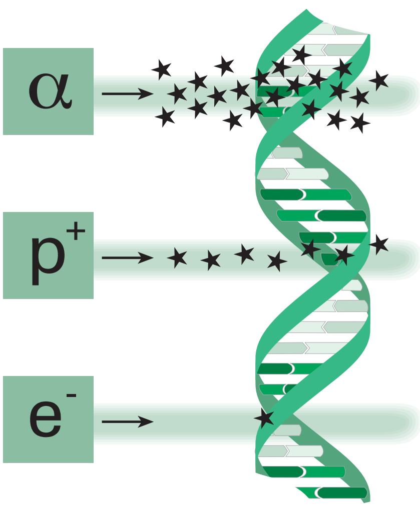


**Figure 1.** $\alpha$ indicates the route of an alpha particle, $p^+$ the route of a proton, $e^-$ the route of an electron, and a star an ionization (Source: Finnish Radiation and Nuclear Safety Authority).

Human exposure to ionizing radiation can originate from natural (e.g. radon) or man-made source (e.g. medical exposures) and it can be external (i.e. radiation from outside the body) or internal (i.e. radioactive material is inside the body). The stochastic harmful health effects of radiation might depend also on the exposure dose rate, i.e., whether the exposure is brief (atomic bombs) or protracted (occupational) despite of the total dose. The relative biological effectiveness describes the ability of radiation to induce biological outcomes such as chromosomal damage or cancer.

The absorbed dose (D) describes the energy deposition in the target material. The unit of the absorbed dose is Gray (Gy) expressed as J/kg. Dose rate means the dose per time unit. Health effects of ionizing radiation depend not only on the magnitude of the absorbed dose but also on the type and energy of the radiation. Thus the concept of equivalent dose (H*(10)) has been developed (ICRP publication 103 2007). To calculate the equivalent dose, the absorbed dose is multiplied with an agreed weighting factor specific for each radiation type. The weighting factor, for example, for gamma radiation and x-ray is 1, for alpha radiation 20 and for neutrons 5 to 20, depending on the energy level. The unit of the equivalent dose is Sievert (Sv).

Tissues in a human body differ by their response to the radiation. Thus the International Commission for Radiological Protection (ICRP) has developed effective dose (E) which describes the health effects of radiation. The effective dose is calculated by multiplying the equivalent dose with tissue-specific weighting factor. The weighting factor, for instance, 0.05 for liver and 0.12 for lungs, represents the probability of harmful stochastic events, e.g., cancer risk, in the organ. The unit of the effective dose is also Sievert.

The vast number of epidemiological studies have shown that most solid cancers are associated with radiation exposure but the evidence is strongest for leukaemia, all solid cancers combined, breast, and thyroid cancer (Gilbert 2009). An IARC working group has concluded that x-rays, gamma and neutron radiation are carcinogenic to humans (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012b). In general, a linear dose-response function describes sufficiently the data on most solid cancers. However, there are uncertainties of the shape of the dose-response curve at low doses of radiation, that is, exposures below 100 mGy, and at low dose rates. Most data support the linear, non-threshold model but the possibility for other dose response functions cannot be ruled out. Epidemiological studies alone are not likely to detect estimates that are more precise than currently known estimates are for risk at exposure at low doses (United Nations. Scientific Committee on the Effects of Atomic Radiation., United Nations. General Assembly. 2010).

#### 2.1.1.2 Exposure to cosmic radiation

Most of the exposure to ionizing radiation to the population worldwide comes from natural sources; the annual dose per person is on average 2.4 mSv (milliSievert) (United Nations. Scientific Committee on the Effects of Atomic Radiation 2000). One of the contributors to natural ionizing radiation exposure is cosmic radiation, on average 0.32 mSv per a year at sea level. Galactic cosmic rays originate from space and on the top of the atmosphere consist of 1) a nucleonic component including protons (88%), alpha particles (11%), and heavy nuclei (1%), and 2) electrons. When the cosmic rays reach the upper layers of the atmosphere, secondary particles such as protons, neutrons and pions, are generated. These secondary nucleons generate tertiary nucleons, which results into a nucleonic cascade and to the dominating component of neutrons at cruising altitudes. Earth geomagnetic shielding reduces the intensity of the cosmic radiation to the atmosphere allowing only highly energetic particles to penetrate at lower geomagnetic latitudes. This results in dose rates being highest near the geomagnetic poles and lowest at the equator. At passenger aircraft cruising altitudes, neutrons contribute 40–80% of the total equivalent dose rate, depending on the altitude, latitude and time in the solar cycle. (United Nations. Scientific Committee on the Effects of Atomic Radiation 2010)

One determinant of cosmic radiation is the sun. The effect of the 11-year cycle in solar activity (heliocentric potential) generates a cycle in cosmic radiation intensity (United Nations. Scientific Committee on the Effects of Atomic Radiation 2000). A high heliocentric potential results in lower levels of cosmic radiation and vice versa. Another determinant of cosmic radiation is solar flares, i.e., charged particles erupting from the sun. Solar flares occur very infrequently so their contribution to the cumulative dose is minimal. However, at the time of a strong flare, the radiation levels are increased by a factor up to one hundred.

#### 2.1.1.3 Exposure of the airline cabin crew to cosmic radiation

##### *2.1.1.3.1 Current guidelines for exposure to cosmic radiation*

Aircraft personnel are exposed to cosmic radiation at much higher rates than at ground level. The dose equivalent rate received by the cabin crew mainly depends on the altitude. The dose rate is approximately 0.03 µSv per hour at sea level and the dose doubles with every 1 500 m increase in altitude. In addition to the altitude, the total dose received on a flight depends on the geomagnetic latitude, flight duration, and the year.

In 1991 the International Commission on Radiation Protection (ICRP) recommended that aircrew should be classified as radiation workers (International Commission on Radiological Protection. 1991). General guidelines for dose limits for occupational exposure have been established by the ICRP. Occupational exposure of non-pregnant worker should never exceed an effective dose (E) of 20 mSv per year averaged over consecutive five years or a dose of 50 mSv per any single year. The council of the European Union sets standards of radiation protection of the workers and the general public, and the standards have to be implemented by all European airlines (*http://europa.eu/legislation_summaries/employment_and_social_policy/health_hygiene_safety_at_work/c11142_en.htm*). According to the standards, the exposure has to be assessed for aircrew potentially exposed to more than 1 mSv annually. In Finland, the national radiation law (Radiation Act 45 §) regulates that airline companies have to monitor the cosmic radiation exposure of personnel. The cosmic radiation effective dose shall not exceed 6 mSv in one year. The purpose of this dose restriction is to ensure that the principle of optimization realizes. (*http://www.stuk.fi/julkaisut_maaraykset/viranomaisohjeet/en_GB/stohjeet/*).

#### *2.1.1.3.2 Dose estimation of cosmic radiation*

In contrast to other persons occupationally exposed to radiation, such as nuclear plant workers, individual dosimetry in an aircraft is not feasible. This is because, for example, cosmic radiation consists of several radiation particles and most detectors detect only certain components of the total radiation. Thus, a specific detector would have to be used for every component. Several detectors have been used for on-board aircraft measurements. Detectors are either active (e.g. tissue equivalent proportional counters, TEPC) or passive dosimeters (e.g. bubble detectors). Passive dosimeters are usually smaller and thus easier to use but less sensitive (Aw 2003). Studies on cosmic radiation doses for aircrew measured with detectors report usually equivalent doses H*(10) which might complicate the comparison to the effective dose limits provided for radiation protection purposes.

As personal dose monitoring is not feasible for the aircrew for a certain period of time, the dose calculation algorithm models are used instead. With such models, the cosmic radiation doses in the atmosphere are estimated as a function of time utilizing detailed information on the spectrum of cosmic radiation measured in the atmosphere (Vartiainen 2003). Several softwares are available for cosmic radiation effective dose calculation for single flights between any two geographic locations, for example CARI, EPCARD, FREE, and SIEVERT. Between the programs, there are differences up to 30% between the results for effective doses. This is mainly explained by different assumptions on the galactic proton distribution and different proton weighting factor (Lindborg et al. 2004). As an example, EPCARD gives an effective dose of 45.2 µSv and

CARI-6 37.6 µSv for a nine-hour-flight from Helsinki to New York with DC-10 in February 1980.

#### *2.1.1.3.3 Retrospective exposure assessment of cosmic radiation*

Very few retrospective individual cosmic radiation exposure studies for aircraft cabin crew are available. This is mainly due to the fact that airline companies have not usually recorded the flights of cabin crew. On the other hand, for pilots, recording of some detail usually exists in flight companies. At Finnair, work history for cabin crew is recorded from the year 1991 onwards. For Finnair pilots, information on every flight since 1971 is available in a computerized database. For pilots, a detailed flight logbook is essential for the sustenance of seniority lists and pilots' certificate. Further, pilots usually have a licence to fly only one aircraft type at a time. Cabin crew are not restricted to one aircraft type or one route and thus, their route distribution can vary substantially in the short term. As an exception, one airline, Pan American World Airways (Pan Am), has detailed recorded work histories also for cabin crew (Grajewski et al. 2002). Table 1 summarizes the cosmic radiation effective doses for cabin crew estimated in different studies with various methods.

**Table 1.** Estimated cosmic radiation effective doses (E) for airline cabin crew.

| Reference | Airline company | Method | No. of cabin crew | Annual dose (mSv*) |
|---|---|---|---|---|
| Wilson et al. 1994 | Australian | a) On board measurements<br>b) Flight records | N.A.** | Average 1 – 1.8 (domestic crew)<br>≤ 3.8 (international crew) |
| Bagshaw et al. 1996 | British Airways | London – Tokyo route<br>+ detectors | N.A.** | ≤ 6 |
| Bottollier-Depois et al. 2000 | Several | TEPC + assessment of E for 700 flight hours | N.A.** | 2 – 5 |
| Grajewski et al. 2002 | 3 companies in the U.S. | Flight records + CARI | 44 | Average 1.5 – 1.7 |
| Van Dijk 2003 | 3 companies in the Netherlands | Flight plans + CARI | 11 000 | Average 1.6 |
| Morkunas et al. 2003 | Lithuanian Airlines | On board measurements and calculations with CARI-6 | N.A.** | ~ 1 |

* milliSievert
** Not available
TEPC Tissue equivalent proportional counter
CARI and CARI-6
A computer program for calculating the effective dose of galactic cosmic radiation received by an individual on a single flight

The lack of detailed recorded work history hinders occupational exposure estimation and therefore other methods have to be used. Various crude indicators of exposure for cosmic radiation have been employed in several cancer incidence and mortality studies, for example, the total duration of employment as a member of cabin crew, the time since recruitment, or the cumulative flight hours (Pukkala, Auvinen & Wahlberg 1995, Haldorsen, Reitan & Tveten 2001, Rafnsson et al. 2001, Ballard et al. 2002, Linnersjo et al. 2003, Reynolds et al. 2002).

### 2.1.2 Exposure to ultraviolet radiation

Ultraviolet radiation is not directly an occupational exposure for cabin crew but it is discussed here because among aircrew the exposure to ultraviolet radiation might be related to work via work flights to sunny destinations.

#### 2.1.2.1 Definition of ultraviolet radiation

Ultraviolet radiation (UVR) forms a part of the electromagnetic radiation spectrum. UVR comprises approximately 5% of total solar radiation energy. UVR is non-ionizing, i.e., it is not able to remove electrons from atoms but it can damage the cellular DNA and thus has a potential in increasing the risk of cancer. (*http://www.who.int/uv/publications/solaradgbd/en/index.html*)

UVR is divided into three bands of wavelengths: UVC (100−280 nm), UVB (280−315 nm), and UVA (315−400) according to their effects. UVC is absorbed by the atmospheric ozone and does not penetrate to the earth's surface. Thus, it has no relevance to human health. The UVR component from the midday sun comprises about 95% UVA and 5% UVB. The IARC working group has concluded that UVR is carcinogenic to humans. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012b)

Radiation from the sun is the main source of UVR to the human population. Other sources include solarium, medical phototherapy, industrial sources, and indoor lighting (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization & International Agency for Research on Cancer 1992b).

#### 2.1.2.2 Exposure of the airline cabin crew to ultraviolet radiation

Several studies have found an increased risk of cutaneous malignant melanoma (CMM) (Pukkala, Auvinen & Wahlberg 1995, Haldorsen, Reitan & Tveten 2001, Rafnsson et al. 2001, Linnersjo et al. 2003, Reynolds et al. 2002) and squamous cell carcinoma (SCC) (Haldorsen, Reitan & Tveten 2001, Rafnsson et al. 2001, Linnersjo et al. 2003) among airline cabin crew. UVR is a central risk factor for all skin cancers (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012b) and thus the increased incidence of skin cancers among cabin crew raises the question of possible excess exposure to UVR among this occupational group. However, cabin crew are not exposed to solar UVR in the aircraft cabin (Diffey, Roscoe 1990).

Only one previous study has estimated aircraft cabin crew's exposure to UVR (Rafnsson et al. 2003a). In that study no substantial differences were found between cabin crew and general population exposure to UVR. In general, retrospective estimation of UVR exposure is very difficult. Ambient UVR can be measured with dosimeters very accurately but it is not possible retrospectively. Further, the amount of UVR absorbed by the skin is much more difficult to determinequantify. There is a great deal of error inherent in the UVR exposure assessment concerning individual level epidemiological studies. Retrospective self-reporting of UVR exposure is prone to recall bias (e.g. (Rosso et al. 2002, Cockburn, Hamilton & Mack 2001, Weinstock 1992)) but despite attempts to develop a measurement method for retrospective UVR exposure assessment, it seems so far to be the only feasible method in epidemiological studies for assessing past exposure (Kojo et al. 2008, Gniadecka, Jemec 1998, Sandby-Moller et al. 2004).

### 2.1.3 Other occupational exposures and potential risk factors

#### 2.1.3.1 Rapid time zone changes

##### *2.1.3.1.1 Jet lag*

Circadian rhythm disruption due to rapid time zone changes is a common problem among airline cabin crew. Circadian disruption causes jet lag which refers to short-term symptoms after a rapid time-zone transition. Jet lag symptoms are caused by discrepancy of the personal endogenous circadian oscillator, i.e., the body clock, relative to the environmental light-dark cycle. The body adjusts slowly to the new time zone causing a difference between the biological and the environmental time (Waterhouse et al. 2005, Harma et al. 1994). Daytime symptoms include, for example, fatigue, a reduction of concentration and motivation, confusion, various aches, and increased irritability (Waterhouse et al. 2005, Winget et al. 1984). Other symptoms include disturbances in sleep and in hormonal rhythms, e.g., menstrual cycle. Generally, the symptoms are the stronger the more time-zones are crossed. In addition, travelling to the east is associated with more severe symptoms than travelling to the west (Zisapel 2001, Waterhouse, Reilly & Atkinson 1997, Suvanto et al. 1993, Preston et al. 1973).

Suvanto and co-workers studied the effects of rapid 10-hour time zone change on the circadian rhythms of 40 female cabin crew members. They concluded that the duration of de- and resynchronization of circadian rhythms measured by oral temperature, alertness, and visual search, takes on average more than nine days after flights over 10 time zones. (Suvanto et al. 1993)

Another Finnish study evaluated the effects of 10-hour time zone change on the circadian rhythms with the measurements of salivary melatonin and cortisol. Their results supported the hypothesis on the difference in the adaptation rate following westward and eastward transmeridian flights; the resynchronization rate after westward flights was faster. (Harma et al. 1994)

#### *2.1.3.1.2 Hormonal disturbances*

Environmental change, e.g., travelling, can alter the menstrual cycle. If the alteration occurs in the preovulatory phase of the cycle, the ovulation is either inhibited or delayed and the menstruation is postponed. There is no effect due to environmental change if it occurs in the postovulatory phase. Some studies have suggested that female cabin crew suffer from various types of disturbances of menstrual cycle. Haugli and co-workers studied the health problems among the Norwegian Scandinavian Airlines (SAS) cabin crew and found that more than 30% of the crew reported experiencing sometimes or often dysmenorrhoea, i.e., painful periods (Haugli, Skogstad & Hellesoy 1994). More than 20% indicated irregular menstrual cycle. The differences between the short-haul and the long-haul personnel were not statistically significant. The prevalence of these menstrual problems in general Norwegian female population is not known. However, the authors state that cabin crews do not seem to have more menstrual problems than other Norwegian shift workers. Iglesias and co-workers studied menstrual disorders among the Mexicana Airline cabin crew (Iglesias, Terres & Chavarria 1980). After recruitment, 20% of the women reported hyper-polymenorrhoea, 17% dysmenorrhoea, 16% complete irregularity in menstrual cycle and 9% of hypo-olygomenorrhoea. Of these women, 24% reported that they had no previous the menstrual disorders prior to starting the work as a member of the cabin crew. In a study by Lauria and co-workers, it was noted that menstrual abnormalities of cabin crew members less than 40 years of age were more common among current than former cabin crew members (20.6% vs. 10.4%) (Lauria et al. 2006).

#### *2.1.3.1.3 Sleep disturbances*

Disruption of circadian rhythm may result in sleep problems. In general, sleep disorders are divided to chronic, periodic, and temporary insomnias. Sleep disorders due to jet lag and shift-work fall into the last category. Melatonin secreted from the pineal gland is an important sleep-wake rhythm regulator. Light and melatonin are in an inverse relation to each other; bright light inhibits the secretion of melatonin, whereas the secretion peak happens at night. In the absence of a normal 24-hour light-dark cycle, disrupted secretion of melatonin results in impaired timing of the circadian rhythm. (Zisapel 2001)

A number of studies have assessed sleep disturbances experienced by the cabin crew. For example, in a study by Preston and co-workers, four cabin crew members were exposed to time zone changes in isolation and other four spent time in isolation without time zone changes (Preston et al. 1973). The daily amount of sleep was approximately five hours for the time-zone change group, whereas the control group achieved almost seven hours of sleep. In another study by Preston and co-workers, 12 male and 12 female cabin crew members kept a sleep log for a period of approximately 14 weeks (Preston, Ruffell Smith & Sutton-Mattocks 1973). On average, the loss of sleep among the cabin crew was associated with number of night-time flights but not to time zone changes. In a study by Smolensky and co-workers, of 3 000 American male and female cabin crew, 71% reported feeling fatigue during the flight, 62% prior to the flight, and 83% between the flights (Smolensky et al. 1982). In a Finnish study, 285 female and 58 male cabin crew members working on transmeridian routes filled out questionnaires on sleep length and quality (Suvanto et al. 1990). The quality of sleep, adjustment, and recovery time were dependent on the direction (east vs. west) of the flight and on the number of time zones crossed. Differences in these outcomes between the subjects were partly explained by age, gender, and mental characteristics. In a Norwegian study conducted among 1 240 members of SAS personnel, health, sleep problems, and mood perceptions were evaluated and compared between the cockpit and the cabin crew (Haugli, Skogstad & Hellesoy 1994). In general, female cabin crew had the highest frequency of health problems. Both the cockpit and the cabin crew commonly reported sleep disturbances. In a Swedish study, 35 SAS cabin crew workers were monitored for nine days for spontaneous sleeping characteristics before the layover, during the layover (i.e., time spent in destination between departure and return flights), and the return to home during a Stockholm – Tokyo return flight (Lowden, Akerstedt 1999). They found that the crew had a period of extended wakefulness during the outbound flight and throughout the study period there was a strong increase in napping behavior. The cabin crew suffered from sleep loss, increased sleepiness, and difficulties in awakening, especially after returning home. There seemed to be no individual differences in the symptoms.

#### 2.1.3.2 Exposure to electromagnetic fields

Cabin crew are exposed to magnetic fields generated by the aircraft's electrical system. Little information is available on the exposure levels among cabin crew. Nicholas and co-workers measured magnetic field levels with a personal dosimeter set in 14 Canadian-based routes and found that the field strength varied with stages of flight, location within the aircraft, and type of the aircraft (Nicholas et al. 1998). The mean levels were less than 0.3 microTesla (μT) in the economy, 0.6 µT in the first class, and 0.8 µT in the front serving areas. The magnetic field levels of the latter two are slightly elevated compared to the normal level at home or in the office (0.1 to 0.3 µT) (Kaune 1993). International Agency for Research on Cancer (IARC) has classified extremely low-frequency magnetic fields as possible carcinogenic factors (*http://www.iarc.fr/en/media-centre/pr/2011/pdfs/pr208_E.pdf*).

#### 2.1.3.3 Other exposures

In the past, cabin crew might have been exposed to chemical toxins such as pesticides. From the 1950s to the 1970s, dichloro-biphenyl-trichloroethane (DDT) was used in the airplane cabin according to recommendations by World Health Organization (WHO) to destroy insects (Wartenberg, Stapleton 1998). Cabin crew sprayed the whole aircraft by hand aerosol dispenser. This may have resulted in considerable exposure but there are no studies estimating DDT levels.

Airline cabin crew were previously exposed to environmental, i.e., second-hand smoking (SHS) in their work. A number of studies have assessed the SHS exposure among cabin crew. For example, an American study concluded that in the past, the aircraft cabin provided SHS conditions similar to any smoking-allowing bars or smoking lounges (Repace 2004). Lindegren and co-workers measured the urinary cotinine levels in SAS non-smoking cabin crew before and after intercontinental flights (Lindgren et al. 1999). They found that the cotinine levels were significantly higher after the flight than before departure. The average cotinine concentration was similar to that of restaurant staff with known SHS exposure. In the U.S., the SHS situations declined after non-smoking compartments were established in 1973 and smoking was banned on routes shorter than two hours in 1988. There have been no studies on smoking in the carriers of Finnish airline companies but Finnair cabin crew have been exposed to SHS. In 1972 Finnair had non-smoking compartments available on all flights, and in 1997 smoking was totally banned on all routes except on flights to Japan. All Finnair routes have been non-smoking since 1999. (*http://www.finnairgroup.com/group/group_14_4_r.html?Id=1045220571.html*)

## 2.2 Cancer risk among airline cabin crew

### 2.2.1 Risk of cancer (all sites)

Several studies have found increased risk of certain cancers but the results are not consistent across different studies. Table 2 summarizes the evidence. The risk of all cancers combined is elevated in all of these studies but the result is statistically significant only for male cabin crew in the Norwegian (Haldorsen, Reitan & Tveten 2001) and the Californian studies (Reynolds et al. 2002). Several cancer sites show statistically non-significant elevated risk but the evidence for increased risk seems to be strongest for breast cancer, cutaneous malignant melanoma (CMM), and non-melanoma skin cancers (NMSC). A Meta-analysis combining results of all these seven incidence studies reported a significant excess for CMM (meta-standardized incidence ratio (meta-SIR) 2.15, 95% posterior interval (PI): 1.56–2.88) and for breast cancer (meta-SIR 1.40, 95% PI: 1.19–1.65) (Buja et al. 2006).

Only a few studies have tried to assess the reasons for the elevated risks (Rafnsson et al. 2001, Linnersjo et al. 2003, Reynolds et al. 2002, Rafnsson et al. 2003a, Rafnsson et al. 2003b). It would be crucial to know if the increased risk is related to occupational exposure to ionizing cosmic radiation. Due to the development of aviation technology, the planes fly longer and at higher altitudes and thus the number of routes, flights, passengers, and the number of cabin crew may continue growing. It is also possible that non-occupational factors explain partly or totally the increased risk of cancers. Distinguishing the effects of different exposures to the cancer risk is difficult since many of the factors are strongly correlated, e.g., cosmic radiation dose, magnetic field exposure, circadian rhythm changes, possible effects of cabin crew work on other factors such as parity etc. Therefore, the detailed exposure information on all factors is important.

**Table 2.** Cancer incidence among aircraft cabin crew published between 1995 and 2006. Statistically significant results are bolded. Available estimates are reported for all sites, breast and skin, and for other sites where the point estimate is at least 1.5 and based on at least 2 cases.

| Reference | Study group | Cancer sites | Observed | SIR* (95% CI****) |
|---|---|---|---|---|
| Pukkala et al.1995 | Finnish crew, Female N = 1 577 | All sites | 35 | 1.2 (0.9 to 1.7) |
| | | **Bone** | **2** | **15.1 (1.8 to 54.5)** |
| | | **Breast** | **20** | **1.9 (1.2 to 2.2)** |
| | | Leukaemia | 2 | 3.6 (0.4 to 12.9) |
| | | CMM** | 3 | 2.1 (0.4 to 6.2) |
| Lynge 1996 | Danish cabin crew, Female N = 915 | Breast | 14 | 1.6 (0.9 to 2.7) |
| Wartenberg et al. 1998 | Retired cabin crew from the U.S., Female | Breast | 7 | 2.0 (1.0 to 4.3) |

* Standardized incidence ratio
** Cutaneous malignant melanoma
*** Non-melanoma skin cancer
**** Confidence interval
# Basal cell carcinoma not included

**Table 2.** Continued.

| Reference | Study group | Cancer sites | Observed | SIR* (95% CI****) |
|---|---|---|---|---|
| Haldorsen et al. 2001 | Norwegian cabin crew, Female N = 3 105, Male N = 588 | *Female* | | |
| | | All sites | 127 | 1.1 (0.9 to 1.3) |
| | | Breast | 38 | 1.1 (0.8 to 1.5) |
| | | CMM** | 19 | 1.7 (1.0 to 2.7) |
| | | NMSC*** | 5 | 2.9 (1.0 to 6.9) |
| | | Rectum | 6 | 2.0 (0.7 to 4.3) |
| | | Soft tissue | 2 | 3.0 (0.4 to 10.7) |
| | | Upper respiratory and gastric tract | 3 | 2.5 (0.5 to 7.2) |
| | | *Male* | | |
| | | **All sites** | **52** | **1.7 (1.3 to 2.2)** |
| | | Brain, nervous system | 3 | 2.2 (0.5 to 6.5) |
| | | **CMM**** | **6** | **2.9 (1.1 to 6.4)** |
| | | **Liver** | **2** | **10.8 (1.3 to 39.2)** |
| | | **NMSC***#** | **9** | **9.9 (4.5 to 18.8)** |
| | | Non-Hodgkin's Lymphoma | 4 | 3.4 (0.9 to 8.8) |
| | | Testis | 2 | 1.5 (0.2 to 5.5) |
| | | **Upper respiratory and gastric tract** | **9** | **6.0 (2.7 to 11.4)** |
| Rafnsson et al. 2001 | Icelandic cabin crew, Female N = 1 532 | All sites | 64 | 1.2 (1.0 to 1.6) |
| | | Breast | 26 | 1.5 (1.0 to 2.1) |
| | | Corpus uteri | 3 | 1.5 (0.3 to 4.3) |
| | | Hodgkin's disease | 2 | 3.8 (0.4 to 13.6) |
| | | **CMM**** | **7** | **3.0 (1.2 to 6.7)** |
| | | Non-Hodgkin's Lymphoma | 2 | 2.1 (0.2 to 7.5) |
| | | Thyroid | 6 | 1.6 (0.6 to 3.4) |
| Reynolds et al. 2002 | Californian cabin crew, Female N = 6 895, Male N = 1 216 | *Female* | | |
| | | All sites | 104 | 1.0 (0.8 to 1.2) |
| | | Urinary bladder | 2 | 2.6 (0.3 to 9.6) |
| | | Breast | 60 | 1.3 (1.0 to 1.7) |
| | | CMM** | 12 | 1.8 (0.9 to 3.2) |
| | | Larynx | 2 | 5.7 (0.5 to 21.1) |
| | | *Male* | | |
| | | **All sites** | **25** | **2.1 (1.4 to 3.2)** |
| | | CMM** | 3 | 2.7 (0.5 to 8.1) |
| | | **Kaposi's sarcoma** | **15** | **7.8 (4.3 to 12.8)** |
| | | Non-Hodgkin's Lymphoma | 2 | 1.6 (0.2 to 6.0) |
| Linnersjo et al. 2003 | Swedish cabin crew, Female N = 2 324, Male N = 632 | *Female* | | |
| | | All sites | 76 | 1.0 (0.8 to 1.2) |
| | | Breast | 33 | 1.3 (0.9 to 1.7) |
| | | **CMM**** | **11** | **2.2 (1.1 to 3.9)** |
| | | Kidney | 2 | 1.7 (0.2 to 6.0) |
| | | Leukaemia | 4 | 1.3 (0.9 to 8.0) |
| | | Pancreas | 2 | 2.2 (0.3 to 8.1) |
| | | *Male* | | |
| | | All sites | 33 | 1.2 (0.8 to 1.6) |
| | | **CMM**** | **6** | **3.7 (1.3 to 8.0)** |
| | | Colon | 3 | 1.6 (0.3 to 4.7) |
| | | **NMSC***#** | **4** | **4.4 (1.2 to 11.3)** |
| | | Urinary bladder | 4 | 2.0 (0.6 to 5.2) |

* Standardized incidence ratio
** Cutaneous malignant melanoma
*** Non-melanoma skin cancer
**** Confidence interval
\# Basal cell carcinoma not included

### 2.2.2 Risk factors of breast cancer

The evidence on the basis of previous incidence studies among cabin crew is fairly strong for breast cancer. The epidemiological studies on the most important known risk factors of breast cancer are summarized below.

#### 2.2.2.1 Ionizing radiation

Numerous epidemiological studies have evaluated breast cancer risk in relation to exposure of ionizing radiation. Table 3 summarizes the results of selected studies from atomic bomb survivors, therapeutic and diagnostic medical exposures, and occupational exposures. The number of studies is so vast that only a fraction is mentioned here.

The Life Span Study cohort of Japanese atomic bomb survivors (LSS) in Hiroshima and Nagasaki from the year 1945 onwards has been a primary source for estimating the cancer risk from external radiation exposure. Its strengths contain a long follow-up time, a large cohort including both genders, all ages, well-known individual doses of wide range, and a high quality of incidence and mortality data. Among the atomic bomb survivors, breast cancer incidence is strongly related to dose, the excess relative risk (ERR) was 0.9 per Gy (90% CI: 0.6–1.3) among those who were exposed at the age of 30 with attained age of 70 years (Preston et al. 2007). Some previous LSS studies have concluded that age at exposure is an apparent effect modificator; the effect is stronger for exposure before 20 years of age compared to exposures at older ages (Land et al. 2003). The incidence study by Preston and co-workers did not support this finding (Preston et al. 2007). They concluded that there is no indication of age at exposure effect on ERR of breast cancer but both attained age and age at exposure have joint effects on the excess absolute risk (EAR). This suggests that the joint effect of radiation and risk factors responsible for baseline breast cancer rates in Japanese population is multiplicative.

Whereas studies on atomic bomb survivors deal with short-term exposure, studies among medically irradiated people for therapeutic purposes offer a chance to study the risk related to dose administered repeatedly in fractions and among non-Japanese populations. Medical radiation has been used for various postnatal diagnostic and therapeutic purposes. In diagnostic procedures the doses are generally low whereas in therapies the total exposure levels are high. Also a range of prenatal irradiation diagnostic methods has been used but those methods are not discussed here nor are those studies where the irradiation was administered only during early childhood. Further, all the medical studies described here concern external exposure. Studies on patients exposed to internal radioisotopes have also been conducted but they are not discussed here.

Among women in the U.S. who were treated with one to ten fractions of x-ray therapy for acute mastitis after childbirth during 1940s and 1950s, the relative risk (RR) of 3.2 (90% CI: 2.3–4.3) for breast cancer was found compared to controls (Shore et al. 1986). The number of fractions the treatment was divided into, the number of days between the treatments or the dose per fraction did not have a clear modifying effect on the risk. In a study among women who were exposed to on average 88 chest x-rays for the treatment of pulmonary tuberculosis, an RR of developing breast cancer was 1.29 (95% CI: 1.1–1.5) (Boice et al. 1991). The effect modification by age was similar to the LSS study by Land and co-workers (Land et al. 2003); the effect was strongest when the exposure took place during adolescence and the risk was smallest for exposure after the age of 40. Increased rates were not seen until approximately 15 years had passed from the first x-ray treatment. There was strong evidence of a linear dose-relation.

Radiotherapy administered to the pelvic area is related to reduced risk of breast cancer. For example, in a study of patients treated with x-ray therapy to uterine bleeding disorders, a standardized mortality ratio (SMR) of 0.5 was observed (Darby et al. 1994). This effect is probably due to the destruction of the hormone producing cells in the ovaries due to the irradiation.

Several studies among populations with occupational exposure to ionizing radiation have been conducted. ICRP has recommended that persons who receive a radiation dose of more than 1 mSv per a year in their work, should be classified as occupationally exposed regardless of the source of radiation (International Commission on Radiological Protection. 1991). Occupational exposure studies offer a chance to provide information on the health effects of exposure to protracted low dose rate and low dose radiation. Most useful are those of nuclear industry workers where individual dose estimates have been obtained with personal radiation detectors. The 15-country study combined more than 400 000 nuclear industry workers from 15 countries with a follow up for mortality (Cardis et al. 2007). The ERR for breast cancer mortality was estimated to be less than zero. Instead, in the study among the subjects of National Registry of Radiation Workers with atomic weapon establishment, nuclear energy production, nuclear fuel cycle, or with science, technology, and healthcare in United Kingdom the ERR for breast cancer mortality was 2.3 per Sv which was however not statistically significant (Muirhead et al. 2009). Doody and co-workers used a questionnaire among female U.S. radiologic technologists to determine a proxy measure for cumulative radiation exposure. They divided the women into four exposure categories based on the year the work was started, the total number of work years, the work facilities, and the calendar period of the work. They found a higher breast cancer risk among those who had a highest level of radiation exposure compared to the lowest (adjusted RR 1.5, 95% CI: 1.0–2.2). (Doody et al. 2006)

**Table 3.** Available risk estimates and 95% confidence intervals (95% CI) from selected incidence (I) and mortality (M) studies on external ionizing radiation exposure and female breast cancer.

| Reference | Study group and exposure | RR* (95% CI) | SIR** (95% CI) | SMR*** (95% CI) | Excess risk $Gy^{-1}$ or $Sv^{-1\#}$ (95% CI) for incidence | Excess risk $Gy^{-1}$ or $Sv^{-1\#}$ (95% CI) for mortality |
|---|---|---|---|---|---|---|
| ***Atomic bomb survivors*** | | | | | | |
| Preston et al. 2007 | The Life Span Study cohort of survivors (γ-radiation with small neutron component) (I) | | | | **0.9** (age 30 at exposure) (0.6–1.3)**** | |
| ***Medical exposures*** | | | | | | |
| Shore et al. 1986 | Women treated for post-partum mastitis (x-rays) (I) | **3.2** (2.3–4.3) | | | **0.4** | |
| Boice et al. 1988 | Women treated for cancer of the cervix (different types of radiation) (I) | **0.9** (0.7–1.1)* | | | **–0.2** | |
| Boice et al. 1991 | Women treated for tuberculosis 1925–54 (x-rays) (I) | | **1.3** (1.1–1.5) | | **0.6** (0.3–1.0) | |
| Hancock et al. 1993 | Women treated for Hodgkin's disease (x-rays) (I) | **4.1** (2.5–5.7) | | | **0.08** (age ≥ 30 at exposure, latency ≥ 15 years) | |
| Darby et al. 1994 | Women treated for methropathia hemorrhagica (x-rays) (M) | | | **0.5** (0.3–0.8) | | |
| Weiss et al. 1994 | Women treated for ankylosing spondylitis (x-rays) (M) | **1.4** (5–24.9 years since first treatment) | | | | **0.1** (–0.3–0.7) |
| Doody et al. 2000 | Women monitored for scoliosis (x-rays) (M) | **4.8** (cumulative dose ≥ 20 cGy vrs. 0 cGy) | | **1.7** (1.3–3.1) | | **2.7** (–0.2–9.3) |
| Ronckers et al. 2008 | Women monitored for scoliosis (x-rays) (I) | **3.1** (≥ 60 x-rays vrs. none) (1.3–7.4) | | | **2.9** (–0.07–8.62) | |

* Relative risk
** Standardized incidence ratio
*** Standardized mortality ratio
**** (90% CI)
\# Grays (Gy) or Sieverts (Sv)

**Table 3.** Continued.

| Reference | Study group and exposure | RR* (95% CI) | SIR** (95% CI) | SMR*** (95% CI) | Excess risk $Gy^{-1}$ or $Sv^{-1}$# (95% CI) for incidence | Excess risk $Gy^{-1}$ or $Sv^{-1}$# (95% CI) for mortality |
|---|---|---|---|---|---|---|
| ***Occupational exposures*** | | | | | | |
| Mohan et al. 2002 | Radiologic technologist in the U.S. (M) | **2.9** (first employment <1940 vrs. 1960≤) (1.2–7.0) | | **1.0** (0.9–1.1) | | |
| Wang et al. 2002 | Medical x-ray workers in China (I) | **1.3** (p<0.05) | | | | |
| McGeoghegan et al. 2003 | Workers in Sellafield Plant (M) | **0.8** (radiation vs. non-radiation workers) | | **0.9** (all radiation workers) | | **6.6** (–25.8–68.1) |
| Doody et al. 2006 | Radiologic technologist in the U.S. (I) | **1.5** (highest radiation exposure proxy level vs. lowest) (1.0–2.2) | | | | |
| Cardis et al. 2007 | Nuclear industry workers from 15 countries (M) | **0.6** (at 100 mSv vs. 0 mSv) (0.1–2.2)**** | | | | **<0** |
| Muirhead et al. 2009 | Radiation workers in the U.K (M & I) | | | **0.7** (0.56–0.90) | **–0.2** (<–1.93–18.09) | **2.3** (<–1.9–38.2) |

* Relative risk
** Standardized incidence ratio
*** Standardized mortality ratio
**** (90% CI)
\# Grays (Gy) or Sieverts (Sv)

Studies on atomic bomb survivors, medically irradiated people or groups occupationally exposed to radiation provide risk estimates from external low-LET radiation. Apart from the studies among aircrew, there are no other studies on populations exposed to cosmic radiation with a considerable fraction of high-LET neutron radiation. In cities that are located at a higher altitude than at sea level, the population is exposed to higher dose rate of cosmic radiation than at sea level. However, there are only few studies on cancer among adults living in high-altitude cities. Mason and Miller conducted an ecological study on cancer mortality in 53 counties of the U.S. with a majority of the areas at altitude higher than approximately 900 m (Mason, Miller 1974). They found no excess mortality for any of the cancer types.

Comparing the risk estimates for breast cancer in different studies is difficult since there usually are several differences between the cohorts to be compared (National Research Council. Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation 2006). In general, the cancer risk estimates obtained from the studies among medically irradiated people are lower than those from the atomic bomb survivor studies. This may be due to the fractionated dose from therapies compared to single dose from an atomic bomb. On the other hand, many medical studies lack individual dose estimates or there is not enough exposure contrast between individuals or the sample size is not high enough.

The estimates from occupational studies vary from no risk observed to risks of a magnitude to those seen in atomic bomb survivors. The variation in estimates is due to the fact that occupational radiation studies have difficulty in providing valid risk estimates because the doses are too small for sufficient statistical power to detect the effect. Also generally there is no information on other occupational or non-occupational confounders. In addition, in occupational studies, there is a possibility of a healthy worker effect, i.e., the workers are healthier than the general population because the general population includes also those people who are not part of the workforce due to their ill health. Consequently, there might be a lack of an appropriate control group for the occupational group under study.

To conclude, the relation between high-dose ionizing radiation and breast cancer is well understood. There still remains an uncertainty on the shape of the dose-effect curve at low doses and whether the estimates from high dose studies could be extrapolated to the low dose circumstances. Also, it is not known what is the effect if the exposure is prolonged regardless of the total dose compared to the brief exposure. In addition, most of the studies on cancer risk and ionizing radiation are on low-LET gamma or x-radiation and results from these studies cannot be straightforwardly generalized to the exposure to high-LET radiation such as neutron radiation.

#### 2.2.2.2 Reproductive factors

Breast cancer is strongly related to reproductive and hormonal factors. Early age at menarche and late menopause are consistently found to be risk factors for breast cancer. The risk generally decreases by 10–24% with each one year delay in menarche and increases by 3% with each one year delay in menopause. In addition, those women whose menstrual cycle become regular within the year from the menarche have a greater risk of breast cancer compared to those whose cycle's regulation takes more time. Short menstrual cycle is related to greater risk of breast cancer. This is due to both greater number of cycles and more time in proportion in luteal phase, when estrogen and progesterone levels are high and proliferative activity in the breast is at the maximum. Luteal phase is a time from ovulation to the onset of menstrual bleeding which generally last 14 days, irrespective of the total length of the cycle. Thus, the more regular menstrual cycles a woman has, the higher is her risk of breast cancer due to the higher exposure to hormones. In animals, estrogen and progesterone promote tumours of the breast and among women, anti-estrogens (e.g. tamoxifene) reduce breast cancer incidence. Out of female sex hormones, estradiol, i.e., one of the estrogen hormones, has the biggest role in breast cancer development. (Colditz, Baer & Tamimi 2006)

Parous women have a smaller risk of breast cancer compared with nulliparous women and each additional birth after the first one reduces the breast cancer risk. In an American case-control study it was found that each full-term pregnancy reduced the risk of breast cancer with 13% among Caucasian younger women (35–49 years) and 10% among older women (50–64 years) (Ursin et al. 2004). Similar findings were observed in a population-based study in Sweden, where each additional birth yielded a 10%-reduction in the risk of breast cancer (Lambe et al. 1996). When the analysis was restricted to women with two or more parities, the risk of breast cancer increased about 13% for each increment in the age at first birth. Similar results of young age at first full-term pregnancy predicting lower lifetime risk of breast cancer have been found in other studies (Colditz, Baer & Tamimi 2006). Also a long duration of breastfeeding is related to lower risk of breast cancer. A large study combining results of 47 epidemiological studies showed a 4.3% decrease in the relative risk of breast cancer for every 12 months of breastfeeding. The result was not markedly changed by age, menopausal status, the number of births, or by any other characteristics the study group was able to examine. (Collaborative Group on Hormonal Factors in Breast Cancer 2002)

Recent studies on the effect of use of oral contraceptives on the breast cancer risk show a small increased risk. Similar results have been observed among postmenopausal hormone users; those women who have ever used postmenopausal estrogen have an increased risk compared to never users. However, the risk is more pronounced among current users or users of long duration. In general, the results of the studies investigating the relation between postmenopausal hormones and breast cancer are somewhat contradictory. In addition, the use of estrogen and progestin combining products after menopause is a recent phenomenon, and thus their effect on the breast cancer risk is not known. (Colditz, Baer & Tamimi 2006)

There have been suggestions on the relation between infertility treatment drugs and breast cancer (Cetin, Cozzi & Antonazzo 2008). Zreik and co-workers conducted a review and a meta-analysis on the topic and found no evidence from the published studies on the association between the use of fertility drugs and a higher risk of breast cancer. However, the authors state that the lack of long term follow-up time in these studies have to be taken into account. (Zreik et al. 2010).

#### 2.2.2.3 Genetic and familial susceptibility

Of all the breast cancers 5% to 10% are due to inherited genetic mutations. A striking characteristic for hereditary breast cancers is the early age at onset of the disease. Up to 60% of the hereditary breast cancers are estimated to be due to mutations in BRCA1 and/or BRCA2 genes. (Colditz, Baer & Tamimi 2006) However, several breast cancer cases can occur in one family sporadically without a hereditary susceptibility since breast cancer is a common disease.

#### 2.2.2.4 Nutritional, anthropometric and socioeconomical factors

The role of nutrition in cancer development has been extensively studied. Yet, the pathway from nutrition to cancer is not fully understood. The current general guidelines are that nutrition plays either a direct role (cancer promoting or protective components in food) or an indirect role (through body composition) in cancer development. (Uauy, Solomons 2005, Key et al. 2004) Nutrition can consist of several nutrients that either might protect from breast cancer or increase its risk. There is some evidence on the relation between excess animal fat intake and increased breast cancer risk. The role of vitamins or other micronutrients is not clear in breast cancer development but there is some evidence that women with high folate intake have a decreased risk. Also the role of phytoestrogens in the development of breast cancer has gained much interest. Phytoestrogens are naturally occurring compounds that may modify the estrogen metabolism in a human body. Fruits and vegetables are the sources of phytogens and the highest contents are found in soya. Several studies have found no evidence of phytoestrogens' protective role against breast cancer. For example, in a case-control study of more than 25 000 participants in the United Kingdom, the mean consumption of phytoestrogens were similar between breast cancer cases and controls but lignan intake was marginally higher among cases (Ward, Kuhnle 2010). In a multivariate logistic regression analysis, lignan intake was not statistically significant in association with breast cancer (Odds ratio (OR) for doubling of intake 1.2, 95% CI: 0.9–1.6).

There is convincing evidence on the adverse effect of alcohol consumption to the breast cancer risk. Even one alcohol unit per day increases the risk and the risk grows rather monotonically with elevating intake of alcohol. (Colditz, Baer & Tamimi 2006) IARC has recently concluded that female breast cancer is causally associated with the consumption of alcohol (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012a). IARC has also concluded that in the light of current the evidence, tobacco smoking is related to increased risk of breast cancer but the dose-response relation is smaller than in other cancers causally related to smoking (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012a). Also a hypothesis of inverse correlation between smoking and breast cancer exists due to the antiestrogenic effect of active smoking. (Thun, Henley 2006) Thus, smoking may have both protective and harmful effects on breast cancer risk (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012a).

In Western countries, the relation between adiposity and breast cancer depends on the menopausal status. Weight is inversely correlated with the risk of premenopausal breast cancer and positively correlated with postmenopausal breast cancer. This might relate to the fact that heavy premenopausal women have more irregular, anovulatory cycles whereas heavier postmenopausal women have higher levels of plasma estrogen. Epidemiological studies have also showed that height is positively related to breast cancer risk. (Colditz, Baer & Tamimi 2006) IARC has estimated that 25% of breast cancer cases worldwide are due to obesity and inactive lifestyle (IARC Working Group on the Evaluation of Cancer-Preventive Strategies., International Agency for Research on Cancer. & World Health Organization. 2002).

Mammographic density, i.e., how the breast tissue (dense connective and epithelian tissue vs. lucent fat) composition appears in a mammogram, is associated with breast cancer. Many studies have shown that the higher the percentual density, the higher the risk of breast cancer. For example, in a large European follow-up study of 3 211 women, it was found that women in the top fourth of percent breast density (≥45.6%) were more likely to develop breast cancer than those in the bottom fourth (<18.7%) (Hazard Ratio (HR) 3.5, 95% CI: 1.7–7.2) (Torres-Mejia et al. 2005).

There are important socioeconomical differences in breast cancer risk; the risk increases with the socioeconomical status (SES). The differences might be explained by differences in reproductive factors, nutrition and alcohol intake between the women with a different SES. (Colditz, Baer & Tamimi 2006) In Finland in 1995, the incidence of breast cancer was 162/100 000 in the highest SES and 87/100 000 in the lowest (Pukkala 1995).

#### 2.2.2.5 Jet lag

Disruptions in circadian rhythm during flights across several time zones have been hypothesized to increase breast cancer risk (Rohr, Herold 2002). This is believed to be due to exposure to light during normal sleeping hours and therefore lower levels of melatonin secreted by the pineal gland. Epidemiological studies on blind women support this melatonin hypothesis; blind people have increased levels of melatonin and decreased rate of breast cancer (Kliukiene, Tynes & Andersen 2001, Verkasalo et al. 1999, Pukkala et al. 2006). Also a few studies have found a positive association between night shift work and breast cancer (Schernhammer et al. 2001, Tynes et al. 1996, Davis, Mirick & Stevens 2001, Hansen 2001). None of the studies among cabin crew summarized in Table 2 tried to estimate the effect of jet lag to the breast cancer risk. IARC has classified shift work that involves circadian disruption as possibly carcinogenic to humans (*http://w2.iarc.fr/en/media-centre/pr/2007/pr180.html*).

Megdal and co-workers conducted a systematic review and a meta-analysis of night shift work and breast cancer risk. Based on 13 studies including seven studies of aircrew and six studies of other night shift workers, they calculated an aggregated SIR of 1.48 (95% CI: 1.36–1.61) for breast cancer. There was no information available on the amount of shift work among cabin crew but for other night shift groups, individual work histories or self-reported data on shift work was available. The aggregate estimate only for cabin crew was fairly similar to the estimate calculated only for other night shift workers, i.e., 1.44 (95% CI: 1.26–1.65) and 1.51 (95% CI: 1.36–1.68), respectively. (Megdal et al. 2005)

#### 2.2.2.6 DDT

Exposure to the environmental organochlorines, e.g., DDT – a pesticide, polychlorinated biphenyls (PCB) – an industrial chemical, and polychlorinated dioxins (PCDD) have been suggested to increase the risk of breast cancer. Among cabin crew, a relation between breast cancer and DDT exposure has been suggested but the evidence remains absent (Wartenberg, Stapleton 1998). From the 1950s to 1970s cabin crew members sprayed the cabin with manual aerosols of DDT to prevent insects on flights to a few destinations but the amount of exposure is unknown. However, recent studies do not support the relation between organochlorines and breast cancer (Colditz, Baer & Tamimi 2006).

### 2.2.3 Risk factors of skin cancers

In addition to breast cancer, the evidence is strongest for skin cancers on the basis of previous incidence studies among cabin crew. The most important risk factors of skin cancers are summarized below.

#### 2.2.3.1 Ionizing radiation

There is hardly any evidence from Life Span Study of atomic bomb survivors (LSS) on the relation between ionizing radiation and cutaneous malignant melanoma (CMM) since the number of CMM cases in LSS cohort is very small, i.e., 17. Non-melanoma skin cancers (NMSCs) were related to the dose with ERR being 0.2/Sv (90% CI 0–0.8) for women. A linear-spline model, i.e., allowing the line to change slope at 1 Gy, fitted the data best. The risk for the two main types on NMSCs differed; a strong association was seen between radiation and basal cell carcinoma (BCC) (ERR for both genders 0.6/Sv, 90% CI: 0.2–1.4) but less for squamous cell carcinoma (SCC) (ERR 0.2/Sv). The figures for BCC and SCC were not given separately for both genders. (Preston et al. 2007)

There is no evidence that ionizing radiation from medical treatments at low or moderate doses would increase the risk of CMM. However, some previous studies have suggested an association between increased CMM risk and treatment of primary malignancy in adulthood with ionizing radiation. Shore and co-workers reviewed studies on cancer treatments and concluded that there were excesses of CMM after treatment of lymphopoietic and testicular cancer and after bone marrow transplantation. However, in some of these studies, the excesses of CMM were seen in less than five years after the treatment whereas the minimum latency period for a solid tumor to is 5 to 10 years according to several studies of ionizing radiation and cancer. This suggests that the excess CMM risk might be attributable to other factors than radiation. (Shore 2001)

There is some more evidence on the relation between NMSC and radiation therapy in adulthood, and the evidence seems to be stronger for BCC and less so for SCC. Karagas and co-workers found as a part of their skin cancer prevention trial that those subjects who reported past radiation therapy for medical condition (acne, other benign dermatology condition, cancer excluding NMSC or other reason) between the ages of 20 to 39 years, had risk (RR 2.2, 95% CI: 1.5–3.0) of BCC compared to those who had received no radiation therapy in the past (Karagas et al. 1996). Radiation treatment was not related to SCC occurrence. In a case-control study of BCC and SCC patients in New Hampshire, U.S., the radiation treatment given first time between ages 20 to 39 was not related to BCC (OR 1.05, 95% CI: 0.46–2.36) or SCC (OR 1.35, 95% CI: 0.55–3.28) but the number of cases was rather small (Lichter et al. 2000).

The first cancer ever documented being associated with ionizing radiation was skin cancer among radiologic workers after exposure to X-rays (Frieben 1902), cited in (Karagas et al. 1996). In the past, radiation workers rather frequently developed SCC to the upper extremities that were exposed to high levels of X-radiation or other radioactive sources. Since then, a number of studies on the relation between skin cancers and occupational exposure to protracted low-doses of ionizing radiation have been conducted. Table 4 shows results of selected studies. Generally the studies of occupational ionizing radiation have limited or no information on UVR exposure. One exception is the cohort study among the U.S. radiologic technologists where information on host characteristics, e.g., eye and skin colours, were obtained with a questionnaire survey (Yoshinaga et al. 2005, Freedman et al. 2003). The residential area was used as an estimate of UVR exposure. The risk estimates, adjusted for host factors and UVR exposure, were not statistically significant for CMM and SCC but elevated and statistically significant for BCC (RR 2.2, 95% CI: 1.1–4.1).

A large cohort study of nuclear industry workers in 15 countries with individual external dose monitoring found no association between radiation dose and CMM mortality (ERR/Sv 0.15, 90% CI: <0–5.44) (Cardis et al. 2007). Another large cohort study among Lawrence Livermore National Laboratory (U.S.) workers, found no statistically significant association between CMM and ionizing radiation among females (SIR 1.7, 95% CI: 0.9–2.8) but found it among males (SIR 1.4, 95% CI: 1.02–1.8) (Whorton et al. 2004).

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has summarized that there is only weak evidence that CMM is induced by the exposure to ionizing radiation (United Nations. Scientific Committee on the Effects of Atomic Radiation. 2006). This is mainly due to inadequate radiation dosimetry and potential confounding by the UVR exposure. Similar drawbacks are inherent to studies on relation between ionizing radiation and NMSC. UNSCEAR has also concluded that there is strong evidence that NMSC, especially BCC, is inducible by ionizing radiation. What is not known, is the interaction between ionizing radiation and UVR exposure. The results so far suggest that the ERR for NMSC might be lower at the body sites that are exposed to UVR but EAR might be higher for such sites (United Nations. Scientific Committee on the Effects of Atomic Radiation. 2006) Similar to breast cancer risk studies, most of the studies on skin cancer risk and ionizing radiation are on low-LET gamma or x-radiation and the results from these studies cannot be straightforwardly generalized to the exposure to high-LET radiation.

**Table 4.** Available risk estimates with 95% confidence intervals (95% CI) from selected studies on occupational ionizing radiation exposure and skin cancer risk.

| Reference | Study group | CMM* (95% CI) | NMSC** (95% CI) | SCC*** (95% CI) | BCC**** (95% CI) | All skin# (95% CI) |
|---|---|---|---|---|---|---|
| Sont et al. 2001 | Radiation workers of several occupations in Canada | SIR€ **1.2** (1.0–1.3) | | | | |
| Mohan et al. 2002 | Radiologic technologists in the U.S. (females) | | | | | SMR£ **0.7** (0.5–0.9) |
| Wang et al. 2002 | Medical x-ray workers in China | | RRα for incidence **4.1** ($p<0.05$) | | | |
| Freedman et al. 2003 | Radiologic technologists in the U.S. comparing those who first worked <1950 to those who first worked >1970 | RRα **1.8** (0.6–5.5) | | | | |
| Whorton et al. 2004 | Workers in LLNLΩ (females) | SIR€ **1.7** (0.9–2.8) | | | | |
| Yoshinaga et al. 2005 | Radiologic technologists in the U.S. comparing those who worked <1940 to those who worked >1960 | | | RRα **0.7** (0.2–2.1) | RRα **2.2** (1.1–4.1) | |
| Cardis et al. 2007 | Nuclear industry workers from 15 countries | ERRβ for mortality **0.2**/Sv (<0–5.4) | | | | |
| Muirhead et al. 2009 | Radiation workers in the U.K | ERRβ for incidence **1.4**/Sv (–0.7–5.6) | ERRβ for incidence **1.5**/Sv (0.1–3.9) | | | |

* Cutaneous malignant melanoma
** Non melanoma skin cancer
*** Squamous cell carcinoma
**** Basal cell carcinoma
\# All malignant neoplasms of the skin
€ Standardized incidence ratio
£ Standardized mortality rate
α Relative risk
Ω Lawrence Livermore National Laboratory, a chemistry and physics research facility
β Excess relative risk

#### 2.2.3.2 Ultraviolet radiation

As stated before, UVR is the principal risk factor for all the skin cancers (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012b). CMMs and NMSCs commonly arise among Caucasians on the sun-exposed sites. At the ecological level, skin cancer incidence increases with ambient UVR levels. It has been estimated that from 50% to 90% of CMMs, 50% to 70% of SCCs, and 50% to 90% of BCCs worldwide are due to UVR exposure (*http://www.who.int/uv/publications/solaradgbd/en/index.html*). However, the causal pattern portraying the relation between UVR and skin cancers is complex and depends, for example, on host characteristics, timing of the exposure in terms of the life span, and on other attributes of the exposure such as temporality. (Green, Whiteman 2006) Risk of CMM seems to be strongly positively associated with intermittent UVR exposure but less strongly with cumulative lifetime UVR exposure. Chronic UVR exposure might be inversely associated to CMM risk. (Gandini et al. 2005b) The evidence for NMSC seems more ambiguous. BCC appears to have a more similar UVR exposure pattern to CMM than SCC, i.e., intermittent UVR exposure increases the risk of BCC whereas chronic exposure does not. Chronic exposure and cumulative exposure to UVR, however, are related to the SCC risk.

In general, there are major challenges in studies of relation between UVR exposure and skin cancers. There is no true reference category available, i.e., a population with no exposure to the UVR. Also the lack of valid method for UVR exposure measurement is a shortage; for example, self-reporting of UVR exposure is prone to recall bias. Skin cancer is one of the few cancer types for which the carcinogenity is strongly implicated only on the basis of descriptive epidemiological data.

Several studies have consistently observed that people with fair skin who burn easily and tan poorly when exposed to UVR are at highest risk of CMM (Gruber, Armstrong 2006). The highest risk of CMM relates to the burning of the skin, particularly in the childhood. However, skin burns in the adulthood are almost as significant as skin burns in the childhood. Gandini and co-workers conducted a meta-analysis of 58 studies and found a pooled risk estimate for skin burns in childhood of 2.24 (95% CI: 1.73–2.89) and for skin burns in adulthood 1.92 (95% CI: 1.55–2.37) (Gandini et al. 2005b). Similar findings apply to NMSCs as well. The large Nurse's Health study in the U.S. suggested RRs of 2.4 for SCC and 4.9 for BCC in case of six or more severe lifetime skin burns compared to none (Grodstein, Speizer & Hunter 1995, Hunter et al. 1990). In a prospective cohort study of pigmentary characteristics and sun exposure and their relation to CMM risk among Norwegian and Swedish women, it was found that sunburns between the ages ten to 39 were associated with the highest risk of CMM (two or more sunburns per a year vs. one or less, RR 1.8, 95% CI: 1.2–2.7) whereas skin burns after 40 years of age had no effect (two or more sunburns per a year vs. none, RR 1.0, 95% CI: 0.4–2.3) (Veierod et al. 2003).

There is evidence that the use of tanning beds, i.e., devices that emit UVR radiation to produce a cosmetic tan, is related to skin cancer risk. For example, in a large study among female nurses in the United States, the average use of tanning devises per year during the age period from school years to 35 years of age was related to BCC (HR 1.2, 95% CI: 1.1–1.2), SCC (HR 1.2, 95% CI: 1.01–1.3), but not to CMM (HR 1.1, 95% CI: 0.97–1.3) risk. The risk was determined as an incremental increase in use of tanning devises of four times per a year. (Zhang et al. 2012) In a systematic review by the International Agency for Research on Cancer Working Group on artificial ultraviolet light and skin cancer, the summary-RR based on 19 studies for ever use of tanning devises was 1.2 (95% CI: 1.0 – 1.3) for CMM, 2.3 (95% CI: 1.1 – 4.7) for SCC based on three studies, and 1.0 (95% CI: 0.6 – 1.9) for BCC based on four studies (International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer 2007).

#### 2.2.3.3 Host factors

People with blonde or red hair are at higher risk than those with brown of black hair. Similarly, people with light-coloured (blue or green) eyes are more likely to develop CMM than those with dark (brown) eyes. However, eye colour is not as strong a risk factor for CMM as other pigmentary characteristics are, i.e., hair colour and skin colour. The frequency of freckles is generally associated with the CMM risk. However, the contribution of freckle count to the CMM risk is unclear mainly due to the fact that most of the studies have not adjusted for sun exposure. For NMSCs, fair skin, light-coloured eyes, and blonde or red hair are also well-established risk factors. Several studies have showed that frequency of freckles is a risk factor for BCC. (Karagas et al. 1996, Gruber, Armstrong 2006)

Nevi on the skin are associated to the CMM incidence but the risk depends on the type of the nevi. Nevi are commonly divided into three categories: congenital, acquired, and atypical. Congenital nevi are present at birth but acquired nevi are developed after six months of age. Atypical nevi are usually greater than five millimetres in diameter and have a slightly irregular border and colouring. (Gruber, Armstrong 2006) The number of acquired nevi is a well-established risk factor for CMM. In a meta-analysis of 46 studies by Gandini and co-workers, it was found that there was a substantial risk in the presence of 101 to 120 nevi in the whole body compared to less than 15 (pooled RR 6.89, 95% CI: 4.63 – 10.25) (Gandini et al. 2005a). More than five atypical nevi on the whole body vs. none, was associated with higher risk of CMM (pooled RR 6.36, 95% CI: 3.80 – 10.33). Some studies have found a weak or moderate relation between nevi count and BCC (Karagas, Weinstock & Nelson 2006).

Several studies have found consistent evidence that SES affects the CMM risk. Among the highest SES, the risk is highest. (Gruber, Armstrong 2006)

Many epidemiological studies have shown that family history is associated with an increased risk of CMM. It was found in a meta-analysis by Ford and co-workers that a risk of CMM was 2.24-fold higher (95% CI: 1.76 – 2.86) in subjects who reported at least one affected first-degree relative compared to the subjects who did not (Ford et al. 1995). The effect was not related to the constitutional factors, i.e., nevus count, hair and eye colour, and freckling. In addition to familial aggregation, CMM incidence is related to several genetic syndromes. These include, for example, dysplastic nevus syndrome and Li-Fraumeni syndrome, whereas NMSCs are related to xeroderma pigmentosum, i.e., subjects who are unable to repair UVB-specific DNA mutations. (Gruber, Armstrong 2006, Karagas, Weinstock & Nelson 2006)

# 3 Aims of the study

The overall goal of this thesis was to develop retrospective exposure assessment methods for occupational exposure to cosmic radiation. Another goal was to assess the contribution of occupational as well as non-occupational factors to breast and skin cancer risk among aircraft cabin crew. A further goal was to describe the cancer incidence among cabin crew with a large cohort. The specific goals of publications summarized in this thesis were as follows:

1. To develop retrospective assessment methods for individual occupational exposure to cosmic radiation based on self-reported flight history and based on flight timetables.

2. To assess the contribution of occupational and non-occupational risk factors to breast cancer among Finnish airline cabin crew.

3. To compare the prevalence of risk factors of skin cancer between the Finnish airline cabin crew and a random sample of the population in Finland, and to assess the contribution of exposure to cosmic radiation to skin cancer risk among airline cabin crew.

4. To describe the cancer incidence among airline cabin crew in four Nordic countries and to assess the contribution of exposure to cosmic radiation and jet-lag to the risk of cancer.

# 4 Materials and Methods

An overview of the materials and methods is given in this chapter. A more detailed description can be found in the original publications I–V.

## 4.1 Subjects

The source population for the study of assessing cosmic radiation exposure based on self-reported flight history (I) and for breast cancer study (II) consisted of Finnish female airline cabin crew who were born in 1960 or before and who had been employed by Finnair or its predecessors for at least two years by the year 2000 (time of the study I and II). A total of 1 098 eligible woman were identified from the files of Finnair and Finnish Cabin Crew Union (SLSY). In the source population, a total of 57 women (5%) could not be traced and thus, 1 041 women were included to the study. A total of 544 (52%) cabin crew members participated in the study (I and II).

The source population for the skin cancer study (IV) was the same as for the studies I and II but without the limitations for the year of birth or employment time. Due to more restrictive privacy policy adopted by Finnair, updated information on the Finnair staff was not available in 2004 (the time of the study IV) and therefore women employed after the year 2000 were excluded. Due to the same reason, information on women born in 1960 or later and still working in the year 2000 was not available for the study IV. All eligible study subjects (N = 1 342) had started their work before the year 2000 and were resident in Finland at the time of the study. In the source population, a total of 97 women (7.2%) could not be traced and the final number of traceable members of female cabin crew was 1 245. Male cabin crew was not included to the study due to their small number (N = 118). A random sample of women (N = 2 000) was selected as referents from the Finnish Population Register Center with matching by age. A total of 702 (56%) cabin crew members and 1 007 (50%) of the reference women participated in the study.

For the Nordic cancer study (V), the cohorts of airline cabin crew were obtained from various national sources in Finland, Iceland, Norway, and Sweden. The Finnish cabin crew cohort comprised 1 578 women and 188 men, identified from Finnair files, who had ever worked for Finnair or its daughter airline companies between 1947 and March 1993. In Iceland, the cohort comprised 1 532 females and 158 males identified from the members list of the Icelandic Cabin Crew Association and from Icelandair and Air Atlanta companies from 1947 to 1997. The Norwegian cohort was established from 3 073 females and 581 men who had a valid cabin crew member licence between January 1950 and

February 1994 identified from the files of the Personnel Licensing Section of the Civil Aviation Administration, the authorization administrative in Norway of cabin crew members. The Swedish cabin crew cohort consisted of 2 324 women and 632 men who were employed by the Swedish part of SAS at any time during 1957–1995 and who were resident in Sweden. The entire cabin crew cohort from the four Nordic countries comprised 8 507 women and 1 559 men. Table 5 shows the number of cabin crew by the study variables.

**Table 5.** Numbers and percentages (%) of airline cabin crew by study variables. The numbers of persons are classified according to the situation at the beginning of the follow-up, while person-years are given according to the dynamic age and time since the first exposure. For the remaining variables (*in Italics*), the numbers of persons are classified according to the situation at the end of the follow-up.

| Variable | Category | Persons | | Person-years | |
|---|---|---|---|---|---|
| | | N | % | N | % |
| **Total** | | **10 066** | **100** | **237 627** | **100** |
| Country | Finland | 1 766 | 18 | 45 827 | 19 |
| | Iceland | 1 690 | 17 | 32 005 | 13 |
| | Norway | 3 654 | 36 | 89 031 | 37 |
| | Sweden | 2 956 | 29 | 70 764 | 30 |
| Age | <35 | 9 718 | 97 | 94 313 | 40 |
| | 35–44 | 313 | 3.1 | 74 974 | 32 |
| | 45–54 | 30 | 0.3 | 44 709 | 19 |
| | 55–64 | 5 | 0.1 | 17 872 | 7.5 |
| | 65–74 | – | – | 5 110 | 2.2 |
| | ≥75 | – | – | 649 | 0.3 |
| *Duration of work (years)* | *<5* | *3 315* | *33* | | |
| | *5–14.9* | *3 772* | *37* | | |
| | *≥ 15* | *2 979* | *30* | | |
| *Estimated dose (mSv*)* | *<5* | *3 063* | *30* | | |
| | *5–14.9* | *3 465* | *34* | | |
| | *15–34.9* | *2 938* | *29* | | |
| | *≥ 35* | *600* | *6* | | |
| *Estimated number of flights over ≥ 6 time zones* | *<50* | *3 571* | *35* | | |
| | *50–149* | *2 424* | *24* | | |
| | *≥ 150* | *4 071* | *40* | | |
| *Number of children, women only* | *0* | *2 054* | *24* | | |
| | *1–2* | *4 577* | *54* | | |
| | *≥ 3* | *1 590* | *19* | | |
| | *Unknown* | *286* | *3.4* | | |

* milliSievert

The breast cancer and skin cancer cases (II and IV) were identified using the personal identification number (PIC) by record linkage with the Finnish Cancer Registry, a population-based registry with a practically complete coverage (Teppo, Pukkala & Lehtonen 1994). For the joint Nordic cohort study (V), the cohorts were linked to national cancer registries by PIC for incident cancer cases. BCC was registered only in the Finnish and the Icelandic Cancer Registries and therefore it was analysed as a separate category but not included in the overall cancer rates.

## 4.2 Exposure assessment

### 4.2.1 Cosmic radiation exposure

In the study of assessing cosmic radiation exposure based on self-reported flight history (I), a postal questionnaire was used to collect information on the monthly number of round trip (to the destination and back) flights within Finland, to Europe, Far East, North America, and to other areas outside Europe (mainly Canary Islands). This information was collected for the 1960s, the 1970s and the 1980s. Information on the first and the last date of active employment were asked, as well as periods of absence from the cabin work.

In addition, information on the frequency of flights on each route was collected from Finnair's flight timetables and representative routes were selected in each route category (domestic, Europe, other areas outside Europe, North America, and Far East) and each decade (the 1960s, 1970s, and 1980s). An expert panel (consisting of three experienced pilots) was consulted to determine the number of representative flights, aircraft types, and flight profiles (ascent and descent time and cruising altitudes). One to four representative routes were selected for each route category and assigned a weighting factor, indicating the proportion of flights within the route category.

In the study I, the cosmic radiation dose for every representative route was calculated using CARI-6, a software package developed for this purpose by the U.S. Federal Aviation Authority (Friedberg 1999). The effective dose of cosmic radiation for each route was calculated as a function of altitude, latitude, solar activity (heliocentric potential), and flight time. As solar activity is a determinant of the dose rate and it varies over time, for simplicity, the average value of each decade's solar activity was used in calculations. The mean solar activity was assigned 709 megavolts for the 1960s, 617 megavolts for the 1970s, and 786 megavolts for the 1980s. The cosmic radiation dose was calculated for all cabin crew members in the study II using the method described in the study I.

For the study of assessing cosmic radiation exposure based on company timetables (III), Information was collected from the Finnair flight timetables on the frequency of flights and craft types used on each route at five-year intervals (from 1960 to 1995). The block hours, i.e., the time from which the plane departs the gate to the time the plane arrives at a gate, for charter flights were obtained from the archived Finnair flight timetables, but they did not cover their flight distribution. According to personal communication to Finnair and the Finnair route map for 1984–1995, 70–80% of the charter destinations situated in the Mediterranean area and 20–30% in the other areas in Europe. Thus, to represent the Mediterranean charter routes, the Helsinki-Athens route was used and for the other areas in Europe, four European routes were used (from Helsinki to London, to Zurich, to Luxembourg, and to Geneva). A flight profile was assigned to each route based on the type of aircraft used.

Also information was collected on the total number of airline cabin crew for every fifth year (from 1960 to 1995). Finnair did not systematically record the number of its personnel for the early years, and thus it had to be estimated based on the narrative literature (Hytönen 1997). The number of cabin crew on board was estimated with the help of expertise information, mainly pilots.

In the study of assessing cosmic radiation exposure based on company time-tables (III), the cosmic radiation dose for every route at five-year intervals was calculated using the European Program Package for the Calculation of Aviation Route Doses (EPCARD), software developed for this purpose by the GSF Institute of Radiation Protection (*http://www.helmholtz-muenchen.de/epcard*). For calculating the cosmic radiation dose for the whole cabin crew career, the information on the beginning and ending of an employment as a cabin crew worker was acquired from the Finnair and SLSY databases. The cosmic radiation dose was calculated for all cabin crew members in the study (IV) using the method described in the study III. Similarly, the cosmic radiation dose was calculated with the method described in the study III, excluding the Norwegian cohort. This was due to the fact that the assumptions utilized in cosmic radiation calculation method were not valid for the Norwegian cabin crew.

### 4.2.2 Other exposures

In order to collect information on other factors possibly contributing to breast cancer in the study II, the same questionnaire as in study I was used to collect information on 1) demographic factors, 2) occupational factors including disturbances of sleep and menstrual cycle 3) other possible risk factors for breast cancer including number of births, age at first birth, breastfeeding, number of spontaneous and induced abortions, age at menarche, age at menopause, use of oral contraceptives, participation to mammography screening, use of menopausal hormonal therapy, family history of breast cancer, previous benign breast disease, alcohol consumption, and smoking habits.

A postal questionnaire was used to collect information both from the cabin crew and the reference population in the skin cancer study IV. Among cabin crew, information was collected on UVR-related occupational factors, i.e., average annual number of days spent in sun resorts due to work, e.g., waiting for the next work shift, by decade. Information was collected from both groups on UVR exposure including 1) skin burns in childhood, i.e., before the age of 15, 2) skin burns in adulthood, i.e., after the age of 15, 3) tanning device use 4) use of topical sunscreens, 5) sunbathing habits, 6) outdoor activities in Finland during summertime, 7) residence in Southern countries with higher UVR exposure, and 8) the average annual number of vacation weeks spent in sun resorts by decade. Further, information was collected on other possible risk factors for skin cancer including hair, eye and skin colour, phototype according to the Fitzpatrick scale (Fitzpatrick 1975), and family history of skin cancer.

For the Nordic cancer study V, the flight timetables of Finnair, Icelandair and SAS Sweden were used to assess the number of flights passing six or more time zones which was used as an indicator of jet lag. As this information was not available on an individual level, the information on the number of flights was obtained for every fifth year. In addition, a similar route distribution was assumed for all cabin crew members who were at work in the same time period. The dates of births for live-born children among female cabin crew were obtained from national population registries.

## 4.3 Calculations and data analysis

(I) For every cabin crew member, the number of active work years was calculated using the reported information on the beginning and ending of employment after excluding major absences from work. The individual cumulative career dose was calculated as the sum of typical radiation doses of different periods and route types:

$$\sum_{i=1960}^{1980} 12 n_i N_i (Dom_i + Eur_i + OutEur_i + NA_i + FarE_i)$$

where
$n_i$ = crew's reported monthly number of round trip flights (in a decade i). $n_i$ was multiplied by 12 in order to obtain the yearly number of flights.
$N_i$ = crew's reported number of active work years during the decade i.

Figure 2 shows the doses for representative routes by different decades.

The mean annual dose was calculated as the cumulative career dose divided by the number of active work years. Linear regression analysis was conducted to estimate the dependency between the cumulative career dose and two possible explanatory variables: number of active work years and starting decade of cabin work.

(II) In the nested case-control study, for each breast cancer case, up to four controls were chosen from within the female cabin crew cohort with matching on the year of birth. Conditional logistic regression model was used for both

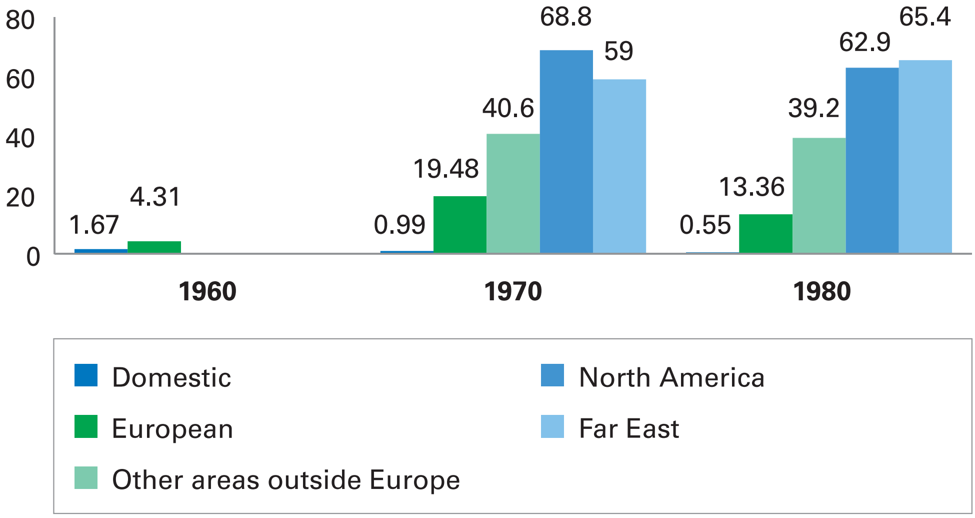


**Figure 2.** The cosmic radiation doses (μSv) per month by decade and route category.

univariate and multivariate analysis with breast cancer status as the outcome measure. The cosmic radiation dose was calculated with the survey method (I). The dose received over the last ten years prior the reference year (diagnosis year of the case and the same year for her controls) was excluded to allow for the induction period of 10 years. The association between breast cancer and cumulative radiation dose was analysed per 10 mSv increment in dose, assuming a linear dose-response relation without a threshold. As older women have a longer recall period and thus, possibly report past exposures with a different degree of accuracy, the modifying effect of age was assessed by dividing study subjects into two groups (50 years or younger and over 50 years) and examining the effect of occupational dose, sleep disturbances, and menstrual disturbances on breast cancer by the age group.

(III) The average annual cosmic radiation dose *(i)* was calculated by multiplying the radiation dose ($E_{ijk}$) received from a single flight with the number of the cabin crew on board ($x_{ijk}$) to obtain the collective dose that the cabin crew members received during that single flight. This dose was multiplied by the frequency of the flights on the same route within that particular year ($l_i$) to obtain the total annual dose on that route. Then, the total annual dose from this route was added up with the other annual doses from all the other routes during that year to obtain the total collective cosmic radiation dose gained by all cabin crew during one year ($\hat{E}_{ci}$). The sum was divided by the number of the cabin crew during that year ($X_i$) to obtain the annual dose for a single member of the cabin crew ($\hat{E}_m$).

$$\hat{E}_{ci} = \sum (E_{ijk} x_{ijk} l_i)$$

$$\hat{E}_m = \frac{\hat{E}_{ci}}{X_i}$$

where
$i$ = year
$j$ = route
$k$ = aircraft

The individual cumulative dose ($\hat{E}_p$) was calculated on the basis of the annual dose and the information on the start ($i_0$) and the end year of the employment ($i_n$). The cumulative dose was calculated for all Finnair cabin crew members who were employed between 1958 and 1997.

$$\hat{E}_p = \sum_{i_0}^{i_n} \hat{E}_{mi}$$

(IV) Risk estimates were obtained for both constitutional and UVR-related behavioral factors from the published meta-analyses for CMM summarizing the research evidence. For each risk factor, a risk factor-specific mean score, i.e., stratified average of the risk estimates, was calculated for both the cabin crew and the reference group. To compare cabin crew and the reference group, an overall mean risk score was calculated combining all the risk factor-specific mean scores to represent the overall risk of skin cancer given the distribution of different exposures. Also overall mean risk scores were calculated combining 1) only the constitutional risk factor-specific scores and 2) only the UVR-behavior related risk factor-specific scores.

In a separate nested case-control analysis, for every skin cancer case among cabin crew all cabin crew members free of skin cancer at the time of the diagnosis of the case and with individual matching on the year of birth and on residential area (Uusimaa district in Finland versus the rest of the country) were selected as controls. The association between skin cancer and cumulative radiation dose was analysed with conditional logistic regression methods per 10 mSv increment in dose, assuming a linear dose-response relationship without a threshold. A multivariable analysis with both estimated cosmic radiation dose and conventional risk factors for skin cancer, i.e., factors related to host and UVR exposure, in the model was used to evaluate the effects of these exposures simultaneously.

All subjects in case-control analysis were assigned a summary risk estimate which was calculated using the risk factor-specific estimates obtained from the meta-analyses. The summary risk estimate was calculated separately both for UVR exposure and constitutional factors. A multivariable analysis with both radiation dose and the summary risk estimates for host factors and UVR behavior was used to evaluate the effects of these exposures simultaneously.

(V) For calculation of cancer incidence, the observed number of cases and person-years at risk were calculated in 5-year age groups and 5-year periods for both genders. The expected number of cases was calculated by multiplying the number of person-years in each stratum by the corresponding national cancer incidence rates. To calculate the SIRs, the observed number of cases was divided by the expected numbers.

A separate case-control analysis among females was utilized in order to study the effect of estimated cosmic radiation dose to breast cancer, skin cancer and leukaemia risks and the effect of jet lag for breast cancer only. For cancer cases among female cabin crew, all cabin crew members without a cancer diagnosis at the time of the diagnosis of the case and with individual matching on the year of birth were selected as controls. A conditional logistic regression analysis was used to assess the possible relations between the factors. In the breast cancer analysis, parity information was added to the model.

# 5 Results

## 5.1 Estimated cosmic radiation exposure of airline cabin crew

The median individual annual radiation dose estimated with the survey method (I) was 3.2 mSv (25% and 75% quartiles 2.0 and 4.2 mSv) among cabin crew. The annual dose rate increases slightly from the 1960s onwards. In the 1960s, the median dose was 0.6 mSv (25% and 75% quartiles 0.3 and 0.8 mSv) per an active work year, in the 1970s 3.3 mSv (25% and 75% quartiles 1.8 and 4.7 mSv), and in the 1980s 3.6 mSv (25% and 75% quartiles 2.5 and 4.6 mSv). When the dose was estimated utilizing the Finnair flight timetables (III), the annual radiation dose increased quite clearly with time, being 0.7 mSv in 1960 and 2.1 mSv in 1995. (Table 6).

**Table 6.** The annual estimated cosmic radiation dose by year and its assessment method among airline cabin crew in Finland.

| Flight timetable method | | Survey method | |
|---|---|---|---|
| Year | mSv* | Year | mSv* (median) |
| 1960 | 0.7 | | |
| 1965 | 1.4 | 1960–1969 | 0.6 |
| 1970 | 1.3 | | |
| 1975 | 1.7 | 1970–1979 | 3.3 |
| 1980 | 1.6 | | |
| 1985 | 2.3 | 1980–1985 | 3.6 |
| 1990 | 1.6 | | |
| 1995 | 2.1 | | |

* milliSievert

With the survey method (I), the median career dose among all cabin crew members was 27.9 mSv (25% and 75% quartiles 11.4 and 47.7 mSv). Among women who had completed their career as a member of cabin crew at the time of the survey, the median career dose was 13.0 mSv (25% and 75% quartiles 2.9 and 38.3 mSv). In the univariate linear regression analysis, the career dose increased with the number of active work years (regression coefficient 3.2, 95% CI: 2.9–3.5, $R^2$ 0.49). When the starting decade of cabin crew work was also included in the model (the multivariate analysis, $R^2$ 0.52), both the number of active work years (the regression coefficient 3.5, 95% CI: 3.2–3.8) and the starting decade of work (regression coefficient 6.0, 95% CI: 3.6–8.4) remained positively associated with the career dose.

With the timetable method (III), the median career dose for those cabin crew members (N = 1 289) whose career lasted at least one year was 20.8 mSv (25% and 75% quartiles 7.3 and 37.0 mSv). This was calculated using the information obtained from Finnair on the start and the end of the career of a cabin crew member. When the annual doses obtained with the flight timetable method were utilized to calculate the career doses only among those (N = 615) who participated the survey (I), the median career dose was 21.5 mSv (25% and 75% quartiles 9.4 and 35.6 mSv). In these latter calculations, self-reported absences from work were taken into account to complement the work history information obtained from Finnair.

## 5.2 Risk of breast cancer among Finnish airline cabin crew

In the univariate (one risk variable in the model) conditional logistic regression analysis, increased odds ratios were observed for family history of breast cancer, alcohol consumption of more than seven units per week, early menarche, number of fertile years, breastfeeding, benign breast disease, smoking, and disruption of sleep rhythm due to flying. Disruption of menstrual cycles due to flying and parity had a protective effect on breast cancer whereas odds ratio for cumulative radiation exposure was close to unity. However, only family history showed borderline statistical significance.

**Table 7.** Odds ratios (OR) and 95% confidence intervals (95% CI) from multivariate conditional logistic regression analysis of breast cancer risk.

| Risk factor | OR* | 95% CI |
|---|---|---|
| *Number of fertile years (per 5 years)* | 1.51 | 0.54 to 4.19 |
| *Parity* | | |
| No children | 1.00 | |
| One child or more | 1.10 | 0.23 to 4.85 |
| *Family history of breast cancer* | | |
| No | 1.00 | |
| Yes | 5.52 | 1.44 to 21.23 |
| *Alcohol consumption* | | |
| 0–7 units per a week | 1.00 | |
| 7.1–28 units per a week | 4.11 | 1.01 to 16.72 |
| *Cumulative radiation dose (per 10 mSv)* | 0.93 | 0.68 to 1.27 |
| *Disruption of sleep rhythm* | | |
| Never or rarely | 1.00 | |
| Sometimes or often | 1.52 | 0.49 to 4.74 |
| *Disruption of menstrual cycle* | | |
| Never or rarely | 1.00 | |
| Sometimes or often | 0.56 | 0.12 to 2.61 |

In the multivariate (several risk variables in the model) analysis, occupational factors and selected non-occupational factors on the basis of strong previous evidence on the relation to breast cancer risk were included into the model (Table 7). Family history of breast cancer and alcohol consumption of more than seven units per a week had the strongest association with breast cancer. Number of fertile years and sleep rhythm disruptions due to flying were positively related to breast cancer, but the results were not statistically significant. Disruption of menstrual cycles due to flying had a statistically non-significant protective effect on breast cancer, whereas the odds ratios for parity and cumulative radiation dose were fairly close to unity.

## 5.3 Risk of skin cancer among Finnish airline cabin crew

The overall mean risk score for skin cancer based on host factors was slightly higher in the reference group (1.44 vs. 1.40, $p < 0.001$) than among the cabin crew. The overall mean risk score based only on the UVR behavioral factors did not differ between the cabin crew and the reference population (1.46 vs. 1.44, $p = 0.13$). The overall mean risk scores, calculated based on all the risk factors, did not differ between the cabin crew and the reference population (1.43 vs. 1.44, $p = 0.24$). In the conditional case-control analysis restricted only to the cabin crew, the estimated cosmic radiation dose was not associated with an increased risk of skin cancer (OR 0.82 per 10 mSv, 95% CI: 0.62–1.10) when adjusted for natural hair colour, natural skin colour, and skin burns in childhood. Including all the host- and UVR-related behavior factors in the model, the OR for cosmic radiation was reduced slightly (OR 0.75, 95% CI: 0.57–1.00). The host factors (OR 1.43, 95% CI: 1.01–2.04) showed statistically significant association with skin cancer, whereas the point estimate for the UVR-related behavior factors (OR 1.52, 95% CI: 0.91–2.52) was statistically non-significant.

## 5.4 Cancer incidence among Nordic aircraft cabin crew

In the cohort analysis, the SIR of all cancers was 1.16 (95% CI: 1.06–1.25) in women and 1.39 (95% CI: 1.17–1.62) in men. The SIR's for cancer sites for which the estimate is more than 1.0 are given in Table 8 for women and Table 9 for men. The statistically significant results are bolded.

In the case-control analysis, the estimated cosmic radiation dose was not statistically significantly associated to any cancer under study. Jet lag, i.e., the number of flights passing six or more time zones, was not related to breast cancer (OR 0.92, 95% CI: 0.77–1.11 per 100 flights passing six or more time zones) when the analysis was adjusted for parity (parous vs. nulliparous).

The results were unchanged with or without allowing a ten year lag and whether the analysis was adjusted with the age at first birth or not.

**Table 8.** Observed and expected numbers of cases and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) among female airline cabin crew. Only sites where the estimated SIR > 1.0 are shown.

| Primary site (ICD-7 code) | Observed | Expected | SIR* | 95% CI |
|---|---|---|---|---|
| **All sites (140–208)** [a] | **577** | **499.2** | **1.16** | **1.06–1.25** |
| Oesophagus (150) | 3 | 1.2 | 2.49 | 0.50–7.28 |
| Rectum (154) | 14 | 12.6 | 1.11 | 0.61–1.87 |
| Gallbladder (155.1) | 3 | 2.2 | 1.34 | 0.27–3.92 |
| Pancreas (157) | 8 | 6.9 | 1.17 | 0.50–2.30 |
| **Breast (170)** | **263** | **175.9** | **1.50** | **1.32–1.69** |
| Bladder (181) | 8 | 6.4 | 1.25 | 0.54–2.47 |
| **Skin melanoma (190)** | **59** | **31.9** | **1.85** | **1.41–2.38** |
| *head and neck (190.0–4)* [b] | *4* | *2.5* | *1.60* | *0.43–4.10* |
| ***trunk (190.5)*** [b] | ***28*** | ***10.3*** | ***2.73*** | ***1.81–3.95*** |
| ***limbs (190.6–7)*** [b] | ***27*** | ***17.4*** | ***1.55*** | ***1.02–2.25*** |
| Other skin (191) [a] | 13 | 7.6 | 1.71 | 0.91–2.92 |
| Thyroid (194) | 17 | 16.9 | 1.01 | 0.58–1.61 |
| Bone (196) | 3 | 1.3 | 2.39 | 0.48–6.98 |
| Hodgkin lymphoma (201) | 4 | 3.6 | 1.12 | 0.30–2.88 |
| **Leukaemia (204–208)** | **14** | **7.4** | **1.89** | **1.03–3.17** |
| *chronic lymphatic (CLL)* [b] | *3* | *1.7* | *1.80* | *0.36–5.25* |
| *non-CLL* [b] | *11* | *5.7* | *1.92* | *0.96–3.43* |
| *acute myeloid (AML)* [b] | *6* | *3.3* | *1.83* | *0.67–3.98* |
| *Not included in the above:* | | | | |
| **Basal cell carcinoma of the skin** [c] | **56** | **23.4** | **2.39** | **1.80–3.10** |

[a] Excludes basal cell carcinoma
[b] Subcategory also included in the main category
[c] Only Finland (1967–2005) and Iceland (1955–2001)
* Standardized incidence ratio

**Table 9.** Observed and expected numbers of cases and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) among male airline cabin crew. Only sites where the estimated SIR > 1.0 are shown.

| Primary site (ICD-7 code) | Observed | Expected | SIR* | 95% CI |
|---|---|---|---|---|
| **All sites (140–208)** [a] | **152** | **109.7** | **1.39** | **1.17–1.62** |
| Mouth (143–144) | 3 | 1.0 | 2.90 | 0.58–8.47 |
| **Pharynx (145–149)** | **8** | **2.6** | **3.12** | **1.34–6.15** |
| Oesophagus (150) | 2 | 1.3 | 1.56 | 0.17–5.63 |
| Colon (153) | 12 | 8.0 | 1.50 | 0.77–2.61 |
| Liver (155.0) | 3 | 1.0 | 3.11 | 0.63–9.09 |
| **Larynx (161)** | **6** | **1.3** | **4.72** | **1.72–10.3** |
| Prostate (177) | 24 | 21.7 | 1.11 | 0.71–1.65 |
| **Skin melanoma (190)** | **18** | **6.0** | **3.00** | **1.78–4.74** |
| *head and neck (190.0–4)* [b] | *1* | *0.7* | *1.44* | *0.02–8.01* |
| ***trunk (190.5)*** [b] | ***15*** | ***3.3*** | ***4.50*** | ***2.52–7.42*** |
| **Other skin (191)** [a] | **10** | **4.1** | **2.47** | **1.18–4.53** |
| **Kaposi sarcoma** | **10** | **0.1** | **86.0** | **41.2–158** |
| Brain, nervous system (193) | 6 | 4.7 | 1.28 | 0.47–2.79 |
| Unspecified sites (199) | 4 | 3.2 | 1.26 | 0.34–3.23 |
| Non-Hodgkin lymphoma (200, 202) | 8 | 4.2 | 1.89 | 0.81–3.72 |
| Leukaemia (204–208) | 4 | 2.6 | 1.56 | 0.42–3.99 |
| *non-CLL* [b] | *3* | *1.5* | *1.96* | *0.39–5.74* |
| *acute myeloid (AML)* [b] | *2* | *0.9* | *2.25* | *0.25–8.12* |
| *Not included in the above:* Basal cell carcinoma of the skin [c] | 2 | 1.4 | 1.39 | 0.16–5.02 |

[a] Excludes basal cell carcinoma.
[b] Subcategory also included in the main category.
[c] Only Finland (1967–2005) and Iceland (1955–2001).
* Standardized incidence ratio

# 6 Discussion

## 6.1 Methodological considerations

### 6.1.1 Cosmic radiation and circadian disruption estimation methods

In epidemiology, valid and reliable exposure assessment of risk factors, confounding factors and modifiers is a prerequisite to achieve valid results on the relation of the outcome of interest and its potential determinants. This is important especially when dose-response relations are studied. In exposure assessment, several aspects and challenges need to be taken into account, for example, low exposure levels, many confounding factors, and timing of the exposure. (Kauppinen 1994)

In the present thesis, two different methods were developed for retrospective assessment of individual cosmic radiation dose. Prior to these studies, there were only rather crude exposure assessment methods available for individual cosmic radiation dose and thus, dose-responses could not be evaluated in previous epidemiological studies. In case no flight records are available for cabin crew, the only sources of information for individual flight history are the cabin crew members themselves. Estimating doses using only the information from the timetables results in a more aggregate level of exposure estimation. Both of these available sources, cabin crew members themselves and flight timetables, have been utilized in the present study. Career doses calculated based on survey method in this work must be interpreted with caution, since the study period did not cover all the years Finnair has operated but only the years from 1960 to 1989. However, flights before 1960 were frequently flown at low altitudes and short haul flights resulted only in minimal cosmic radiation exposure. The doses received by the cabin crew were actually highest from the 1970s and 1980s onwards, with the introduction of the jet aircraft with higher flight altitudes and a higher frequency of long-haul flights. In addition, the survey method was initially developed for the breast cancer study where the doses after 1990 were not needed to allow a 10-year lag time prior to cancer diagnosis for the cases and the corresponding reference date for controls.

There are limitations in collecting questionnaire data. It requires more resources than the collection of exposure information from flight timetables, at least, if the timetables are computerized. At Finnair, the tables were available in paper form and they had to be first entered in computer.

In the survey, the participation activity proportion was only 52% which might have caused a systematic error, i.e., a selection bias in case the flight histories were different between the participants and nonparticipants (Armstrong, White & Saracci 1992). The participating cabin crew members' own estimation on the number of past flights had to be relied on in dose estimation and this dependence may have led to recall bias. Recall bias, if not related to the outcome status, can lead to non-differential exposure misclassification which generally dilutes the true association between exposure and outcome (Flegal, Brownie & Haas 1986). The cabin crew in the survey reported that it was very difficult to remember the past number of flights and route types. These pitfalls were avoided with the flight timetable method since no survey data were needed. However, as the flight timetable method assumes a similar flight schedule for every cabin crew member at work during the same time period, the calculated dose is not a truly individual one and the cumulative career dose depends mainly on the timing and the length of the career. This may lead to misclassification of the doses if the route distribution of the cabin crew is more heterogeneous. This is also known as the "Classical" random error which attenuates the dose-response and result in underestimation of risk coefficients (Armstrong, Oakes 1982). Based on the narrative information from the Finnair staff, it might be possible that the flight distribution depends on the seniority, i.e., the more experienced personnel have a greater flexibility of selecting the routes and they prefer the long-haul flights. Thus, the cumulative dose calculated with the flight timetable method may result in overestimated values for those with a short career and, analogously, underestimated values for those with a long career.

In the survey method, the use of one to four representative routes per flight category simplified the exposure assessment considerably. It would be laborious to collect information on all actual flights, at least when the flight timetables are in a paper form. The more flights are used in the dose assessment, the greater is the precision. Also in the flight timetable method, routes and radiation doses were collected for every fifth year. At Finnair, the route distribution did not change very much within a 5-year period but for other flight companies shorter intervals might have to be used.

With the flight timetable method, the total number of cabin crew members employed during various times as well as the number of crew on board had to be estimated from different sources. The number of crew on board depends mainly on the route and the craft type. One of the sources was the cabin crew and the pilots themselves as well as the other staff at Finnair and SLSY with a possibility of a recall bias.

As the 11-year cycle of solar activity affects the dose rate, the average value of each decade's solar activity was used in calculations with the survey method. In the flight timetable method, the yearly variation in the heliocentric potential was not taken into account since a 5-year period for dose estimation was used. A sensitivity analysis showed that this simplification might misclassify the dose estimates but the magnitude of the misclassification is minor.

In the Nordic airline cabin crew incidence study (V) jet lag was assessed from flight timetables when the number of flights crossed at least six time zones. This method assumes a similar flight distribution for all cabin crew members at work during the same time period and thus there is a possibility of misclassification of the number of jet lags if the flight distribution varies among the personnel. Further, this method involves a strong simplification of the aspects related to circadian disruption, but at the same time, it was the only assessment method feasible without individual flight histories. There are no standard methods available for quantification of the impact of circadian disruption. A study conducted among cabin crew in the U.S. demonstrated that the number of time zones crossed is a useful indicator of both melatonin and sleep desynchronation (Grajewski et al. 2003). However, using the number of time zones crossed has some limitations; for example, it does not take into account the work at night. In the Finnish case-control study of breast cancer (II), the circadian disruption was assessed by asking the cabin crew whether they had experienced any sleep or menstrual cycle disruptions related to the long flights, which may have led to bias.

### 6.1.2 Breast and skin cancer studies

A main limitation in the studies of breast (II) and skin cancer (IV) in Finland was the small number of cases which restricts the statistical power. However, as the source population included all eligible female airline cabin crew in Finland, this constraint could not be eliminated. Since all the cases were identified by a record linkage from the Finnish Cancer Registry with a high completeness of registration, the disease status ascertainment in this study is high. However, due to the reduced sensitivity of disease status ascertainment for the BCC, the possible undercount of cases might have resulted in lower precision (Brenner, Savitz 1990).

In the breast cancer and skin cancer surveys, 52% and 56% respectively, the response proportion among cabin crew was not satisfactory. Even if there was information about the study in a Finnair cabin crew job bulletin before and during the study and reminder letters for the questionnaire non-respondents were sent, their effect in increasing the response proportion was not adequate. Low participation can lead to selection bias in case the exposure distribution differs between the participants and non-participants. Such bias may distort the estimates towards either direction. In the breast cancer study, the young cabin crew had a higher participation activity than the older members of the crew. The differences by age were studied by dividing the study subjects into two groups (50 years of age or younger and over 50 years of age) after which the effect of occupational exposures on breast cancer by age group was examined. No clear effect modification of age on the risk of breast cancer was observed. This suggested that the lower participation activity among the older crew members did not distort the main results. In the skin cancer study, the non-participation was not associated with age.

In the skin cancer study (IV), a sample of women was selected as a reference group from the Finnish population by the Finnish Population Register Center in order to compare the risk factors of skin cancer between the cabin crew and general population. Of the reference group, 1 000 were selected from the Uusimaa district and 1 000 from the rest of Finland in order to take into account regional differences in skin cancer incidence. As the majority of the cabin crew lived in the Uusimaa district (approximately 86%), the distribution of the reference women by region differed from that of the cabin crew. This, however, did not affect the results since the risk estimates were weighted based on the area distribution of the cabin crew.

Case-control studies are suitable for studying rare diseases with long induction periods such as cancer. Case-control studies also allow the assessment of contribution of several exposures to the risk of disease under study. The selection of appropriate controls is a crucial issue in case-control studies, i.e., the controls must come from the same source population as the cases. In the present study, both the case-control analyses were conducted nested in the airline cabin crew population, i.e., the controls were selected among the cabin crew. This ensures that the cases and controls are drawn from the same source population. The breast and skin cancer studies were both analyzed as matched case-control studies. Individual matching on the year of birth was used because age is a strong determinant of cancer risk and also correlated with the cumulative radiation dose, i.e., age is a confounding factor. In the skin cancer study, the calculated cosmic radiation dose was only moderately associated with the year of first employment. Hence, there was no concern of overmatching even if the year of birth notably defined the year of first employment.

Case-control studies are prone to information bias in exposure assessment. This is due to the fact that subjects with the disease (cases) more likely ponder the possible causes of the illness, which leads to more complete reporting. There is also a possibility of overreporting, i.e., the cases give answers that fit to their believes on the causes of their disease. The cases might also be more likely to be aware of relatives' diagnosis of similar disease. Such bias leads to higher sensitivity of exposure assessment among cases and overestimation of the risk estimates (Elwood 1998). The recall bias can be minimized by keeping the study subjects unaware of the hypothesis of the study. In surveys conducted in this work, the subjects were aware of the aims of the specific risk factor assessment in the breast (II) and skin (IV) cancer studies.

In the breast and skin cancer case-control studies, only the prevalent cases at the time of the studies were included into the analysis. It is possible that the prevalent cases do not represent all cases but as the exposure information was collected with self-administered questionnaires, all incident cases, for example, those who were deceased could not be included into the study. Information on all the potential confounders could not have been obtained with any other method.

### 6.1.3 Nordic cancer study

The Nordic study (V) can be considered as having the highest potential worldwide to evaluate cancer incidence among airline cabin crew. This is because the study cohort included most of the cabin crew ever certified in the four Nordic countries and because only a few areas outside the Nordic countries have population-based registration of cancer with several decades of registration. The use of systematically registered cancer incidence data, instead of mortality data, avoids bias caused by better cancer survival between a population with a relatively high educational level such as the airline cabin crew and the reference population (Pokhrel et al. 2010). Furthermore, the use of incident cancers as outcome allows evaluation of risks for cancers that are rarely lethal, such as the NMSC.

To conclude, these methodological limitations discussed above have to be considered when interpreting the results of this thesis. However, the present study provides unique information on cosmic radiation dose estimation among the cabin crew. Other novelties of the present study include an attempt to quantify the effects of low-dose of protracted neutron exposure on cancer incidence combined with the information on potential confounders. Further, due to the accurate population and cancer registration systems in all Nordic countries and the large study cohort, the incidence study provides the most reliable setting for cancer incidence estimation.

## 6.2 Risk of cancer among the Nordic airline cabin crews

In the follow-up study of airline cabin crew in the four Nordic countries, the overall cancer risk was slightly elevated for women, but not statistically significant, whereas for men, the elevated risk of all cancers combined was statistically significant. Cabin crew undergoes frequent medical checkups, enhancing the possibility of early detection of cancer, compared to general population. However, as the incidence of prostate and thyroid cancer, where the diagnostic activity plays a major role, were not different from the general population, it is not likely that the detection bias solely explains the results.

It can be concluded that there is convincing evidence on somewhat elevated overall cancer risk among the cabin crew compared to the general population. The risk estimates for separate cancer sites were similar to previous national results. The highest risks were detected in BCC for women and Kaposi sarcoma for men. The largest number of excess cases was in breast cancer. There were 87 cases more than the 176 cases that would have been expected based on the average national cancer incidence rates.

## 6.3 Cosmic radiation exposure

The annual cosmic radiation doses for cabin crew calculated with the survey method and the flight timetable method were of the similar magnitude. However, the mean annual dose calculated with the survey method was slightly lower than the annual dose estimated with the flight timetable method in the 1960s. From the 1970s onwards, the yearly dose estimates calculated with the survey method were almost twice as high as those estimated with the flight timetable method. Nonetheless, the annual doses calculated with both methods increased with calendar period reflecting the increasing proportion of high-altitude and long-haul flights. The survey method yielded higher career doses compared to the flight timetable method, due to the higher annual dose estimates obtained with the survey method.

One explanation for the survey method resulting higher annual estimates than the flight timetable method is that the survey participants overestimated their number of flights, i.e., the information bias. Another possible explanation is that those with the highest exposure were more likely to participate in the survey, i.e., the selection bias. In a previous study conducted among 45 female cabin crew members in the United States, overestimation in the self-reported flight hours compared to the flight hours obtained from the company records was found (Grajewski, Atkins & Whelan 2004). For example, for cabin crew flying in the Seattle domicile, the crew reported on average 906 block hours per year, whereas the mean number of block hours recorded by the company was 629.

The doses calculated with these two different methods are not straightforwardly comparable because different softwares were used for dose calculation. EPCARD, which was used with the flight timetable method, gives approximately 30% higher doses than the CARI-6 used with the survey method for the northern routes. For the southern routes, the situation is the opposite, as the EPCARD gives approximately 20% lower doses. As most of the Finnair routes were northern, approximately 30% higher doses calculated would be expected with the flight timetable method compared to the survey method.

However, in this study, the flight timetable method gave lower annual dose estimates, and therefore, the differences between the estimated doses could not be due to the software. Nonetheless, in order to obtain comparable doses, the same software package should have been used in the dose calculation. Reliability and validity of cosmic radiation calculation software is out of the scope of this present study. It should be noted that the selection of appropriate weighting factor for the neutron dose estimates converted to equivalent doses is important as the high-LET neutrons contribute a great proportion of the total equivalent dose of cosmic radiation (National Research Council . Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation 2006).

Few previous studies have estimated the cosmic radiation dose for cabin crew without company records on flight frequencies. In a study of airline cabin crew formerly working at Pan Am from the year 1952 onwards, questionnaire data were collected in order to estimate the occupational cosmic radiation dose (Anderson et al. 2011). Similar to this study, they also had information on the start and end of employment from the company records and the number of flight hours was obtained with the questionnaire. The route distribution that a cabin crew member flew, was inferred based on the working domicile (Hong Kong, Honolulu, London, Los Angeles, Miami, New York, San Francisco, Seattle, or Washington DC) reported by the cabin crew. The estimated mean cosmic radiation dose was 2.5 +/– 1.0 mSv per a year and the mean career dose was 30 mSv, that are comparable with the doses estimated with the survey method (I) in the present study.

Airlines in the United States usually maintain flight history records for periods ranging from one to five years. Utilizing this information and the CARI software, Grajewski and co-workers calculated the annual doses for 44 female cabin crew in the 1990s to range from 1.5 to 1.7 mSv (Grajewski et al. 2002). These doses were very similar to the results of this study obtained with the flight timetable method.

To conclude, the cosmic radiation doses seem to be higher if they are estimated based on the self-reported number of past flights, whereas utilizing flight history records provided by companies result in lower cosmic radiation estimates. With both methods, the calculated median annual doses fall well below the annual maximum limit of 6 mSv defined in Finland by the Radiation Act. The present study shows that even if the quantification of individual occupational cosmic radiation doses is complicated, it is feasible. Therefore, surrogates for doses, for example, the number of working years should not be used in further studies on the relation of cosmic radiation exposure and possible health effects among cabin crew.

## 6.4 Potential explanations for increased cancer incidence

### 6.4.1 Breast cancer

In the present study, no definite explanation for the excess risk of breast cancer was found. In the case-control study conducted among the Finnish airline cabin crew (II), self-reported family history of breast cancer, alcohol consumption, and number of fertile years were the risk factors most strongly associated with breast cancer. As breast cancer is previously known to be strongly related to hormones and reproductive factors, it is plausible that the increased risk of breast cancer among cabin crew could also be due to these factors. Among the Finnish general female population, the total fertility rate, i.e., the number of live birth during the fertile years, was 1.81 in 1995 (Artama M. at National Institute of Health and Welfare, personal communication, June 29, 2012), whereas in the Finnish cabin crew cohort it was 1.29. As reproductive and hormonal factors are strongly correlated with each other, i.e., age at menarche, number of births, number of fertile years, etc., the contribution of a single factor to the breast cancer risk is difficult to study.

Alcohol consumption is also a known risk factor, with a risk increase starting from a one daily dose (Colditz, Baer & Tamimi 2006). A recent review showed that consumption of low doses of alcohol, less than one drink per day, is related to increased risk of oral, pharyngeal and esophageal squamous cell cancer (Pelucchi et al. 2011). However, as there was no increased risk of these cancers seen among female cabin crew in the study of the four Nordic countries (IV), it suggests alcohol consumption is not a positive confounder for breast cancer.

Genetic susceptibility is a possible explanation for the increased incidence of breast cancer especially in early onset of the disease. However, as the majority of breast cancer cases among cabin crew were diagnosed above the age of 40 (in II and IV), heredity is not a probable explanation. Further, it is not realistic to assume, that genetical susceptibility of breast cancer and occupation are associated with each other.

The relation between breast cancer and circadian disruption, i.e., jet lag, remained inconclusive in the present study. However, all the metrics used on jet lag, i.e., assessed either from flight timetables as the number of flights passing six or more time zones (IV) or with a questionnaire on experienced symptoms related to jet lag (II), were rather crude or subject to non-differential or differential bias. Thus, it would be essential to have precise estimates on jet lag and also on night shift work in further studies.

None of the analyses showed any relation between estimated cosmic radiation dose and breast cancer. The highest credible values of risk, estimated as the upper limit of 95% confidence interval of OR, were very similar in the Finnish case-control study (II) and in the case-control analysis of the four Nordic countries (IV), i.e., 27% and 20% per 10 mSv, respectively. Even though cosmic radiation estimation methods used in this study were more valid compared to the most previous studies in this field, they were still subject to limitations discussed in the section of methodological considerations of this thesis. Thus, there still remains a need for more precise estimation methods, preferably based on company records on actual flights for the whole career. It need to be kept in mind that the lack of statistically significant findings cannot be interpreted as evidence against relation between cosmic radiation and breast cancer. It can indicate that the study has not enough statistical power to reveal the relations. Thus, the optimal approach would be to apply the more precise cosmic radiation exposure estimates, combined with the detailed information on the potential confounders, to a large cabin crew population to obtain the sufficient power.

Health risks among the cabin crew due to flying might be applicable to frequent flyers as well. Those who travel as passengers in an aircraft are also subject to cosmic radiation exposure and jet lag, even though to a lesser extent than cabin crew. However, frequent flyers were not in the scope of the present study.

#### 6.4.2 Melanoma and non-melanoma skin cancer

No explanation for the increased incidence of skin cancer among cabin crew was found in this study. There were no differences in risk factors between the Finnish female cabin crew and the general female population that could explain the incidence. In the nested case-control study among the Finnish female cabin crew (IV), the host factors were associated with skin cancers, which was expected since skin cancers commonly occur to those susceptible to UVR damage, for example, people with fair skin. Factors related to UVR exposure were also associated with skin cancer in the case control analysis but the results were not statistically significant.

Even though the present study could not reveal a statistically significant relation between UVR exposure and skin cancers, the exposure to UVR is the most likely explanation for the increased risk of skin cancers since up to 90% of all skin cancers is thought to be attributable to UVR exposure (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, World Health Organization & International Agency for Research on Cancer 1992a). As there is no increased ambient UVR exposure in the aircraft cabin, the risk of skin cancers could not be due to occupational UVR exposure. Thus, the possible excess exposure to UVR must occur during leisure time or the time partly related to work, e.g., waiting for the next work shift in a sun resort. In the Finnish study

(IV), the cabin crew did report more use of tanning devices than the reference population. Also intermittent UVR exposure was somewhat more common the among cabin crew than the reference population and this might indicate that the days spent in sunny resorts, possibly due to work, increases their total UVR exposure. However, no difference in the overall UVR exposure between the cabin crew and reference population was found. A previous Icelandic study reported similar results, i.e., no major differences in the UVR exposure between the Icelandic aircrew and the population sample were found. The Icelandic cabin crew spent more time in sun resorts and also used more sunscreen than the general population (Rafnsson et al. 2003a).

The estimated cosmic radiation dose was not associated with the risk of skin cancers in the present study. The highest plausible risk of skin cancer for cosmic radiation can be estimated as the upper limit of the OR's confidence interval (1.09) in the Finnish case-control study (IV), i.e., 9% per 10 mSv. The present study is the first assessing the contribution of the cosmic radiation and UVR to the skin cancer risk among cabin crew. Among male pilots in the U.S., a web survey was conducted in order to investigate the potential association of the occupational and lifestyle factors as well as skin type with NMSC (Nicholas, Swearingen & Kilmer 2009). The results showed that among pilots whose flying career before the skin cancer diagnosis was shorter than 20 years, skin type, sunburns in childhood and family history of NMSC were factors associated with the increased risk, whereas sunscreen use in free time and family history of CMM were protective. Among those pilots with a career length of 20 years or longer, childhood sunburns, family history and flight time at high latitude were positively correlated to NMSC. The study was limited by low response proportion (19%) but the results suggest that exposure to cosmic radiation, i.e., flying at higher latitude with greater cosmic radiation doses compared to lower latitude flights, might be associated with NMSC.

### 6.4.3 Other cancer types

In the study of cabin crew cancer incidence in the four Nordic countries (V), excesses of leukemia, Kaposi sarcoma, laryngeal and pharyngeal cancers were observed. Leukemia (non-CLL) is a cancer type suitable as an indicator of health effects of ionizing radiation since it has high relative excess risk and few confounders. Excess incidence of leukemia has earlier been observed among different populations of medical workers (Linet et al. 2010). In a cohort of Chinese medical diagnostic x-ray workers, the RR of leukemia was 2.4 among those who were employed before 1970 (Wang et al. 2002). The average cumulative dose was estimated to be 551 mGy, i.e., notably higher than average cumulative doses calculated for the Nordic cabin crew where over 90% of cumulative doses were below 35 mSv. However, as approximately 40% to 80% of cosmic radiation consists of neutrons, which are more effective in inducing biological damage than x-radiation, the studies among medical workers and cabin crew cannot be straightforwardly compared. There are practically no studies available on the health effects of external exposure to neutron radiation. In the present study, there was not enough statistical power to find out statistically significant results of the effect on cosmic radiation dose on leukemia, mainly due to the fact that the doses were low. There was an indication of an increased risk of leukemia at the highest dose level of cosmic radiation exposure. No other factors than radiation exposure are evident in explaining the excess risk.

There was a significant excess of Kaposi sarcoma observed among male cabin crew. Human herpesvirus 8 is the necessary cause for Kaposi sarcoma (Mueller et al. 2006) and commonly seen in AIDS patients with impaired immunodeficiency. Kaposi sarcoma is not related to any work exposure.

Alcohol consumption has been consistently linked to laryngeal and pharyngeal cancer (Marshall, Freudenheim 2006). IARC has concluded that alcohol consumption causes cancers of larynx and pharynx (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2012a). It is also possible that these cancers among cabin crew are associated with HIV infection since excess risk of the mouth, pharynx, and liver have been demonstrated among persons with human immunodeficiency virus (HIV) (Clifford et al. 2005). It is not likely that cancers of the larynx and pharynx among cabin crew are related to exposures at work.

# 7 Conclusions

- The present study introduces two different methods for individual cosmic radiation exposure assessment retrospectively for airline cabin crew. The selection of which approach to use in further studies, depends on the feasibility of the study, i.e., can the survey data be collected or are the flight timetables from the flight company available.
- Neither of the cosmic radiation assessment methods developed can be considered as a golden standard as they are prone to bias inherent to the methods. However, they provide improved means for cosmic radiation exposure assessment compared to studies where cruder indicators such as the number of work years for occupational exposure were used. Thus, the methods developed in this study are recommended to be used in further studies instead of cruder indicators.
- There is convincing evidence for a slightly elevated overall cancer risk among airline cabin crew in the Nordic countries as compared to the general population. Of specific cancer types, the highest estimates are observed for breast cancer, cutaneous malignant melanoma, non-melanoma skin cancers, leukaemia, Kaposi sarcoma, laryngeal and pharyngeal cancer.
- This work could not provide an explanation for the elevated breast cancer incidence among the airline cabin crew. Breast cancer is known to be most strongly related to hormonal factors and, thus, the plausible explanation for the increased risk of breast cancer also among cabin crew could be these factors. The contribution of occupational exposures to the risk remained unclear.
- The present study could not find out the causes for the elevated skin cancer incidence among the cabin crew. Exposure to UVR is the most likely explanation for the increased risk of skin cancers, but there is no evidence on excessive exposure of the airline cabin crew to UVR as compared to the general population.
- Finding a cause for the increased incidence of cancer among the cabin crew warrants further studies. A prospective follow-up study in a large cohort with actual flight history records combined with detailed information on potential confounders, including more precise UVR exposure estimation, would be the optimal study approach.
- This work did not show any relation between estimated occupational exposure to cosmic radiation and cancer risk. Thus, there is no need to neither depart from the current occupational radiation protection principles nor from the exposure limitations of cosmic radiation of the airline cabin crew.

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**KOJO K, ASPHOLM R, AUVINEN A (2004): Occupational radiation dose estimation for finnish aircraft cabin attendants. Scandinavian Journal of Work, Environment & Health 30: 157–163.**

*Original article*

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# Occupational radiation dose estimation for Finnish cabin attendants

*by Katja Kojo, MSc,[1,2] Rafael Aspholm, MD,[3] Anssi Auvinen, MD[1,2]*

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**Objectives** The objective of this study was to develop a method for assessing dose radiation of the basis of individual flight history and to estimate whether this method is applicable for cabin attendants without flight log data.

**Methods** Questionnaire data was collected to determine attendants' flight history covering up to three decades. Finnair timetables and an expert panel of pilots were used to determine one to four representative flights in five route categories. The cumulative career and annual doses were calculated on the basis of the flight histories and route-specific exposure data.

**Results** Questionnaire data were obtained from 544 flight attendants. The mean number of active work-years was 10.5 (range 0–30) years, and the mean cosmic radiation dose was 3.2 (range 0–9.5) mSv per active work-year. The mean cumulative career dose for all the cabin attendants was 34.0 (range 0–156.8) mSv.

**Conclusions** If no flight log data are available, survey data are needed for individual dose estimation when possible radiation effects on cabin crew are evaluated in epidemiologic studies. This method provides a crude procedure for assessing cosmic radiation exposure among attendants when survey data are missing.

**Key terms** cabin crew, cosmic radiation, epidemiology, occupational exposure.

The assessment of cosmic radiation exposure became of interest when the International Commission on Radiation Protection (ICRP) recommended that aircrew be classified as radiation workers (1). Aircraft personnel are exposed to cosmic radiation that mainly consists of neutrons, protons, electrons, and photons (2). Quantification of individual cosmic radiation doses is necessary if the potential health effects of such occupational exposure is to be assessed. Several cosmic radiation dose measurements and dose rate assessments for cabin crew and pilots have been performed using various methods (3–13). However, none of them have tried to assess individual dose rates.

Unlike pilots, who have a license for a specific aircraft type with a limited range of routes at a time, Finnair cabin attendants fly a variety of routes and aircraft at any time during their work history. At Finnair, the route distribution depends mainly on seniority. Young and newly graduated cabin attendants fly primarily domestic routes, while more experienced personnel have a wider selection of options and typically prefer to fly European and intercontinental routes. Hence the routes vary both between workers and for a given flight attendant over his or her career. As seniority largely defines the routes, variability over time is more pronounced than variability between workers.

Despite the need for individual dose information in retrospective epidemiologic research, few previous studies have attempted to develop methods applicable to individual exposure assessment. Such methods would be especially important for cabin crews, as most airline companies have not routinely recorded their flight histories.

Neutron dosimetry is more complex than the assessment of gamma radiation, and personal dosimetry systems are inadequate for this purpose. Furthermore, retrospective exposure estimation is not possible with personal portable dosimeters.

For Finnair pilots, information on every flight since 1971 is available in a computerized database. This database contains information on aircraft type, flight route, and block times (ie, time from departure from the gate to the arrival at the gate including taxi time, climb, and descent). For Finnair cabin crews, such information is

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not available for years prior to 1991, and therefore questionnaire data are the only source of information for the number and type of flights. The aims of our study were, first, to develop a method for assessing occupational exposure to cosmic radiation on the basis of individual flight history and, second, to estimate whether this method is applicable also for attendants without survey data. The rationale was to develop an exposure assessment method applicable also to flight attendants without questionnaire information (eg, those who were deceased).

## Participants and methods

Finnair is a Finnish airline company that has been in operation since 1923. It operates a range of short-haul and long-haul routes. In 2001, the Finnair fleet consisted of 60 planes: nine Aerospatiale ATR-72 short-haul turbopropellers (ATR 72), 40 McDonnell Douglas and Airbus medium-haul turbojets (MD-82, MD-83, DC-9, A319, A320, A321), and four McDonnell Douglas long-haul turbojets (MD-11). Seven Boeings (B757) constituted the charter fleet, and these jets have been used in both medium- and long-haul operations. Currently Finnair has approximately 10 000 employees. The company flew approximately 7 million passengers in 2001 [from: About Finnair. Available from: URL: http://www.finnair.com (accessed 22.01.2003)].

We used a self-administered questionnaire to collect information on the monthly number of domestic and European round-trip flights, as well as on destinations in the Far East, North America, and other areas outside Europe (mainly the Canary Islands). This information was collected separately for the 1960s, 1970s, and 1980s (study period). In addition, the first and last dates of active employment were asked, as well as leaves of absence from cabin work. The number of active work-years in the study period was calculated using this reported information. A total of 1041 cabin attendants, who were born before 1960 and had worked for at least 2 years for Finnair, were identified from the files of Finnair and the Finnish Cabin Crew Union. A questionnaire was mailed to all 1041, and a total of 544 cabin attendants returned a completed questionnaire. All the study participants gave their written consent for participation. Any cabin attendants who reported only clerical work for Finnair and no cabin work were excluded.

On the basis of the individual flight histories, a typical flight pattern was constructed by decade on the basis of the number of flights by destination. This group-level estimation was assessed by comparing dose estimates calculated according to the individual questionnaire data (number of flights reported by attendants) with dose estimates calculated using information at the group level (average number of flights to different destinations during a decade). Group-level information on number of flights was obtained using Finnair timetables with the aggregate number of flights to different destinations divided by the average number of flight attendants in a decade.

To complement the questionnaire data, we also collected information on frequency of flights on each route from Finnair's timetables and selected representative routes in each route category (domestic, Europe, outside Europe, North America, and Far East) and each decade (1960s, 1970s, and 1980s). A route was selected if it had both a representative flight time and a relatively large proportion of flight hours in the flight category. We also consulted an expert panel of pilots (consisting of three experienced pilots who had flown a range of different aircraft from the 1950s or 1960s until the 1980s or 1990s) to determine the number of flights, aircraft types, and flight profiles (ascent and descent time, as well as cruising altitudes). One to four routes were selected for each route category and assigned a weighting factor representing the proportion of flights within the route category (table 1). For example, in the 1980s, three representative domestic routes were Helsinki–Kuopio flown with DC9 jets, Helsinki–Turku and Helsinki–Vaasa both flown with ATR turbopropeller aircraft. Approximately 40% of the domestic flights were comparable to the Helsinki–Turku route, providing a weighting factor of 0.4. Approximately 20% of the flights were comparable with the Helsinki–Vaasa flight, giving a weighting factor of 0.2, and for the Helsinki–Kuopio flight the weighting factor was 0.4. These flights were used to represent the entire domestic flight schedule in the 1980s.

The cosmic radiation dose for every route was calculated using CARI-6, a software package developed for this purpose by the United States Federal Aviation Authority (14). The effective dose of galactic cosmic radiation for each route was calculated as a function of altitude, latitude, solar activity (heliocentric potential), and flight time. The CARI-6 effective dose is calculated from the particle fluences (15). As solar activity is a determinant of the dose rate and it varies over time, for simplicity, the average value of each decade's solar activity was used in calculations. The mean solar activity was assigned as 709 MV for the 1960s, 617 MV for the 1970s, and 786 MV for the 1980s. We did not have any empirical measurement data. However, the doses calculated using CARI software were consistent with direct measurements.

The cumulative career dose in the study period was calculated as the sum of the cosmic radiation doses received in all the five flight categories during a career. The annual dose was calculated as the cumulative career dose divided by the number of active work-years.

**Table 1.** Representative routes (destinations from Helsinki airport) of Finnish airline companies by time and route category with the weighting factor, aircraft, flight profile information, dose rate, and dose per round trip flight given.

| Route category | Weighting factor | Aircraft | Ascent time (min) | 1. altitude | | 2. altitude (time, min) | | Descent time (min) | Dose rate (μSv/h) | Dose (μSv) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Feet [a] | Time (min) | Feet [a] | Time (min) | | | |
| Domestic | | | | | | | | | | |
| In 1960s | | | | | | | | | | |
| Helsinki-Oulu | 0.4 | Convair | 15 | 15000 | 35 | · | · | 15 | 0.32 | 0.70 |
| Helsinki-Oulu | 0.5 | Caravelle | 15 | 30000 | 15 | · | · | 15 | 1.87 | 2.80 |
| Helsinki-Turku | 0.1 | Convair | 5 | 5500 | 20 | · | · | 5 | 0.08 | 0.08 |
| In 1970s | | | | | | | | | | |
| Helsinki-Kuopio | 0.5 | DC9 | 10 | 24500 | 15 | · | · | 10 | 1.17 | 1.36 |
| Helsinki-Turku | 0.4 | Convair | 5 | 5500 | 20 | · | · | 5 | 0.08 | 0.08 |
| Helsinki-Oulu | 0.1 | Caravelle | 15 | 30000 | 15 | · | · | 15 | 1.73 | 2.80 |
| In 1980s | | | | | | | | | | |
| Helsinki-Kuopio | 0.4 | DC9 | 10 | 24500 | 15 | · | · | 10 | 1.08 | 1.26 |
| Helsinki-Turku | 0.4 | ATR | 10 | 7500 | 10 | · | · | 5 | 0.09 | 0.07 |
| Helsinki-Vaasa | 0.2 | ATR | 10 | 7500 | 20 | · | · | 5 | 0.10 | 0.11 |
| Europe | | | | | | | | | | |
| In 1960s | | | | | | | | | | |
| Helsinki-Stockholm (Arlanda) | 0.4 | Convair | 15 | 11500 | 35 | · | · | 15 | 0.18 | 0.40 |
| Helsinki-Copenhagen (Kastrup) | 0.25 | Caravelle | 20 | 33000 | 45 | · | · | 15 | 3.15 | 8.40 |
| Helsinki-Stockholm (Arlanda) | 0.25 | Caravelle | 15 | 28000 | 10 | · | · | 15 | 1.29 | 1.72 |
| Helsinki-Frankfurt (Main) | 0.1 | Caravelle | 20 | 33000 | 100 | · | · | 15 | 3.60 | 16.20 |
| In 1970s | | | | | | | | | | |
| Helsinki-London (Heathrow) | 0.6 | Caravelle | 20 | 34000 | 130 | · | · | 20 | 4.24 | 24.00 |
| Helsinki-Stockholm (Arlanda) | 0.1 | Convair | 15 | 11500 | 35 | · | · | 15 | 0.19 | 0.42 |
| Helsinki-Frankfurt (Main) | 0.3 | Caravelle | 20 | 33000 | 100 | · | · | 15 | 3.73 | 16.80 |
| In 1980s | | | | | | | | | | |
| Helsinki-London (Heathrow) | 0.4 | DC9 | 20 | 34000 | 130 | · | · | 20 | 3.92 | 22.20 |
| Helsinki-Hamburg | 0.3 | DC9 | 15 | 33000 | 60 | · | · | 15 | 3.33 | 10.00 |
| Helsinki-Stockholm (Arlanda) | 0.2 | DC9 | 15 | 33000 | 15 | · | · | 15 | 2.27 | 3.40 |
| Helsinki-Copenhagen (Kastrup) | 0.1 | DC10 | 20 | 34000 | 45 | · | · | 20 | 3.18 | 9.00 |
| Other European | | | | | | | | | | |
| In 1970s | | | | | | | | | | |
| Helsinki-Las Palmas (Gran Canaria) | 1.0 | DC8 | 20 | 34000 | 295 | · | · | 25 | 3.58 | 40.60 |
| In 1980s | | | | | | | | | | |
| Helsinki-Las Palmas (Gran Canaria) | 1.0 | DC10 | 20 | 34000 | 300 | · | · | 20 | 3.46 | 39.20 |
| North America | | | | | | | | | | |
| In 1970s | | | | | | | | | | |
| Helsinki-NY (KJFK) | 0.8 | DC10 | 20 | 31000 | 185 | 35000 | 210 | 30 | 4.65 | 69.00 |
| Helsinki-Montreal | 0.2 | DC10 | 20 | 33000 | 395 | · | · | 20 | 4.69 | 68.00 |
| In 1980s | | | | | | | | | | |
| Helsinki-NY (KJFK) | 0.7 | DC10 | 20 | 31000 | 185 | 35000 | 210 | 30 | 4.26 | 63.20 |
| Helsinki-Montreal | 0.3 | DC10 | 20 | 33000 | 395 | · | · | 20 | 4.30 | 62.20 |
| Far East | | | | | | | | | | |
| In 1970s | | | | | | | | | | |
| Helsinki-Bangkok [b] | 1.0 | DC8 | 20 | 33000 | 560 | · | · | 20 | 2.95 | 59.00 |
| In 1980s | | | | | | | | | | |
| Helsinki-Bangkok | 0.5 | DC8 | 20 | 28000 | 240 | 33000 | 310 | 20 | 2.28 | 44.80 |
| Helsinki-Tokyo (New Tokyo) [c] | 0.5 | DC10 | 25 | 29000 | 515 | 33000 | 250 | 20 | 3.19 | 86.00 |

[a] 1 foot = 0.3048 meters. [b] Via Tashkent. [c] Polar route.

The individual career dose was calculated as the sum of typical radiation doses of different periods and route types as follows:

$$\sum_{i=1960}^{1980} 12 n_i N_i (Dom_i + Eur_i + OutEur_i + NA_i + FarE_i)$$

where $n_i$ represents the attendant's reported monthly number of round trip flights (in a given decade i). $n_i$ was multiplied by 12 in order to obtain the yearly number of flights. $N_i$ stands for the attendant's reported number of active workyears during decade *i*. Explanations for the other symbols in the equation are given in table 2.



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**Table 2.** Radiation doses and number of flight attendants' reported flights in a month by decade and route category (Finnair destinations from Helsinki airport).

| Route category by decade | Radiation dose (μSv) | Flights | |
|---|---|---|---|
| | | Mean number | 95% CI |
| Domestic | | | |
| 1960 (Dom60) | 1.67 | 7.9 | 6.9–8.9 |
| 1970 (Dom70) | 0.99 | 7.8 | 7.3–8.3 |
| 1980 (Dom80) | 0.55 | 4.7 | 4.3–5.1 |
| European | | | |
| 1960 (Eur60) | 4.31 | 8.7 | 7.4–9.9 |
| 1970 (Eur70) | 19.48 | 8.8 | 8.3–9.3 |
| 1980 (Eur80) | 13.36 | 8.8 | 8.4–9.3 |
| Other European | | | |
| 1960 (OutEur60) | . | . | . |
| 1970 (OutEur70) | 40.60 | 1.1 | 1.0–1.2 |
| 1980 (OutEur80) | 39.20 | 1.3 | 1.2–1.4 |
| North America | | | |
| 1960 (NA60) | . | . | . |
| 1970 (NA70) | 68.8 | 1.1 | 1.0–1.2 |
| 1980 (NA80) | 62.90 | 1.1 | 1.0–1.2 |
| Far East | | | |
| 1960 (FarE60) | . | . | . |
| 1970 (FarE70) | 59.00 | 0.5 | 0.4–0.5 |
| 1980 (FarE80) | 65.40 | 0.8 | 0.7–0.9 |

We calculated career doses on the assumption that all flights were flown at an optimal altitude. In practice, the optimal altitude is selected in terms of velocity, available flight levels, and also optimal fuel consumption. The optimal altitude is determined mainly by aircraft type, length of flight, and aircraft weight (fuel and passengers carried aboard). However, flying at the optimal altitude is not always possible due to, for instance, other traffic or weather. In order to assess the impact of the assumed altitude, we carried out a sensitivity analysis using cosmic radiation doses received on a lower flight altitude than the optimal altitude. We presumed that all flights that, under optimum conditions, would have been flown at an altitude of ≥28 000 feet (≥8534.4 m) were flown 2000 feet (609.6 m) below the optimal altitude. Flights normally flown at ≤27 999 feet (≤5834.09 m) were assumed to be flown 1000 feet (304.8 m) below the optimal altitude in the sensitivity analysis. The career doses calculated at optimal altitude were then compared with doses that were calculated using either 2000 feet (609.6 m) or 1000 feet (304.8 m) lower altitudes.

We carried out a linear regression analysis to estimate the dependency between the career dose and the following two possible explanatory variables: number of active workyears and starting decade of cabin attendant work. STATA-7 software was used in all the statistical and mathematical procedures (16).

## Results

### Flight history

The participation rate in the survey was 52%. Attendants who were still working (typically younger) responded more frequently (62%) than those who no longer did cabin work (typically older) (43%). The mean number of workyears was 20.7 (range 2–39, median 22.0, SD 9.1) years for all the cabin attendants (N=539) in the analysis. The mean number of active workyears during the study period was 10.5 (range 0–30, median 10.0, SD 6.5) years. Work as a cabin attendant was started on the average at 23 (range 19–32, median 24, SD 2.1) years of age. The average monthly number of cabin attendants reporting round trip flights by decade and route category varied from 0.5 to 8.8 (table 2).

### Career dose

The mean career dose calculated for the study period for all the cabin attendants was 34.0 (range 0–156.8, median 27.9, SD 29.4) mSv. For the women who had already completed their career as a cabin attendant (N=180), the mean career dose was 26.4 (range 0–127.4, median 13.0, SD 31.1) mSv. The average career dose for the attendants' whose entire career was included in the study period (N=101) was 18.2 (range 0–99.4, median 10.9, SD 19.7) mSv.

Career doses seemed to increase in a fairly linear fashion with the number of active workyears (figure 1). In addition, the starting decade of cabin work was related to career dose. For the attendants (N=37) who started cabin work in the 1950s, the mean career dose was lower, 21.0 (range 0–117.2, SD 35.6) mSv, than for those who started work in the 1960s (N=105), 45.3 (range 0–156.8 mSv, SD 40.6) mSv, or the 1970s (N=279), 38.9 (range 0–113.9, SD 24.5) mSv. For the attendants (N=113) who started work in the 1980s, the average career dose was 16.7 (range 0–51.3, SD 11.4) mSv.

The mean career dose calculated from the individual questionnaire information was considerably higher than that obtained from the aggregate data using timetables, 19.3 (range 0–49.8, median 17.6, SD 13.4) mSv. The analyses at the individual level showed that the career doses calculated from the individual information obtained with the questionnaire were approximately 80% higher than those calculated using information at the group level [regression coefficient $\beta_1$ 1.8, 95% confidence interval (95% CI) 1.7 to 1.9, $R^2$ 0.70] (figure 2).

### Annual dose

The mean annual dose per active workyear was 3.1 (range 0–9.5, median 3.2, SD 1.7) mSv for all the attendants combined. Overall, there was some variability in the annual doses, even among those with a similar number of active workyears. The attendants who worked only a few years had more dose variation than those who worked longer.

The annual dose rate tended to increase slightly from the 1960s on. In the 1960s, the mean dose was 0.6 (range 0–1.4) mSv per active workyear, whereas the corresponding value was 3.3 (range 0–8.2) mSv in the 1970s and 3.5 (range 0–9.5) mSv in the 1980s. The first decade of cabin work was also related to annual dose. The mean annual dose was 1.1 (range 0–4.9) mSv for the attendants who started their cabin work in the 1950s, 2.5 (range 0–6.0) mSv for those who started during the 1960s, 3.6 (range 0–9.5) mSv for those who started in the 1970s, and 3.2 (range 0–7.9) mSv for those who started in the 1980s.

### *Sensitivity analysis*

When the actual flight altitude for all flights was assumed to be either 2000 feet (609.6 m) or 1000 feet (304.8 m) below the optimal altitude, the mean career dose decreased by approximately 16%, 34.0 (range 0–156.8) mSv versus 28.5 (range 0–131.7) mSv.

### *Linear regression analysis*

In the univariate linear regression analysis, the career dose increased with the number of active workyears (regression coefficient $\beta_1$ 3.2, 95% CI 2.9–3.5, $R^2$ 0.49). When the starting decade of cabin attendant work was also included in the model (multivariate analysis, $R^2$ 0.52), both the number of active workyears (regression coefficient $\beta_1$ 3.5, 95% CI 3.2–3.8) and starting decade of work (regression coefficient $\beta_2$ 6.0, 95% CI 3.6–8.4) remained positively associated with career dose.

## Discussion

Our Finnish cabin attendant cohort provided little exposure contrast for our epidemiologic study, primarily because there was not much variability in the annual doses of those who worked in the same time periods (eg, among those who were approximately the same age) even though the variability in annual dose was more pronounced between cabin attendants than between different calendar periods. The annual doses increased slightly with calendar period, and this finding reflects the increasing number of high-altitude, long-haul flights due to the increasing proportion of jet aircraft. Thus the starting period of cabin work was used as a determinant of the annual dose. Women with a higher number of active workyears did not necessarily have higher annual doses, in spite of the assumption that the more the attendant worked, the more he or she flew on longer routes. Therefore, our findings indicate that the number of active workyears does not appear to be a valid surrogate measure for annual dose for cabin crew. However, the career dose did increase in a rather simple fashion with active workyears. Therefore, it may be possible to use active workyears as a rough surrogate measure for career dose. However, results on career doses must be interpreted with caution, since the study period investigated did not represent the whole career for all the cabin attendants in the study (eg, those who started before 1959 and those working after 1989).

Questionnaire data provide the only opportunity for individual dose assessment if valid records, such as flight log data, are not available. Yet, individual questionnaire data may be difficult to collect, and information on aggregate level can be obtained more easily. In addition, the information on duration of career as a cabin attendant, as well as leaves of absences, is usually available even if the flight distribution is not recorded. Ac-

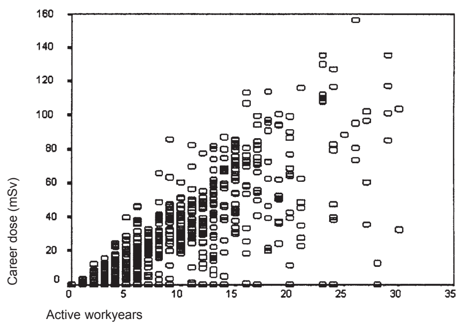


**Figure 1.** Career dose by number of active workyears in the study period for Finnish airline cabin crews.

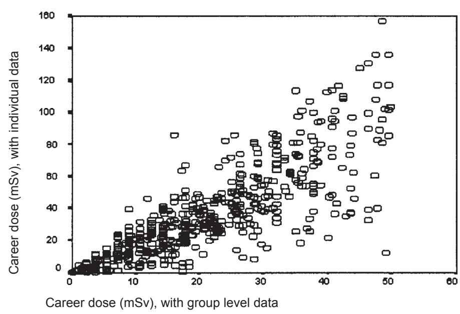


**Figure 2.** Career doses calculated with the use of the individual questionnaire data (of number of flights) and doses with the use of aggregate data on timetables (of number of flights) to different destinations.

cording to our results, the career doses calculated at the group level (using average number of flights estimated on Finnair timetables) gave lower estimates of career doses than those derived from individual questionnaire data, this outcome suggesting that aggregate data may underestimate the true career doses. An alternative explanation is that participating cabin attendants overestimate their number of flights (information bias) or those with the highest exposure are more likely to participate in a survey (selection bias). Thus the typical flight pattern obtained from survey data may overestimate the true cosmic radiation exposure. In addition, the cabin attendants indicated that the number of flights by decade and route category was particularly difficult to remember. Therefore, any results on calculated annual and career doses must be interpreted carefully. However, the cabin attendants were able to provide fairly detailed information on active workyears.

The doses calculated for suboptimal flight altitudes gave approximately 16% lower career doses than those calculated for optimal flight altitudes. Yet this scenario is not realistic, since, in reality, only a minor proportion of flights is actually flown below optimal altitude. Our results indicate, however, that flight altitude is an important exposure determinant. Deviations from true flight altitudes may lead to dose estimation error, even in less extreme situations.

The use of a few representative routes per flight category simplified the exposure assessment considerably. It would be extremely laborious to collect information on all actual flight sectors, which can amount to up to hundreds per year for large airline companies. Our method can be used for radiation dose estimation also in other companies, provided that information on routes corresponding to the flight distribution is available. The selection of the number of typical flights depends solely on the flight distribution of a given flight company. Thus a larger flight company than Finnair would have to consider taking into account more flight categories and more typical flights in a given category. The more flights used in typical flight assessment, the greater precision. Similarly, the use of the average value of each decade's solar activity simplified the calculations considerably. This simplification did not impair the dose assessment either, since the variability of cosmic radiation to aircrew exposure due to occasional solar particle events is minor.

The participation rate in the survey was relatively low and, therefore, may have caused selection bias if the flight history was different among the participants and nonparticipants. The group that we used for dose estimation may not have been representative of all Finnish flight attendants. Furthermore, flight information was not obtained from deceased attendants. However, the career doses were the most influenced by flights from the 1980s on since the predominance of jet aircraft with higher flight altitudes and a larger number of long-haul flights resulted in higher dose rates. We had to rely on the participating cabin attendants' own estimations of number of flights, and dependence may have led to random error. Therefore, information on flight distribution should be collected prospectively to improve validity.

A cohort study of the incidence of cancer among Finnish cabin attendants showed a significant excess of breast cancer and bone cancer and a nonsignificant excess of leukemia and melanoma (17). In that study the radiation dose was estimated at 2–3 mSv a year, and the cumulative career dose was 15–20 mSv. In the cohort study, the annual dose corresponded with our results, but the career dose estimates were considerably lower than ours.

Our results suggest that cabin crew members are typically exposed to relatively low doses of cosmic radiation during their career. Although career doses are increasing, they are so low that a cancer risk of expected magnitude would be almost impossible to detect by epidemiologic means (18). Yet there is variability between individuals in both annual and career doses. Individual career or yearly cosmic radiation doses cannot be assessed accurately enough for epidemiologic purposes using only the number of active workyears or flight hours. They provide only preliminary, rough estimates for the whole cabin attendant population, and information from questionnaires or work history records is needed. On the average, the Finnish population is exposed to a radiation dose of 3.7 mSv a year, which translates into a gamma radiation level of approximately 2 mSv (1 mSv from medical exposures and 1 mSv from terrestrial gamma radiation) (2). All cabin attendants are assumed to be exposed to the same levels of background radiation. Because this study focuses on an internal comparison among cabin attendants, nonoccupational radiation dose becomes irrelevant.

In conclusion, individual quantification of occupational cosmic radiation dose is difficult, and thus the assessment of possible health effects is complicated. Our method provides an option for estimating individual and longitudinal dose rates and indicates that survey data are needed if flight log data are not available. This method provides only a crude assessment of cosmic radiation exposure for attendants without survey data.

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**II**

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ORIGINAL ARTICLE

# Breast cancer risk among Finnish cabin attendants: a nested case-control study

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**Background:** Earlier studies have found increased breast cancer risk among female cabin crew. This has been suggested to reflect lifestyle factors (for example, age at first birth), other confounding factors (for example, age at menarche), or occupational factors such as exposure to cosmic radiation and circadian rhythm alterations due to repeated jet lag.
**Aims:** To assess the contribution of occupational versus lifestyle and other factors to breast cancer risk among cabin attendants in Finland.
**Methods:** A standardised self-administered questionnaire on demographic, occupational, and lifestyle factors was given to 1041 cabin attendants. A total of 27 breast cancer cases and 517 non-cases completed the questionnaire. Breast cancer diagnoses were confirmed through the Finnish Cancer Registry. Exposure to cosmic radiation was estimated based on self-reported flight history and timetables. A conditional logistic regression model was used for analysis.
**Results:** In the univariate analysis, family history of breast cancer (OR = 2.67, 95% CI: 1.00 to 7.08) was the strongest determinant of breast cancer. Of occupational exposures, sleep rhythm disruptions (OR = 1.72, 95% CI: 0.70 to 4.27) were positively related and disruption of menstrual cycles (OR = 0.71, 95% CI: 0.26 to 1.96) negatively related to breast cancer. However, both associations were statistically non-significant. Cumulative radiation dose (OR = 0.99, 95% CI: 0.83 to 1.19) showed no effect on breast cancer.
**Conclusions:** Results suggest that breast cancer risk among Finnish cabin attendants is related to well established risk factors of breast cancer, such as family history of breast cancer. There was no clear evidence that the three occupational factors studied affected breast cancer risk among Finnish flight attendants.

Earlier studies of cancer incidence and cancer mortality among aircrew personnel have shown that overall cancer risk incidence and mortality are comparable with that in the general population.[1] However, several studies have found increased breast cancer risk among female cabin crew.[2–9] This has been suggested to reflect occupational exposure to cosmic radiation, hormonal alterations due to repeated jet lag, lifestyle factors, or confounding by factors such as age at menarche and menopause. The contribution of various factors has remained unclear, due to the fact that all earlier reports have limited extent of information on potential confounders—that is, the well known risk factors for breast cancer.

We conducted a nested case-control study of breast cancer among cabin attendants in Finland. The purpose of the study was to assess the contribution of occupational versus non-occupational factors to breast cancer risk among cabin crew.

## METHODS

### Data collection

The source population consisted of all Finnish female airline cabin attendants, who were born in 1960 or before. A total of 1098 eligible woman were identified in the source population from the files of Finnair and Finnish Cabin Crew Union (table 1).

In the source population, a total of 57 women (5%) could not be traced because of death (n = 32), unknown current address (n = 17), or other reasons (n = 8). A standardised self-administered questionnaire (followed by two reminder letters for non-respondents) was mailed to all women with known addresses (n = 1041). Information was collected on: (1) demographic factors; (2) occupational factors including duration of active employment as cabin attendant, the monthly number of short, medium, and long haul flights, disturbances of sleep and menstrual cycle related to disruptions of circadian rhythm; and (3) other possible risk factors for breast cancer including number of births, age at first birth, breast feeding, number of spontaneous and induced abortions, age at menarche, age at menopause, use of oral contraceptives, participation in mammography screening, use of hormonal replacement therapy, family history of breast cancer, benign breast disease, alcohol consumption, and smoking habits.

Only those attendants who had ever worked as cabin attendants for Finnish flight companies for at least two years were included in the study. Short term employees were excluded as they have only negligible occupational exposure and may differ from the rest of the population in several respects, including breast cancer risk.

A total of 45 breast cancer cases were diagnosed in 1975–2000 among cabin attendants; 36 of those could be traced. The breast cancer cases were identified by a record linkage with the Finnish Cancer Registry, a nationwide, population based registry with a practically complete coverage of solid cancer cases in Finland.[10]

Radiation dose from occupational exposure to cosmic radiation was estimated based on reported flight history and Finnair timetables. Information on the average monthly number of flights by decade (1960s, 1970s, and 1980s) and flight category (domestic, Europe, Far East, North America, and other long haul) was collected using a self-administered

**Abbreviations:** mSv, millisievert; OR, odds ratio; CI, confidence interval; ERR, excess relative risk

**Main messages**

- Finnish female cabin attendants have increased risk of breast cancer.
- Cabin attendants have the same risk factors for breast cancer as the general female population.
- There was no clear evidence that the three occupational factors studied affect breast cancer risk.

**Policy implications**

- There is no need to take occupational factors into account in breast cancer prevention among cabin attendants.

questionnaire. The questions concerning the flight history are shown in the Appendix. To complement the questionnaire data, we collected information on the frequency of flights from Finnair timetables and selected representative routes for each flight category. The radiation dose for every flight category was calculated using CARI-6 software, developed for this purpose by the US Federal Aviation Authority.[11] Using the information on self-reported flight history and radiation dose by flight category, the cumulative occupational dose was calculated as the sum of radiation doses received in the 1960s through the 1980s. The dose received over the last 10 years prior the reference year was excluded to allow for the induction period of at least 10 years for radiation induced solid tumours.[12] The occupational radiation dose assessment method has been described in detail elsewhere.[13]

All the study subjects gave written informed consent for participation. The Finnish Advisory Board for Radiation Safety approved the study protocol.

### Statistical analysis

Information on all variables was taken into account before the reference year—that is, the year of breast cancer diagnosis for the cases and the date of diagnosis of the case for the controls.

The number of cumulative fertile years was calculated for postmenopausal women from age at menarche to the age at menopause, excluding periods of pregnancy and breast feeding. For premenopausal women, the number of cumulative fertile years was calculated from age at menarche to the reference year, excluding periods of pregnancy and breast feeding. The association between number of fertile years and breast cancer was analysed per five year increment in fertile years. Alcohol consumption was measured as a number of units (0.33 litres of beer or cider, 12 cl wine, 8 cl fortified wine, or 4 cl spirits) per week. Alcohol consumption was categorised into two groups: 0–7 units per a week, and >7 units of alcohol consumed per a week. Family history of breast cancer was categorised into two groups: absence versus presence of breast cancer cases among first degree relatives (mother, sister, daughter). Miscarriages and abortions were merged as a one variable with two categories (no miscarriages or abortions and one or more miscarriages or abortions).

The association between breast cancer and cumulative radiation dose was analysed per 10 mSv increment in dose, assuming a linear dose-response relation without a threshold. Active work years were defined as the time from beginning of cabin work to the end of work, less major absences from work, for example, maternity leaves or long sick leaves. Reported disturbances of sleep rhythm during long flights were categorised into two groups (never or rarely versus sometimes or often), as well as disturbances of menstrual cycle (never or rarely versus sometimes or often).

For each case, up to four controls were chosen with matching on year of birth ($\pm 1$ year). A conditional logistic regression model was used for both univariate and multivariate analysis with breast cancer status as the outcome measure. Univariate analysis was done by including one independent variable of interest in the model. Multivariate analysis was used to study whether non-occupational factors affect the estimates obtained for occupational risk factors, and thus both occupational and non-occupational variables were included in the model. Non-occupational factors were selected on the basis of a priori criteria—that is, strong evidence on the relation to breast cancer risk. Confidence intervals reported are likelihood based.[14]

To assess possible selection bias (differences between participants and non-participants and their effect on the results), we calculated the odds ratio for breast cancer for all the subjects in the cabin attendant cohort (44 breast cancer cases and 921 non-cases, including those untraced subjects and non-participants whose start and end of cabin works was known) using crude exposure data available for every subject. Occupational dose was estimated based on number of active work years assessed from the dates of start and end of cabin work obtained from Finnair and the Finnish Cabin Crew Union. This information was combined with the estimated mean annual cosmic radiation dose by calendar period,[13] to obtain a crude estimate of cosmic radiation dose for every person. The analyses were adjusted with age. Further, older women—that is, those who more likely have a longer recall period—might report flight activity, menstrual cycle distortions, and sleeping distortions with a different degree of accuracy than younger women. Thus, we assessed the modifying effect of age by dividing the study subjects into two groups (50 years of age or younger, and over 50 years of age) and examined the effect of occupational dose, sleep disturbances, and menstrual disturbances on breast cancer by age group.

## RESULTS

A total of 544 flight attendants (27 cases and 517 non-cases) returned a completed questionnaire, corresponding to a response proportion of 60% for cases and 52% for non-cases. For each case, up to four controls were chosen; 27 cases and 103 controls were therefore included in the final analysis. Response proportions were similar for subjects living abroad

**Table 1** Number of study participant cabin attendants by age group, date of hire, and case status

| | Cases n = 27 (45) | Controls n = 103 (1053) | Total n = 130 (1098) |
|---|---|---|---|
| **Age group** | | | |
| 38 to 45 | 5 (12) | 20 (187) | 25 (199) |
| 46 to 55 | 16 (20) | 66 (320) | 82 (340) |
| 56 to 65 | 5 (10) | 16 (151) | 21 (161) |
| 66 to 81 | 1 (2) | 1 (49) | 2 (51) |
| **Date of hire** | | | |
| 1950s | 5 (15) | 16 (68) | 21 (83) |
| 1960s | 10 (13) | 43 (196) | 53 (209) |
| 1970s | 11 (15) | 38 (437) | 49 (452) |
| 1980s | 1 (1) | 5 (214) | 6 (215) |
| 1990s | 0 (0) | 0 (6) | 0 (6) |

The number of cabin attendants in the whole source population are given in parentheses. Totals differ in some cases because of missing data on specific characteristics.

and those living in Finland (51% and 54% respectively). Those still working as a cabin attendant (typically younger) had higher participation rates (62%) than those who had already quit their work (typically older) (43%).

In the univariate analysis, family history of breast cancer (OR = 2.67, 95% CI: 1.00 to 7.08) had a borderline significant association with breast cancer (table 2). Non-significantly increased odds ratios were observed for alcohol consumption (OR = 2.67, 95% CI: 0.96 to 7.38), early menarche (age of 12 or earlier) (OR = 2.04, 95% CI: 0.79 to 5.30), number of fertile years (OR = 1.33, 95% CI: 0.70 to 2.52), breast feeding (OR = 3.56, 95% CI: 0.40 to 32.02), benign breast disease (OR = 1.67, 95% CI: 0.63 to 4.43), smoking (OR = 1.82, 95% CI: 0.78 to 4.23), and disruption of sleep rhythm (OR = 1.72, 95% CI: 0.70 to 4.27). Disruption of menstrual cycles (OR = 0.71, 95% CI: 0.26 to 1.96) had a statistically non-significant protective effect on breast cancer, whereas cumulative radiation dose (OR = 0.99, 95% CI: 0.83 to 1.19) showed no effect on breast cancer.

There was no substantial change in the occupational estimates when non-occupational factors were included into the model in the multivariate analysis. Family history of breast cancer (OR = 5.52, 95% CI: 1.44 to 21.23) and alcohol consumption (OR = 4.11, 95% CI 1.01 to 16.72) had the strongest association with breast cancer in multivariate analysis (table 2). Also, number of fertile years (OR = 1.51, 95% CI: 0.54 to 4.19) and sleep rhythm disruptions (OR = 1.52, 95% CI: 0.49 to 4.74) were positively related to breast cancer, but the confidence intervals were wide. Disruption of menstrual cycles (OR = 0.56, 95% CI: 0.12 to 2.61) had a statistically non-significant protective effect on breast cancer, whereas parity (OR = 1.10, 95% CI: 0.23 to 4.85) and cumulative radiation dose (OR = 0.93, 95% CI: 0.68 to 1.27) showed negligible effects on breast cancer.

When the odds ratio (age adjusted) for breast cancer for all the subjects in the cabin attendant cohort was calculated using crude cosmic radiation exposure data, the occupational radiation dose was not associated with breast cancer (OR = 0.96, 95% CI: 0.83 to 1.11).

When the effect of occupational dose, sleep disturbances, and menstrual disturbances was assessed by age group, the mean cumulative occupational dose for women 50 years of age or younger was 27.2 mSv (range 0–103.5 mSv, 95% CI: 20.9 to 33.4 mSv), and for women over 50 years of age, 34.8 mSv (range 0–136.8 mSv, 95% CI: 26.9 to 42.7). For women 50 years of age or younger, the occupational dose was not associated with breast cancer (OR = 0.86, 95% CI: 0.52 to 1.42) and the result was similar among older women (OR = 1.02, 95% CI: 0.84 to 1.24). Among women 50 years age or younger, 58% reported having sleep disturbances sometimes or often; the percentage was 51% among women over 50 years of age. The association of sleep disturbances with breast cancer risk was negative among younger women (OR = 0.70, 95% CI: 0.19 to 2.58) and positive among older women (OR = 3.62, 95% CI: 0.93 to 14.08). Thirty per cent of women 50 years age or younger reported having menstrual disturbances sometimes or often; the percentage was 27% among women over 50 years of age. The association of menstrual disturbances with breast cancer risk was negligibly protective, both in younger women (OR = 0.89, 95% CI: 0.19 to 4.12) and in older women (OR = 0.52, 95% CI: 0.13 to 2.04).

## DISCUSSION

An earlier study[2] showed a significant excess in the incidence of breast cancer (SIR 1.87) among Finnish cabin attendants. Based on updated follow up, the age adjusted breast cancer incidence is 81.2/100 000. In comparison, the breast cancer rate for general Finnish female population is approximately 57.4/100 000 (adjusted with the age distribution of cabin attendants). This result implies that the excess risk in the incidence of breast cancer among Finnish cabin attendants has persisted.

In our study family history of breast cancer was the strongest determinant of breast cancer. Earlier studies have also suggested family history as one of the strongest risk factors for breast cancer, especially in early onset disease.[15] Yet, in a retrospective study recall bias may also occur—that is, people with a disease are more likely to be aware of a similar diagnosis in a relative.[16] This leads to higher sensitivity in exposure assessment among cases and differential misclassification with overestimation of the effect. However, an evaluation on precision of reported family history of breast cancer in Finland suggested that self-reported family history is quite accurate.[17] Alcohol consumption seemed to be associated with breast cancer. Even if the well established risk factors for breast cancer are hormone related, there is strong previous evidence of the effect of

**Table 2** Odds ratios and 95% confidence intervals from conditional logistic regression of breast cancer risk; results from univariate and multivariate analysis

| Risk factor | OR (95% CI) Crude | Adjusted* |
|---|---|---|
| Cumulative radiation dose (per 10 mSv) | 0.99 (0.83 to 1.19) | 0.93 (0.68 to 1.27) |
| Number of fertile years (per 5 years) | 1.33 (0.70 to 2.52) | 1.51 (0.54 to 4.19) |
| Parity | | |
| No children | 1.00 | 1.00 |
| 1 child or more | 0.64 (0.23 to 1.79) | 1.10 (0.23 to 4.85) |
| Family history of breast cancer | | |
| No | 1.00 | 1.00 |
| Yes | 2.67 (1.00 to 7.08) | 5.52 (1.44 to 21.23) |
| Alcohol consumption | | |
| 0–7 units per a week | 1.00 | 1.00 |
| 7.1–28 units per a week | 2.67 (0.96 to 7.38) | 4.11 (1.01 to 16.72) |
| Disruption of sleep rhythm | | |
| Never or rarely | 1.00 | 1.00 |
| Sometimes or often | 1.72 (0.70 to 4.27) | 1.52 (0.49 to 4.74) |
| Disruption of menstrual cycle | | |
| Never or rarely | 1.00 | 1.00 |
| Sometimes or often | 0.71 (0.26 to 1.96) | 0.56 (0.12 to 2.61) |

*In the multivariate modelling, each variable was controlled for all other variables in the model (cumulative radiation dose, number of fertile years, parity, family history of breast cancer, alcohol consumption, disruption of sleep rhythm, and menstrual cycle).

alcohol consumption, even moderate, on breast cancer risk.[18 19] Differential recall bias might also occur with respect to alcohol consumption—that is, people with the disease are prone to exaggerate the exposures they think are related to the disease.

Furthermore, the number of fertile years—that is, the cumulative number of ovulatory cycles—had a minor positive relation to breast cancer. There is previous evidence that the cumulative number of ovulatory cycles (that is, cumulative oestrogen exposure due to early menarche, late menopause, etc) is a major determinant of breast cancer.[15] However, the phenomenon is difficult to study since many other exposures (age at menarche, breast feeding, parity, etc) are strongly associated with number of fertile years. There is strong previous evidence for the protective effect of parity against breast cancer in general.[15] In this study, protective association was found but the confidence intervals were wide. Among parous women, breast feeding increased the risk of breast cancer in univariate analysis. This is opposite to previous evidence for a minor protective effect of breast feeding from breast cancer.[20]

Disruptions in sleeping pattern or menstrual cycle during flights across several time zones have been suspected to increase breast cancer risk.[21] This is believed to be due to excess exposure to light during normal sleeping hours and thus impaired pineal secretion of melatonin.[22] The melatonin hypothesis is supported by epidemiological studies on blind people. Blind people have increased levels of melatonin and have approximately half the rate of breast cancer.[23 24] The relation is still not fully understood and needs further research. In this study, reported sleeping disorders seemed to increase the risk of breast cancer but the relation was not statistically significant.

Menstrual cycle disruptions are common in flight attendants.[25] In our study, menstrual disruptions were negatively associated with breast cancer but the relation was not statistically significant. There is some previous evidence that short menstrual cycle might increase breast cancer risk.[15] The nature of the menstrual cycle disruptions of the cabin attendants is not known.

Risk of breast cancer was not associated with the cumulative occupational radiation dose. The expected magnitude of risk was small and we could not exclude a minor effect. The highest credible value was estimated as the upper limit of 95% confidence interval (1.274)—that is, 27.4% per 10 mSv. The validity of cosmic radiation exposure assessment has been thoroughly evaluated. However, a validation study is not possible, since in the Finnish setting the cabin attendants themselves are the only source of information on flight hours. There is a possibility of recall bias given the long recall period. In a previous study, we compares doses calculated from the flight hours based on questionnaires (individual data) with those based on number of flights per flight attendant, extracted from flight timetables (aggregate data).[13] The results suggest that cabin attendants may overestimate their flight hours. A similar phenomenon was observed in an American study, where it was found that cabin attendants considerably overestimate their block hours.[26] Yet, it is difficult to assess the potential recall bias from these findings mainly pertaining to reliability (random error).

Among atomic bomb survivors, breast cancer is one of the cancers most strongly related to radiation dose (ERR = 1.68 per Sv, 90% CI 1.31 to 2.10; that is, ERR = 0.0168 per 10 mSv).[27] The effect is strongest for exposures at young age, but weaker for women exposed after menopause. Similar results have been obtained in other studies of high dose rate exposures such as chest fluoroscopy.[28] Yet, few studies have evaluated the effect of protracted exposure, for example, at work. Radiological technologists in the United States did not have an increased breast cancer mortality overall, but those certified prior to 1950 had an excess risk, with SMR of 1.5.[29] Similar results have been obtained in a cohort of Chinese medical *x* ray workers.[30] However, both of these studies were limited by the lack of radiation dose estimates.

The main limitation of the study was the small number of cases, which restricts the statistical power. However, as the source population included practically all Finnish flight attendants, this constraint could not be overcome. Some results were inconsistent with earlier studies, which might be partly attributable to chance. Another limitation was that information on exposure was collected retrospectively. The case ascertainment was retrospective and therefore eight cases (18%) were deceased and one case (2%) had no current address. They were, therefore, unavailable for the study. The loss is assumed to be greater among breast cancer cases due to excess mortality and, therefore differential misclassification of exposure is possible, which may bias the result either away or towards the null.

To study the selection bias (participants versus non-participants), we calculated the odds ratio for breast cancer for the whole cabin attendant cohort using crude exposure data. The results showed that the occupational radiation dose was not associated with breast cancer. This result is comparable with that obtained in the main analyses (with smaller number of subjects) and indicates that selection bias attributable to incomplete tracing and participation did not substantially affect our findings.

One more limitation of the study was the suboptimal response proportion. If the selection effect is dissimilar among cases compared with controls (that is, exposure distribution in participants differs either more or less between participants and non-participants), selection bias could occur. Younger attendants actually had higher participation rates than older attendants. We assessed the modifying effect of age by dividing the study subjects into two groups (50 years of age or younger, and over 50 years of age) and examined the effect of occupational exposures on breast cancer by age group. No clear effect modification of age on the risk of breast cancer related to occupational exposures was observed. As expected, older women have accrued higher occupational doses, but the relation between radiation dose and breast cancer risk is fairly similar in the two groups. Results pertaining to the effect of sleep or menstrual disturbances on breast cancer risk are more difficult to interpret, as the estimates do differ, especially when the effect of sleep problems was assessed. However, the estimates can still be regarded as comparable due to wide confidence intervals. This suggests that the lower participation among older attendants did not distort the results.

In conclusion, our results suggest that breast cancer risk among Finnish cabin attendants is related to general, well established risk factors of breast cancer, such as family history of breast cancer. Occupational factors do not seem to exert an influence on breast cancer risk, but the evidence remains inconclusive.

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## APPENDIX

Part of the questionnaire sent to cabin attendants (the questions concerning flight history). Original questionnaire was in Finnish.

1. In which year did you start your cabin work at the first time? *Year 19_____*
2. Are you still doing the same work?
   - *No I am not, the year I stopped was 19_____*
   - *Yes I am*
3. Which duties did you perform during your cabin work?
   - *Cabin attendant from year 19_____ to 19_____*
   - *Service chef/Finn hostess from year 19_____ to 19_____*
   - *Assistant purser from year 19_____ to 19_____*
   - *Purser from year 19_____ to 19_____*
4. Were you away from your work, for example because of maternity leaves, nursing leaves or absences from duty?
   - *No I was not*
   - *Yes, from year 19_____ to 19_____. (_____ months) and*
   - *from year 19_____ to 19_____. (_____ months) and*
   - *from year 19_____ to 19_____. (_____ months) and*
   - *from year 19_____ to 19_____. (_____ months) and*
   - *from year 19_____ to 19_____. (_____ months) and*
   - *from year 19_____ to 19_____. (_____ months)*
5. Did you do any part time cabin work at any time?
   - *No I did not*
   - *Yes I did, ___% or ___ hours per week from year 19___ to 19___, total of ___ months*
   - *and ___% or ___ hours per week from year 19___ to 19___, total of ___ months*
6. Have you done other work, with some cabin work or no cabin work at all?
   - *No, I was not absent from cabin work*
   - *Yes. What work? _______________ from year 19___ to 19___, total of ___ months and*
   - *What work? _______________ from year 19___ to 19___, total of ___ months*
7. How many round-trip flights did you have to Far East during different periods? For example Bangkok from year 1976, Tokyo from year 1983 and Singapore from year 1985 with aircraft DC8S during 1976–1982, DC10 during 1979–1996 and MD11 from year 1992.
   - *1970s on the average _____ flights per a month*
   - *1980s on the average _____ flights per a month*
8. How many round-trip flights did you have to North America during different periods? For example to New York, Florida, California and Canada with aircraft DC8S during 1969–1982, DC10 from year 1975 and MD11 from year 1992.
   - *1970s on the average _____ flights per a month*
   - *1980s on the average _____ flights per a month*
9. How many round-trip flights did you have to other outside-European destinations during different periods? For example charter flights to Canary Islands from year 1969.
   - *1970s on the average _____ flights per a month*
   - *1980s on the average _____ flights per a month*
10. How many round-trip flights did you have to Europe during different periods?
    - *1960s on the average _____ flights per a month*
    - *1970s on the average _____ flights per a month*
    - *1980s on the average _____ flights per a month*
11. How many round-trip flights did you have to domestic destinations during different periods?
    - *1960s on the average _____ flights per a month*
    - *1970s on the average _____ flights per a month*
    - *1980s on the average _____ flights per a month*

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# ECHO

## Search continues for causes of lead toxicity in Nigeria

Please visit the *Occupational and Environmental Medicine* website [www.occenvmed.com] for a link to the full text of this article.

Combating lead toxicity in children in developing countries seems a distant prospect with the failure of a study to identify the main causes of exposure in urban Nigerian children with high lead concentrations in their bloodstream.

Multivariate analysis confirmed a link between a range of variables and high blood lead concentrations in two mostly Muslim administrative wards in Jos, Nigeria, one with a population with high amounts of lead in the bloodstream and one whose population had lower amounts. These were age ⩽5 years; male sex; chipped (lead based) paint in the home; a nearby outfit selling gasoline or a nearby battery smelter; cosmetic use of lead ore eye pencils in children; and, rather surprisingly, parental education. Together they accounted for just 38% of total variance. Living in the ''high lead'' ward remained significantly related to raised blood lead, suggesting a residual cause not already accounted for. Among adults and children with complete data from 34 households, 137 lived in the high lead (mean blood concentration 37 (SD13) mg/l) and 138 in the low lead (mean 17 (10) mg/l) ward; 92 (34%) had values ⩾10mg/l.

Adults and children were questioned about sources of exposure, and lead in the blood was measured from blood spot samples taken from a washed finger.

Seventy per cent of children aged 6–35 months in Jos have raised blood lead concentrations. Lowering lead exposure is a key step in reducing its toxic effects on cognitive development, especially in children, combined with calcium, iron, and vitamin C supplements in developing countries.

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**III**

**KOJO K, HELMINEN M, LEUTHOLD G, ASPHOLM R, AUVINEN A (2007): Estimating the cosmic radiation dose for a cabin crew with flight timetables. Journal of Occupational and Environmental Medicine 49: 540–545.**

# Estimating the Cosmic Radiation Dose for a Cabin Crew With Flight Timetables

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***Objective:*** *Because of the lack of recorded flight history for cabin crew, a retrospective assessment of exposure to cosmic radiation is complicated. Our aim was to develop an assessment method for occupational exposure based on flight timetables.* ***Methods:*** *The frequency of flights, aircraft types, and flight profiles from timetables were collected. The cosmic radiation dose was calculated with the EPCARD software. Based on annual doses and work history, the cumulative dose was estimated.* ***Results:*** *The annual dose increased linearly: 0.7 milliSievert (mSv) in 1960, 1.6 mSv in 1980, 2.3 mSv in 1985, and 2.1 mSv in 1995. The median cumulative dose was 20.8 mSv (minimum 0.4 mSv, maximum 61.6 mSv).* ***Conclusions:*** *This method provides a simple algorithm for occupational dose assessment for cabin crew and can be used in other research settings as well.* (J Occup Environ Med. *2007;49: 540–545*)

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Cosmic radiation dose rates are considerably higher at cruising altitudes than at ground level. At sea level, the dose rate is less than 0.1 milliSievert (mSv) per hour, and it doubles by every 1500 meters of altitude.[1] Exposure to cosmic radiation may increase the risk of cancer among aircraft pilots and cabin crew. Therefore, the International Commission on Radiation Protection (ICRP) has recommended that aircrew be classified as radiation workers.[2]

Besides the Finnish company Finnair, the lack of systematically recorded flight history information for cabin crew is a problem for other airlines. Today, individual data on flight history for each flight for the Finnair pilots is available. This database contains information on the aircraft type, flight route, and block times (ie, the time from the gate departure to the gate arrival at destination). This information is not available for the Finnair cabin crew (flight attendants) before 1991. Therefore, other sources of information on number and type of flights have to be used. There is ample literature describing in-flight cosmic radiation based on tissue equivalent proportional counters and other methods suitable for neutron dose estimation. Several occupational dose assessments for aircrew have been published in the past 10 years.[3–14] Different approaches have been used, each with their own strengths and limitations. Monitoring of current exposure with use of personal dosimetry is relatively simple, but reconstructing the entire occupational exposure history is more problematic, though highly desirable for assessment of occupational hazards. In prospective dosimetry studies, the average annual dose for cabin crew has been estimated to range from 1.0 to 1.8 mSv,[3] and in another study, the range is more than 1.0 mSv but less than 20 mSv,[7] depending on aircraft and routes.

Retrospective approaches are needed for reconstructing exposures throughout the work history. Detailed flight logs similar to those of the cockpit crew are rarely available for the cabin crew. Duration of employment has been used as an indicator of occupational radiation, but it is a relatively crude measure and is prone to nondifferential misclassification. Survey data have been used to obtain individual dose estimates. However, the coverage of questionnaire surveys is incomplete, and cabin attendants may not correctly recall the number of past flights, which may induce random error and bias. Certain airline companies have information on individual records of flight history. For example, in 2002, Grajewski et al[10] estimated that for US airline cabin attendants, the average annual occupational dose was from 1.5 to 1.7 mSv, whereas Wilson et al[3] in 1994 estimated the annual dose for the Australian international cabin crew had reached 3.8 mSv.

The aim of this study was to develop a retrospective assessment method for occupational exposure to cosmic radiation based on flight timetables. The rationale was to develop a simple exposure assessment method applicable to Finnair flight attendants without flight history information or survey data, and a method that could be applied with other airlines.

## Materials and Methods

### Data Collection

We collected information from the Finnair timetables on the frequency of flights and craft types used on each route at 5-year intervals (from 1960 to 1995). The Finnair timetables were available for all the planned years, but for certain years, either a summer or winter timetable was missing. Approximately 6% of the winter and 50% of the summer timetables were not available. For example, for 1975, the summer timetables were missing, and therefore, the summer tables for 1974 were used instead. Similarly, if any other period for a certain year were missing, an adjacent year for the same season was used. The block hours for charter flights were obtained from the Finnair archives, but the timetables did not cover their flight distribution. Yet, according to former pilots and the Finnair route map for 1984 through 1995, 70% to 80% of charter destinations were situated in the Mediterranean area and 20% to 30% in the rest of Europe. Thus, to represent the Mediterranean charter routes, the Helsinki-Athens route was used, and for the rest, four European routes were used (from Helsinki to London, Zurich, Luxembourg, and Geneva). A flight profile (ie, taxiing, descent, and ascent time; and cruising altitude and time), was assigned to each route based on the type of aircraft used.

We collected information on the total number of cabin crew (flight attendants) for every fifth year (from 1960 to 1995).[15] Finnair did not systematically record the number of its personnel for the previous years, which is why it had to be estimated based on the narrative literature, as well as on information from the present and former Finnair personnel and pilots. The number of cabin crew on board was estimated with the help of expertise information, mainly pilots. This number depends mainly on the aircraft type used and, further, on the route type and time period. On a certain aircraft, there is usually less personnel aboard on domestic routes than on international routes, which are typically longer. Also on charter flights, there might have been fewer personnel aboard than on a similar scheduled flight.

Information about starting and ending employment as a cabin crew worker for the calculation of individual cumulative dose was acquired from the Finnair archives and from the database of the Finnish Flight Attendants Association (SLSY).

### Radiation Dose Calculation

The cosmic radiation dose for every route at 5-year intervals was calculated using the European Program Package for the Calculation of Aviation Route Doses (EPCARD), software developed for this purpose by the GSF Institute of Radiation Protection.[16] Galactic cosmic rays create secondary charged and uncharged particles in the Earth's atmosphere, which constitutes the radiation in the cruising altitudes. The dose rates and relative contribution of the particles (neutrons, protons, pions, electrons, muons and photons) depend on the solar activity (solar shielding), the geographic position (geomagnetic shielding) and on the flight altitude (shielding effect of the atmospheric layer).

The EPCARD is based on the results of Monte Carlo radiation transport calculations, which take into account all the physical processes and effects, using the most recent nuclear reaction cross-section data and the cosmic ray data of NASA. The solar deceleration potential indicating the solar activity is derived from the continuously operating ground level neutron monitor at Climax, Colorado. For the effect of geomagnetic shielding, data in terms of the vertical cut-off rigidity are used. The resulting particle fluence rates are converted into dose quantities by the conversion factors provided by ICRP60.[2]

First, the average annual cosmic radiation dose was calculated by multiplying the radiation dose ($E_{ijk}$) received from a single flight with the number of the cabin crew on board ($x_{ijk}$) to obtain the collective dose that the cabin crew members received during that single flight. The dose was then multiplied by the frequency of the flights on the same route within that particular year ($l_i$) to obtain the total annual dose on that route. Then, the total annual dose from this route was added up with the other annual doses from all the other routes during that year in order to obtain the total collective cosmic radiation dose gained by all cabin crew during one year ($\hat{E}_{ci}$). Secondly, the sum was divided by the number of the cabin crew during that year ($X_i$) to obtain the annual dose for a single member of the cabin crew ($\hat{E}_m$).

$$\hat{E}_{ci} = \sum(E_{ijk}x_{ijk}l_i)$$

$$\hat{E}_m = \frac{\hat{E}_{ci}}{X_i}$$

where
$i$ = year
$j$ = route
$k$ = aircraft

For example, for 1965, the annual dose was calculated as follows. The radiation dose received from a single flight (for example, Helsinki – Leningrad, 0.73 μSv) was multiplied with the number of the cabin crew on board (on Helsinki-Leningrad route Convair Metropolitan aircraft with two cabin crew members) to obtain the collective dose for cabin crew members (0.73 μSv*2 = 1.46 μSv) on that particular route. This was multiplied by the total number of the flights (Helsinki-Leningrad route was flown 74 times during 1965) to obtain the annual dose on the route (1.46 μSv*74 = 108.04 μSv). This was summed with other annual doses received from all the other routes during 1965 (167235.40 μSv) to obtain the collective dose gained by all cabin crew during 1965 (167235.40 μSv + 108.04 μSv = 167343.80 manμSv). This was divided with the total number of the cabin crew during 1965 (120 persons) in order to obtain the annual dose (167343.80 manμSv/120 persons = 1394.53 μSv/person = 1.39 mSv/person).

The annual cosmic radiation dose can be used for the calculation of the individual cumulative dose ($\hat{E}_p$). This requires the information from the airline company on the start ($i_0$) and the end year of the employment ($i_n$) for a single cabin crew member.

$$\hat{E}_p = \sum_{i_0}^{i_n} \hat{E}_{mi}$$

As the annual doses are estimated for every fifth year, in cumulative dose calculation they were assumed constant for adjacent years as well. For example, the dose for the year 1975 can be used for the years from 1973 to 1977 and similarly, the dose for 1980 can be used for the period from 1978 to 1982. We calculated the individual cumulative dose until 1997 for all Finnair cabin crew members who were employed between 1958 and 1997.

For example, if a cabin crew member had a 20-year career, from 1975 to 1995 (assuming the start and the end at the midpoint of the year), the individual cumulative dose could be calculated as follows. The calculated radiation dose was 1.67 mSv in 1975 with the same dose for 1976 and 1977 which gives a total dose of 4.18 mSv (1.67 mSv*2.5) for 1975 to 1977. The dose received from 1978 to 1995 is 32 mSv (1.56 mSv*5 + 2.27 mSv*5 + 1.55 mSv*5 + 2.07 mSv*2.5 = 32.08 mSv), and hence, the total career dose, 36.26 mSv (32.08 mSv + 4.18 mSv), is estimated for the whole 20-year career. Only those who had at least one year of employment were included in the cumulative dose calculations.

Changes in cosmic radiation levels occur as a result of changes in solar activity (heliocentric potential). A sensitivity analysis was performed to assess the impact of the use of the doses of adjacent years in the individual cumulative dose calculation. Finnair route distribution for 1980 was selected, and the annual cosmic radiation dose was calculated for 1978 to 1982, using the heliocentric potential specific to each year.

A sensitivity analysis was performed to assess the impact of the charter route distribution allocation to 70% to 80% Mediterranean and 20% to 30% European routes. The cosmic radiation dose was calculated for 1975 when the charter route distribution was allocated for Mediterranean route (Helsinki-Athens) and alternatively, the charter route distribution was allocated for the European route (Helsinki-Zurich).

There is a possibility of under- or overestimation of annual doses due to possible misestimating on the total number of cabin crew used in our study. Thus, we calculated the annual dose for 5-year intervals (from 1960 to 1995) assuming either 10% smaller or 10% greater total number of cabin crew.

To complement the information from the airline company regarding the start and the end of cabin work, we also used information on self-reported absences concerning cabin work. This information was obtained from a survey conducted among female Finnish cabin attendants in 2004. In that survey, a self-administered questionnaire was sent to all female Finnish cabin attendants to obtain information on their work history (eg, long absences from the cabin work). We calculated the individual cumulative dose for those who participated in the survey and who were employed between 1958 and 1997 both using 1) only the airline information on the start and the end of the career and 2) information on self-reported absences.

## Results

The number of Finnair routes doubled from 1960 to 1995. In previous years, there were no long-haul flights (at least 6 hours). For example, flights to the Far East did not start until the 1970s. In 1995, approximately 8% of all routes were long haul.

In 1960, the number of Finnair cabin crew was estimated to be 70; in 1995, the number was 1250 (Table 1). The number of cabin crew on board varied considerably. For example, in the 1960s, there was only one cabin crew member on board on domestic flights in the DC-3 aircraft,

**TABLE 1**
Number of Finnair Cabin Crew on Board by Aircraft, Route Type, and Decade, and Total Number of Cabin Crew by 5-Year Intervals

| | Domestic | International | Total Number of Crew (yr/no) |
|---|---|---|---|
| 1960s | | | |
| DC-3 | 1 | — | 1960 (70) |
| Metropolitan | 1 | 2 | 1965 (120) |
| Caravelle | 3 | 4 | |
| S. Caravelle | 3 | 4 | |
| 1970s | | | |
| DC-3 | 1 | — | 1970 (180) |
| Metropolitan | 1 | 2 | 1975 (400) |
| S.Caravelle | 3 | 4 | |
| DC-8 series | — | 4 | |
| DC-9 series | 3 | 4 | |
| DC-10 | — | 12 | |
| 1980s | | | |
| DC-8 series | — | 5 | 1980 (640) |
| DC-9 series | 4 | 5 | 1985 (640) |
| DC-10 | — | 12 | |
| S. Caravelle | 3 | 4 | |
| A300B4 | — | 8 | |
| ATR-72 | 2 | — | |
| ATR-42, Fokker-27, SAAB 340, EMB | 1 | — | |
| 1990s | | | |
| DC-9 series | 4 | 5 | 1990 (1100) |
| DC-10 | — | 12 (14*) | 1995 (1250) |
| MD-80 series | 4 | 5 | |
| MD-11 | — | 12 | |
| A300B4 | — | 8 | |
| ATR-72 | 2 | — | |
| ATR-42, Cessna, SAAB-340, EMB | 1 | — | |

*On flights between Helsinki and Tokyo.

whereas in the 1990s, up to 14 cabin crew members were on board a DC-10 on international flights.

The calculated cosmic radiation dose for a cabin crew member in 1960 was 0.71 mSv. The dose increased over time to 1.56 mSv in 1980, with a peak of 2.27 mSv in 1985 and 2.07 mSv in 1995 (Fig. 1). There were 1399 Finnair cabin crew members

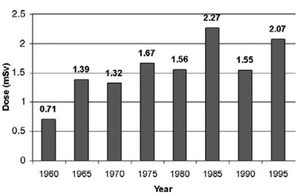


**Fig. 1.** The calculated cosmic radiation (mSv) dose by year.

who were employed between 1958 and 1997. The distribution for cumulative dose was nonnormal (Shapiro-Wilkinson test for normality, $P = 0.000$). The median cumulative career dose for those 1289 cabin crew members whose career lasted at least 1 year was 20.8 mSv (minimum 0.4 mSv, maximum 61.6 mSv) calculated on the basis of information obtained from Finnair on the start and end of the crew members' career.

When the annual cosmic radiation doses were calculated for 1978 to 1982 with the yearly heliocentric potentials and route distribution for 1980, there were some changes. The annual dose for 1978 was 1.99 mSv; for 1979, 1.83 mSv; 1981, 1.30 mSv; and 1982, 1.42 mSv. Therefore, the cumulative dose for 1978 to 1982 was 8.1 mSv. When the annual cosmic radiation dose was calculated allocating the charter route distribution for the Mediterranean route (Helsinki-Athens), the dose for 1975 was 1.71 mSv. When the route distribution was allocated for the European route (Helsinki-Zurich), the annual dose was 1.63 mSv.

When the annual cosmic radiation dose was calculated, assuming either a 10% lesser or 10% greater number of the total cabin crew, the change in the dose seemed to be linear. For example, in 1970, with the lesser or greater number of the total cabin crew assumed, the annual dose was 1.46 mSv and 1.20 mSv, respectively. In 1990, the corresponding figures were 1.72 mSv and 1.41 mSv.

When the cumulative dose was calculated only for those who participated in the survey, were employed between 1958 and 1997, and had a career of at least 1 year ($N = 615$), the median individual cumulative dose was 30.2 mSv (minimum 0.4 mSv, maximum 60.6 mSv) with only the information obtained from the airline. When only the active work-years were used (excluding self-reported absences from work), the median individual cumulative dose was 21.5 mSv (minimum 0 mSv, maximum 59.9 mSv).

## Discussion

The aim of this study was to develop an assessment method for cosmic radiation exposure based on flight timetables. Our method provides a retrospective assessment that does not require the use of any survey data or flight history database. The method is quick, inexpensive, and applicable to all other airlines that have past timetables. The purpose of this report was to describe this novel method. Applying the method to the Finnair data serves only as an illustration and is not meant to represent any other airlines.

Dose assessment methods that employ survey data are prone to random error (ie, cabin attendants might not remember correctly the number or types of flights they have flown).

This can be avoided with our method because survey data are not needed. If the flight timetables are available for other airlines, they might be archived in paper form. Computerizing and organizing them as a matrix is relatively easy and affordable.

The routes and radiation doses were collected for every fifth year, and the annual doses for each crewmember were calculated with these data. It would be much more time consuming and laborious to collect the route data for each year. The route distribution at Finnair is relatively stable within a 5-year period. Thus, the doses, estimated at 5-year intervals, are representative for adjacent years as well. For other airlines, this time window might be too wide. If the flight distribution changes more rapidly, a 5-year interval might be too long and a shorter interval should be used. However, when doses are estimated at 5-year intervals, the yearly variation in the heliocentric potential is not taken into account. A sensitivity analysis on use of the adjacent year's dose in the individual cumulative dose calculation suggested that this simplification might misclassify the dose estimates. The cumulative dose for 1978 to 1982 calculated with the route distribution of 1980, but with the year-specific heliocentric potentials, was approximately 4% greater than the cumulative dose calculated for the same time period with the annual dose in 1980. A sensitivity analysis on the allocation of the charter route distribution suggested a negligible variation as a result of changes in the allocation of charter route distribution. Allocation of the charter route distribution, either to the Mediterranean or European route, gave approximately 2% higher or lower doses, respectively.

Our method cannot provide the truly individual doses because we assume a similar flight schedule for all cabin crew. This method provides an estimate of cosmic radiation dose in which the variability on individual cumulative dose depends mainly on the timing and length of career. Thus, the method is prone to misclassification (ie, random error that depends on the interindividual variability in the route distribution). There is considerable diversity in allocation of routing between airlines. At Finnair, cabin crew bid their routes from the entire flight schedule based on seniority, with preferences probably reflecting lifestyle factors. For other airlines, this should be taken into consideration because the method provides an average dose for the entire airline crew, and heterogeneity in route distribution within the crew reduces its applicability at an individual level.

Our previous study,[12] which relied on survey data on the number and type of flight attendants' routes, suggested that the flight schedule is not similar to all cabin crew members. In that study, the mean cosmic radiation dose per year from 1960 to 1990 was 3.1 mSv (range, 0 to 9.5 mSv). The attendants who had a short career had more variation in the dose than those who had worked longer. The annual doses in our previous study were considerably higher than in this study. Those flying more may participate more actively in occupational surveys. Another possibility is that cabin attendants who participated in the previous survey overestimated the number of past flights. Grajewski et al[17] also found overestimation in the self-reported flight hours of flight attendants compared with the flight hours obtained from company records.

We were not able to accommodate certain few sources of cosmic radiation that might contribute to the total dose of cabin crew. Commuting flights (ie, from home to the airport where the work flight will take off), and deadheading flights (ie, the crew is flying as passengers while on duty), also contribute to the cosmic radiation exposure. We had no information on these flights and thus could not assess the dose due to them.

The annual cosmic radiation dose for cabin crew has increased steadily since the 1960s, mainly because high-altitude jet aircrafts have gradually replaced low-altitude piston-engine aircrafts. Long-haul flights have become more common, too. The total number of cabin crew members was not recorded for all the studied years, so they had to be estimated from different sources, which may present a potential source of uncertainty. Narrative literature was the most comprehensive source of information on the total number of cabin crew with Finnair, but even in the literature, the number of personnel was not recorded for each year. Consequently, the number of personnel for specific time periods had to be estimated based on the information from Finnair staff and flight personnel (both working and retired), with a possible recall bias. However, for specific years, information was reported on the total number of Finnair cabin crew, both in the literature and by the Finnair staff. The estimates were highly consistent. For example, in 1965, the literature reported 117 members of the cabin crew, whereas Finnair staff reported 120. To assess the effect of possible misclassification on the number of cabin crew on annual doses, we calculated the doses for the study period, assuming either 10% lesser or 10% greater total number of cabin crew. The annual dose was inversely proportional to the number of cabin crew. When the total number of cabin crew was assumed to be 10% lesser, the annual dose was approximately 11% greater. With the assumption of 10% greater total number of cabin crew, the dose was approximately 10% lesser.

When self-reported absences were also taken into account, the median calculated cumulative dose was less (29%) than the dose calculated with only the information obtained from the airline. For the Finnair cabin crew, the information on longer absences might be available for specific years, but this may not be the case for the cabin crew of other airline companies. If absences from work are not known (from the airline or at least self-reported) in further studies, the cumulative dose estimation can be made based only on the length of career and on an approximated mean absence from work.

To obtain comparable radiation doses, consistent methods, such as the same software package for dose estimation, should be used throughout the study. Of the two most widely used dose calculation programs, the EPCARD gives approximately 30% higher doses than the CARI-6 for the northern routes. For the southern routes, the situation is opposite, as the EPCARD gives approximately 20% lower doses. This seems to be a consequence of differences in the weighting factors for different particles.[18] The doses calculated with the EPCARD have shown good agreement with the ambient dose equivalent measured at aircraft altitudes.[19]

Certain studies have tried to develop a method for retrospective assessment of occupational cumulative exposure to cosmic radiation for cabin crew without work history records. Our previous study[12] relied on survey data, whereas certain studies[8] used surrogate measures (ie, the length or start of employment), to compensate for the lack of a precise work history. In our previous study, the mean cumulative career dose for all Finnish flight attendants was 34.0 mSv (range, 0 to 156.8 mSv). This dose was substantially higher than the cumulative dose calculated in this study. This might suggest that the number of past self-reported flights by cabin attendants is overestimated. In those studies in which the surrogate measures are used for occupational exposure, there is no attempt to assess the actual cosmic radiation doses. So far, our previous study is the only one in a similar setting: attempting to estimate the individual cumulative career dose without the work history (ie, recorded information on the number of flights). However, our annual doses (0.7 to 2.3 mSv throughout the study period) are fairly comparable with the annual dose from other studies. For example, Grajewski et al[10] developed an algorithm from work histories and estimated an average annual occupational dose of 1.5 to 1.7 mSv for US airline attendants.

The method based on flight timetables provides a simple and robust algorithm for the occupational radiation dose assessment for cabin crew. Unlike the questionnaire data, it is not prone to information bias. This method will be used in a cohort study of the incidence of cancer among the cabin crew in the Nordic countries, where the similar dose assessment will be applied for SAS and Iceland air personnel as well.

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**IV**

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**V**

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# Cancer incidence among Nordic airline cabin crew

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**Airline cabin crew are occupationally exposed to cosmic radiation and jet lag with potential disruption of circadian rhythms. This study assesses the influence of work-related factors in cancer incidence of cabin crew members. A cohort of 8,507 female and 1,559 male airline cabin attendants from Finland, Iceland, Norway and Sweden was followed for cancer incidence for a mean follow-up time of 23.6 years through the national cancer registries. Standardized incidence ratios (SIRs) were defined as ratios of observed and expected numbers of cases. A case-control study nested in the cohort (excluding Norway) was conducted to assess the relation between the estimated cumulative cosmic radiation dose and cumulative number of flights crossing six time zones (indicator of circadian disruption) and cancer risk. Analysis of breast cancer was adjusted for parity and age at first live birth. Among female cabin crew, a significantly increased incidence was observed for breast cancer [SIR 1.50, 95% confidence interval (95% CI) 1.32–1.69], leukemia (1.89, 95% CI 1.03–3.17) and skin melanoma (1.85, 95% CI 1.41–2.38). Among men, significant excesses in skin melanoma (3.00, 95% CI 1.78–4.74), nonmelanoma skin cancer (2.47, 95% CI 1.18–4.53), Kaposi sarcoma (86.0, 95% CI 41.2–158) and alcohol-related cancers (combined SIR 3.12, 95% CI 1.95–4.72) were found. This large study with complete follow-up and comprehensive cancer incidence data shows an increased incidence of several cancers, but according to the case-control analysis, excesses appear not to be related to the cosmic radiation or circadian disruptions from crossing multiple time zones.**



Airline cabin crew are occupationally exposed to ionizing radiation with doses 2–6 mSv per year.[1] This is roughly twice the average annual dose from natural and medical sources received by the general population. Cosmic radiation in the common cruising altitudes (8,000–10,000 m) consists mainly of gamma and neutron radiation, with some heavy nuclei. In 1990, the International Commission on Radiological Protection recommended that in-flight radiation exposure to jet aircrew should be regarded as occupational exposure.[2]

Of the radiation-related cancers, only breast cancer has shown increased incidence rates among airline personnel consistently in several studies. Out of the seven cohort studies of cabin crew,[3–9] all but one[6] indicate an increased incidence of breast cancer. However, the excess risks seem to be higher than can be explained by the low radiation doses received,[10] and several other factors may contribute to the observed excess.

Cabin crew also work in shifts including work at night and are exposed to jet lags (a temporary condition after air travel across several time zones) dependent on time, distance and direction (east-west *vs.* north-south) of flight routes. Such exposures may contribute to circadian disruption, including suppression of the chronobiotic neurohormone melatonin, which has anticancer properties.[11–13] There is accumulated epidemiologic and biologic evidence that circadian disruption, which is characterized by desynchronization of the internal clock with the external environmental light, may contribute to the development of certain cancers, in particular breast and prostate cancer.[12–14] Night shift work that involves circadian disruption was recently classified by the

**Key words:** occupational exposure, cosmic radiation, circadian disruptions, cohort study, registries, record linkage, neoplasms
**Abbreviations: BCC: basal cell carcinoma; CI: confidence interval; CLL: chronic lymphatic leukemia; OR: odds ratio; SAS: Scandinavian Airlines; SIR: standardized incidence ratio; SMR: standardized mortality ratio; UVR: ultraviolet radiation**
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International Agency for Research on Cancer as probably carcinogenic to humans (category 2A), based on sufficient evidence in experimental animals and limited evidence for human breast cancer.[15]

It is important to determine if the risk of cancer among flight personnel is elevated due to ionizing radiation or other work-related factors and whether current occupational standards provide sufficient protection. The aim of our study was to describe the cancer incidence among airline cabin crew from four Nordic countries. In the cabin crew studies published so far, there has been a rather limited possibility for internal comparisons to characterize possible dose-response patterns related to cosmic ionizing radiation. We also evaluated the dose-dependence of cancer incidence in terms of time since first employment, cosmic radiation and number of flights crossing six time zones as a surrogate for jet lag.

## Material and Methods

### Study population

National cohorts of airline cabin crew were identified from various registers in Finland, Iceland, Norway and Sweden. In Finland, all cabin crew personnel who had ever been working for Finnair and its daughter airline flight companies between 1947 and March 1993 were identified from the files of the Finnair company.[3] Persons deceased before 1967 were excluded. The final cohort included 1,766 persons (1,578 women and 188 men).

The Icelandic cohort comprised 1,690 cabin crew members (1,532 females and 158 males) identified from the computerized members list from the Icelandic Cabin Crew Association and from airline companies Icelandair and Air Atlanta for the period 1947–1997.[7]

In Norway, the cohort was established from the files at the Personnel Licensing Section of the Civil Aviation Administration, which authorizes cabin crew members.[6] The cohort included all cabin crew members who had a valid license between January 1950 and February 1994 and that were resident in Norway for some time after 1961 (and hence got the Norwegian personal identity code (PIC) used in computerized record linkages). The final number of persons included in this analysis was 3,073 women and 581 men.

The Swedish study population consisted of cabin crew employed by the Swedish part of Scandinavian Airlines (SAS) at any time during 1957–1994 and resident in Sweden.[9] The cabin crew at SAS was identified using administrative company registers of employees and archival records at the Swedish part of SAS. The final number of persons included in this analysis was 2,324 women and 632 men.

The cohorts were linked to the national population registers by PIC, and the possible dates of immigration, emigration or death were obtained for every cohort member. Since the 1960s, all residents of the Nordic countries have had a unique PIC that is used in all major registers and allows automatic, accurate record linkages.

The dates of birth for live-born children among the women were obtained by linkage to the Population Register in Finland, register of the Genetical Committee of the University of Iceland and Statistics Norway. For female cabin attendants in Sweden the dates of birth of their children were obtained using the Multi-Generation Register at Statistics Sweden and the National Medical Birth Register.

Follow-up for incident cancer cases was conducted through record linkage with the national countrywide cancer registries existing in all Nordic countries.[16] All these registries cover entire national populations in a nonselective way and have similar coding principles that allow, *e.g.*, classification by subsite or morphological type of the cancer. This possibility was used in our study for skin cancers and leukemia. Basal cell carcinoma (BCC) of the skin was only registered in the Finnish and Icelandic Cancer Registries. It was analyzed as a separate category but was not included in the overall cancer rates.

Follow-up for cancer for each individual started at the date of first employment, at immigration or on the date of the beginning of cancer registration, availability of the linkage key (the PIC in Norway) or availability of computerized information of causes of death (Sweden), whichever was latest. The follow-up ended at emigration, at death or on a common closing date (the date until which cancer registration was complete at the time of the record linkage), whichever was first. For those emigrating out of the country, the observation period was terminated at the time of first emigration, irrespective of eventual later remigration (to avoid selective follow-up). In Finland, the maximal follow-up period was thus from 1953 to 2005, in Iceland from 1955 to 1997, in Norway from 1962 to 2002 and in Sweden from 1961 to 2003. During these periods a National Cause of Death Register as well as a National Cancer Register was in operation in each respective country.

The observed numbers of cases and person-years at risk were counted by gender in 5-year age groups and 5-year calendar periods. The expected numbers of cases for all cancer sites combined and for specific cancer types were calculated by multiplying the number of person–years in each stratum by the corresponding national cancer incidence rate. The specific cancer types selected *a priori* for the analysis included the cancer sites related to ionizing radiation or circadian disruption, cancers with a suggestion of exceptional risk levels in earlier studies and other common cancer types to understand the overall cancer profile of airline cabin crew.

To calculate the standardized incidence ratios (SIRs), the observed numbers of cases were divided by the respective expected numbers. The exact 95% confidence interval (CI) for each SIR was defined based on the assumption that the number of observed cases followed a Poisson distribution.

### Case-control analysis

Case-control data for women were constructed to estimate the effect of cosmic ionizing radiation on the risk of breast

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cancer, skin cancers and leukemia [excluding chronic lymphatic leukemia (CLL)] and the effect of jet lags (breast cancer only). All female cabin crew members without cancer diagnosis of the same site as the case at the time of the diagnosis, born in the same year as the case and alive at the date of cancer diagnosis of the case, were used as controls. Conditional logistic regression, using control selection mentioned above, was used to assess possible relations between the factors and to estimate the statistical significance of the trends. In the models related to breast cancer, the available parity information was added to the model either as dichotomous (any *vs*. no children) variable or categorical factor combined from the number of children (0, 1–2 and 3+) and age at first birth (<25 and 25+). In the analysis of breast cancer, the proportion of nulliparous women was 18%, women with one or two children was 59%, women with three or more children was 23% and women given first birth at age 25 or older was 65% among cases. Corresponding figures for the controls were 22, 57, 21 and 66%.

### Assessment of cosmic radiation exposure

The estimates of the annual doses per cabin crew member were based on the assumption that the crew members flew a random selection of all types of routes operated by the airline company in each year of employment. Based on the information from airline companies, we know that cabin crew flies approximately a variety of routes at any time during their work unlike pilots who have a license for a specific aircraft type and thus they have a limited range of routes at a given time. For the SAS cabin crew members in Norway exact flight histories are available (however not in a format that could be used for exposure estimation for the entire cohort). Based on a sample of these records, the Norwegian part of the study group concluded that the assumption that each cabin crew member flew proportionally their share of the routes operated per year and company was not appropriate for the Norwegian cohort. Therefore, Norway was excluded from the dose-response analysis part of our study. Information on the frequency of flights and aircraft types used on each route at 5-year intervals (from 1960 to 1995) was collected from the SAS, Finnair and Icelandair timetables.

No information was available on charter flights for SAS and Icelandair. For Finnair, the charter block hours were obtained from the Finnair archives. With the help of former Finnair pilots and the route map for the years 1984–1995, the charter hours were assigned to typical charter destinations situated in the Mediterranean area and the rest of the Europe.[17] The number of cabin crew on board was estimated based on expert consultations and literature.[18] The number depends mainly on the aircraft type, but also on route and time period.

The radiation dose for each flight was constructed by combining information on flight profile (time of ascent, time at cruising altitude and time of descent) and the so-called block hours (time from pulling out from the gate at departure airport until docking at arrival airport), with the dose rate based on altitude, and with some variation by calendar period reflecting heliocentric potential.[17] The cosmic radiation dose for every route was calculated using the European Program Package for the Calculation of Aviation Route Doses (EPCARD) software developed for this purpose by the GSF Institute of Radiation Protection. EPCARD is based on the results of Monte Carlo radiation transport calculations, which take into account all the physical processes and affects using the most recent nuclear reaction cross-section data and the cosmic ray data of NASA.[2]

The collective dose from a single flight was estimated from the dose on that route based on the number of cabin crew on board during the flight. The collective dose was then multiplied by the frequency of the flights on the same route within that particular year to obtain the cumulative annual collective dose on that route. Then, the cumulative annual collective doses from all routes during that year were summed up to obtain the overall collective dose received by all cabin crew during 1 year. It was divided by the number of cabin crew during that year to estimate the average annual dose for the cabin crew, and it was assigned to each cabin crew member employed for that year.

The cumulative dose was calculated as the sum of the average annual cosmic radiation doses summed over the active work-years. For this purpose, the information on the starting and the ending year of the employment for each cabin crew member was obtained from the airline companies. Available information on maternity leaves and other work breaks was also used. Doses were estimated separately for Finnair, Icelandair and SAS Sweden (Table 1). Some of the Swedish cohort members had also worked for other airline companies than SAS. Because we did not have dose estimates for the other companies, SAS doses were applied to the years worked for other companies as well. Since the annual doses were only estimated for every fifth year, in cumulative dose calculation they were assumed constant for adjacent years as well. For example, the dose for the year 1975 was used for the period 1973–1977.

### Circadian rhythm disruption

Circadian disruption was estimated by the average annual number of flights passing six or more time zones (Table 1). Since this information was not available on an individual level, information on flight duration and frequency was obtained from historical airline timetables for every fifth year of Finnair, Icelandair and SAS Sweden, and a similar route distribution was assumed for all cabin crew members of the airline company working at a same time period. Each one-way flight passing six time zones is counted as one "jet lag." Alternative variables for jet lag exposure, based on thresholds of passing four and five time zones, were defined in a similar way.

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Table 1. Annual average number of flights passing six or more time zones and annual average cosmic radiation doses (mSv), for every fifth year

| | Flights passing 6+ time zones | | | Cosmic radiation dose (mSv) | | |
|---|---|---|---|---|---|---|
| Year | Icelandair | SAS | Finnair | Icelandair | SAS | Finnair |
| 1960 | 0 | 7.66 | 0 | 0.88 | 0.83 | 0.71 |
| 1965 | 0 | 7.80 | 0 | 0.64 | 1.31 | 1.39 |
| 1970 | 3.83 | 10.41 | 11.27 | 1.04 | 1.16 | 1.32 |
| 1975 | 5.64 | 8.83 | 6.54 | 1.92 | 1.22 | 1.67 |
| 1980 | 3.43 | 8.89 | 11.73 | 1.88 | 0.85 | 1.56 |
| 1985 | 2.62 | 11.10 | 17.03 | 1.29 | 1.06 | 2.27 |
| 1990 | 0 | 17.32 | 15.41 | 0.99 | 1.11 | 1.55 |
| 1995 | 0 | 19.37 | 14.17 | 1.63 | 2.26 | 2.07 |

## Results

### Cohort analyses

The combined cohort comprised 8,507 women and 1,559 men. The average length of follow-up was 23.6 years. Almost 75,000 person-years were in the follow-up category of $\geq$20 years since the time of first employment (Table 2). The cohort was rather young; only 10% of the person-years were above 55 years of age. At the end of follow-up, 6% of the cabin crew members had reached an estimated cumulative dose of at least 35 mSv and 40% at least 150 flights over six or more time zones (Table 2). Reproductive history was incomplete for the Finnish and Norwegian women born before 1935, altogether 3.4% of the female cohort members (Table 2).

During the follow-up, 577 cases of cancer were diagnosed in women; the expected number was 499.2 corresponding to an SIR of 1.16 with 95% CI of 1.06–1.25 (Table 3). Female cabin crew had a statistically significantly increased SIR for breast cancer (SIR 1.50, 95% CI 1.32–1.69), skin melanoma (1.85, 95% CI 1.41–2.38) and leukemia (1.89, 95% CI 1.03–3.17). The SIR for BCC (only registered in Finland and Iceland) was also increased among female cabin personnel (SIR 2.39, 95% CI 1.80–3.10). The SIR for breast cancer did not vary significantly between the decades of follow-up.

Among men, 152 cancers were observed versus 109.7 expected (SIR 1.39, 95% CI 1.17–1.62) (Table 4). A high relative excess risk was observed for Kaposi sarcoma (SIR 86.0, 95% CI 41.2–158). The SIRs were also significantly elevated for laryngeal cancer (4.72, 95% CI 1.72–10.3), pharyngeal cancer (3.12, 95% CI 1.34–6.15), skin melanoma (3.00, 95% CI 1.78–4.74) and nonmelanoma skin cancer (2.47, 95% CI 1.18–4.53).

The incidence of alcohol-related cancers (oral cavity, pharynx, esophagus, liver and larynx; as defined by Dreyer *et al.* 1997) combined among male cabin crew members was increased by three-fold (SIR 3.12, 95% CI 1.95–4.72). The SIR increased with age; it was 1.6 (95% CI 0.0–8.7) in ages $<$45, 2.8 (95% CI 1.5–5.0) in ages 45–64 and 4.1 (95% CI 1.9–7.8) in ages $\geq$ 65 years. The SIR of the alcohol-related cancers for women was 0.67 (95% CI 0.25–1.45).

Altogether, the SIR did not vary substantially with increasing time since first employment (Table 5). There was some (nonsignificant) tendency of a higher SIR in the follow-up category $\geq$20 years in breast cancer and skin melanoma of the trunk. This was also the case for alcohol-related cancers as defined above (data not shown).

### Case-control analyses

In the conditional logistic regression case-control analyses, exposure to cosmic radiation did not have a significant dose-response association for any cancer under study (Table 6). For leukemia, excluding CLL, the odds ratio (OR) per 10 mSv increase in dose with a lag of 10 years was 1.66 (95% CI 0.77–3.55). Rather high point estimates of OR were observed in categorical analysis, but the ORs were nonsignificant because of the very small numbers of cases (Table 6).

The OR for breast cancer calculated per estimated 100 flights passing $\geq$6 time zones was 0.92 (95% CI 0.77–1.11), adjusted for parity (parous *vs*. nulliparous) when no lag time was used in the model. This result was unaffected by allowing a lag time of 10 years or by adjustment with age at first live birth (results not shown). Change of the criterion of jet lag from passing $\geq$6 time zones to $\geq$5 or $\geq$4 time zones did not markedly change the results.

The correlation of the estimated dose and number of flights passing $\geq$6 time zones was so high (0.88 with a lag time of 10 years) that mutually adjusted results were unstable.

## Discussion

This Nordic study confirmed the findings of earlier reports concerning the elevated risk of skin cancers and breast cancer among airline cabin personnel. The narrow confidence intervals of the joint estimate, based on the large combined cohort, and consistent results in each of the four independent cohorts indicate that these findings cannot be attributed to chance.

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Table 2. Numbers and percentages (%) of airline cabin crew, by study variables

| Variable | Category | Persons | | Person-years | |
|---|---|---|---|---|---|
| | | Number | % | Number | % |
| Total | | 10,066 | 100 | 237,627 | 100 |
| Country | Finland | 1,766 | 18 | 45,827 | 19 |
| | Iceland | 1,690 | 17 | 32,005 | 13 |
| | Norway | 3,654 | 36 | 89,031 | 37 |
| | Sweden | 2,956 | 29 | 70,764 | 30 |
| Sex | Female | 8,507 | 85 | 201,048 | 85 |
| | Male | 1,559 | 15 | 36,579 | 15 |
| Age (years) | <35 | 9,718 | 97 | 94,313 | 40 |
| | 35–44 | 313 | 3.1 | 74,974 | 32 |
| | 45–54 | 30 | 0.3 | 44,709 | 19 |
| | 55–64 | 5 | 0.1 | 17,872 | 7.5 |
| | 65–74 | – | – | 5,110 | 2.2 |
| | ≥75 | – | – | 649 | 0.3 |
| Time since first employment (years) | <10 | 9,842 | 98 | 87,351 | 37 |
| | 10–19.9 | 218 | 2.2 | 75,446 | 32 |
| | ≥20 | 6 | 0.1 | 74,830 | 31 |
| *Duration of work (years)* | *<5* | *3,315* | *33* | | |
| | *5–14.9* | *3,772* | *37* | | |
| | *≥15* | *2,979* | *30* | | |
| *Estimated cosmic radiation dose (mSv)* | *<5* | *3,063* | *30* | | |
| | *5–14.9* | *3,465* | *34* | | |
| | *15–34.9* | *2,938* | *29* | | |
| | *≥35* | *600* | *6* | | |
| *Estimated number of flights over ≥ 6 time zones* | *<50* | *3,571* | *35* | | |
| | *50–149* | *2,424* | *24* | | |
| | *≥150* | *4,071* | *40* | | |
| *Number of children, women only* | *0* | *2,054* | *24* | | |
| | *1–2* | *4,577* | *54* | | |
| | *≥3* | *1,590* | *19* | | |
| | *Unknown* | *286* | *3.4* | | |

For the variables used in cohort analyses (country, sex, age and time since first employment), also the numbers of person-years at follow-up are given. On these rows, the numbers of persons are classified according to the situation at the beginning of the person-year calculation, while person-years are given according to the dynamic age and time since first exposure. For the remaining variables (*in Italics*), the numbers of persons are classified according to the situation at the end of the follow-up.



**Estimation of cosmic radiation**

Yearly average dose estimates were constructed for the study, but flight histories for each individual cabin crew member have not been documented equally precisely as for airline pilots,[19] and such information cannot be obtained in a comprehensive and objective fashion from cabin crew members themselves.[20] Our exposure estimates were based on the assumption that most of the cabin crew members flew a random allocation of all types of routes operated by the airline company each year. The available flight history information indicated that this assumption was not appropriate for SAS cabin crew in Norway, and, therefore, Norway was excluded from the dose-response analyses of our study. Besides three small case-control studies on breast cancer incidence among Finnish, Swedish and Icelandic cabin attendants,[9,20,21] this is the first cabin crew study of cancer incidence with an attempt to quantify the dose-response pattern. We acknowledge that exposure estimation method used in our case-control analyses may lead to exposure misclassification similar to studies based on job exposure matrices and may dilute risk estimates toward unity.

Table 3. Observed and expected numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (CI) among female airline cabin crew in Finland, Iceland, Norway and Sweden, by cancer site

| Primary site (ICD-7 code) | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|
| All sites (140–208)[1] | 577 | 499.2 | 1.16 | 1.06–1.25 |
| Lip (140) | 0 | 0.6 | 0 | 0.00–6.05 |
| Mouth (143–144) | 0 | 1.8 | 0 | 0.00–2.05 |
| Pharynx (145–149) | 2 | 3.6 | 0.56 | 0.06–2.01 |
| Esophagus (150) | 3 | 1.2 | 2.49 | 0.50–7.28 |
| Stomach (151) | 4 | 8.3 | 0.48 | 0.13–1.24 |
| Colon (153) | 18 | 23.9 | 0.75 | 0.45–1.19 |
| Rectum (154) | 14 | 12.6 | 1.11 | 0.61–1.87 |
| Liver (155.0) | 1 | 1.7 | 0.60 | 0.01–3.36 |
| Gallbladder (155.1) | 3 | 2.2 | 1.34 | 0.27–3.92 |
| Pancreas (157) | 8 | 6.9 | 1.17 | 0.50–2.30 |
| Larynx (161) | 0 | 0.7 | 0 | 0.00–5.40 |
| Lung (162) | 20 | 24.1 | 0.83 | 0.51–1.28 |
| Breast (170) | 263 | 175.9 | 1.50 | 1.32–1.69 |
| Cervix uteri (171) | 26 | 31.7 | 0.82 | 0.54–1.20 |
| Corpus uteri (172) | 16 | 24.5 | 0.65 | 0.37–1.06 |
| Ovary (175) | 20 | 29.7 | 0.67 | 0.41–1.04 |
| Kidney (180) | 4 | 8.2 | 0.49 | 0.13–1.24 |
| Bladder (181) | 8 | 6.4 | 1.25 | 0.54–2.47 |
| Skin melanoma (190) | 59 | 31.9 | 1.85 | 1.41–2.38 |
| Head and neck (190.0–4)[2] | 4 | 2.5 | 1.60 | 0.43–4.10 |
| Trunk (190.5)[2] | 28 | 10.3 | 2.73 | 1.81–3.95 |
| Limbs (190.6–7)[2] | 27 | 17.4 | 1.55 | 1.02–2.25 |
| Other skin (191)[1] | 13 | 7.6 | 1.71 | 0.91–2.92 |
| Kaposi sarcoma | 0 | 0.1 | 0.00 | 0.00–28.4 |
| Brain, nervous system (193) | 20 | 23.7 | 0.85 | 0.52–1.31 |
| Thyroid (194) | 17 | 16.9 | 1.01 | 0.58–1.61 |
| Bone (196) | 3 | 1.3 | 2.39 | 0.48–6.98 |
| Soft tissue (197) | 3 | 3.1 | 0.97 | 0.20–2.85 |
| Unspecified sites (199) | 3 | 8.7 | 0.34 | 0.07–1.01 |
| Hodgkin lymphoma (201) | 4 | 3.6 | 1.12 | 0.30–2.88 |
| Non-Hodgkin lymphoma (200, 202) | 12 | 13.0 | 0.92 | 0.48–1.61 |
| Multiple myeloma (203) | 1 | 3.7 | 0.27 | 0.00–1.49 |
| Leukemia (204–208) | 14 | 7.4 | 1.89 | 1.03–3.17 |
| Chronic lymphatic (CLL)[2] | 3 | 1.7 | 1.80 | 0.36–5.25 |
| Non-CLL[2] | 11 | 5.7 | 1.92 | 0.96–3.43 |
| Acute myeloid (AML)[2] | 6 | 3.3 | 1.83 | 0.67–3.98 |
| Not included above: | | | | |
| Basal cell carcinoma of the skin[3] | 56 | 23.4 | 2.39 | 1.80–3.10 |

[1]Excludes basal cell carcinoma; [2]Subcategory also included in the main category; [3]Only Finland (1967–2005) and Iceland (1955–2001).

**Estimation of circadian disruptions**

Simulated chronic jet lag in mice has been shown to disrupt circadian rhythms and significantly accelerate tumor growth.[22] Our way of estimating the number of flights passing six time zones is a strong simplification of the complex aspects related to circadian disruption, but this was the most detailed assessment feasible without individual flight histories and improvement compared to previous cancer incidence

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**Table 4.** Observed and expected numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (CI) among male airline cabin crew in Finland, Iceland, Norway and Sweden, by cancer site

| Primary site (ICD-7 code) | Observed | Expected | SIR | 95% CI |
|---|---|---|---|---|
| All sites (140–208)[1] | 152 | 109.7 | 1.39 | 1.17–1.62 |
| Lip (140) | 0 | 0.8 | 0 | 0.00–4.75 |
| Mouth (143–144) | 3 | 1.0 | 2.90 | 0.58–8.47 |
| Pharynx (145–149) | 8 | 2.6 | 3.12 | 1.34–6.15 |
| Esophagus (150) | 2 | 1.3 | 1.56 | 0.17–5.63 |
| Stomach (151) | 2 | 4.3 | 0.47 | 0.05–1.69 |
| Colon (153) | 12 | 8.0 | 1.50 | 0.77–2.61 |
| Rectum (154) | 2 | 5.3 | 0.38 | 0.04–1.36 |
| Liver (155.0) | 3 | 1.0 | 3.11 | 0.63–9.09 |
| Gallbladder (155.1) | 0 | 0.4 | 0 | 0.00–8.34 |
| Pancreas (157) | 1 | 2.8 | 0.36 | 0.00–1.99 |
| Larynx (161) | 6 | 1.3 | 4.72 | 1.72–10.3 |
| Lung (162) | 11 | 12.3 | 0.89 | 0.45–1.60 |
| Prostate (177) | 24 | 21.7 | 1.11 | 0.71–1.65 |
| Testis (178) | 2 | 2.9 | 0.68 | 0.08–2.47 |
| Kidney (180) | 1 | 4.2 | 0.24 | 0.00–1.33 |
| Bladder (181) | 7 | 7.3 | 0.96 | 0.38–1.98 |
| Skin melanoma (190) | 18 | 6.0 | 3.00 | 1.78–4.74 |
| Head and neck (190.0–4)[2] | 1 | 0.7 | 1.44 | 0.02–8.01 |
| Trunk (190.5)[2] | 15 | 3.3 | 4.50 | 2.52–7.42 |
| Limbs (190.6–7)[2] | 1 | 1.5 | 0.66 | 0.01–3.66 |
| Other skin (191)[1] | 10 | 4.1 | 2.47 | 1.18–4.53 |
| Kaposi sarcoma | 10 | 0.1 | 86.0 | 41.2–158 |
| Brain, nervous system (193) | 6 | 4.7 | 1.28 | 0.47–2.79 |
| Thyroid (194) | 0 | 0.8 | 0 | 0.00–4.43 |
| Bone (196) | 0 | 0.3 | 0 | 0.00–11.3 |
| Soft tissue (197) | 0 | 0.8 | 0 | 0.00–4.41 |
| Unspecified sites (199) | 4 | 3.2 | 1.26 | 0.34–3.23 |
| Hodgkin lymphoma (201) | 0 | 1.1 | 0 | 0.00–3.41 |
| Non-Hodgkin lymphoma (200,202) | 8 | 4.2 | 1.89 | 0.81–3.72 |
| Multiple myeloma (203) | 0 | 1.6 | 0 | 0.00–2.24 |
| Leukemia (204–208) | 4 | 2.6 | 1.56 | 0.42–3.99 |
| Chronic lymphatic (CLL)[2] | 1 | 1.0 | 0.97 | 0.01–5.37 |
| Non-CLL[2] | 3 | 1.5 | 1.96 | 0.39–5.74 |
| Acute myeloid (AML)[2] | 2 | 0.9 | 2.25 | 0.25–8.12 |
| Not included above: | | | | |
| Basal cell carcinoma of the skin[3] | 2 | 1.4 | 1.39 | 0.16–5.02 |

[1]Excludes basal cell carcinoma; [2]Subcategory also included in the main category; [3]Only Finland (1967–2005) and Iceland (1955–2001).

studies. Further, our methods might underestimate the number of flights crossing six time zones since flights containing stopovers are dealt as separate flight segments not as a single flight. However, this problem could not be defeated since only available information is from flight timetables where all flight segments are recorded separately. There are no applicable standard methods for quantification of the impact of circadian disruption by crossing multiple time zones or in the night work shift, which would be essential in the evaluation of possible carcinogenicity. Most studies on endocrine phase alterations and phase adaptation after transmeridian flights have dealt with changes over 6–10 time zones.[23] Sleep

**Table 5.** Observed (Obs) and expected (Exp) numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (CI) among airline cabin crew in Finland, Iceland, Norway and Sweden, by cancer site and time since first employment

| | Entire follow-up | | | | Time since first employment | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | <20 years | | | | 20+ years | | | |
| Primary site | Obs | Exp | SIR | 95% CI | Obs | Exp | SIR | 95% CI | Obs | Exp | SIR | 95% CI |
| ALL SITES[1] | 729 | 608.9 | 1.20 | 1.11–1.29 | 213 | 178.5 | 1.19 | 1.04–1.36 | 516 | 430.4 | 1.20 | 1.10–1.31 |
| Mouth | 3 | 1.03 | 2.90 | 0.58–8.47 | 0 | 0.58 | 0 | 0.00–6.33 | 3 | 2.24 | 1.34 | 0.27–3.91 |
| Pharynx | 10 | 6.15 | 1.63 | 0.78–2.99 | 0 | 1.50 | 0 | 0.00–2.44 | 10 | 4.63 | 2.16 | 1.03–3.97 |
| Esophagus | 5 | 2.49 | 2.01 | 0.65–4.69 | 0 | 0.19 | 0 | 0.00–19.2 | 5 | 2.30 | 2.18 | 0.70–5.08 |
| Stomach | 6 | 12.6 | 0.48 | 0.17–1.04 | 2 | 3.03 | 0.66 | 0.07–2.38 | 4 | 9.52 | 0.42 | 0.11–1.08 |
| Colon | 30 | 32.0 | 0.94 | 0.63–1.34 | 5 | 5.71 | 0.88 | 0.28–2.04 | 25 | 26.3 | 0.95 | 0.62–1.41 |
| Rectum | 16 | 17.9 | 0.90 | 0.51–1.45 | 4 | 2.80 | 1.43 | 0.39–3.67 | 12 | 15.1 | 0.80 | 0.41–1.39 |
| Liver | 4 | 2.62 | 1.53 | 0.41–3.91 | 0 | 0.52 | 0 | 0.00–7.08 | 4 | 2.09 | 1.91 | 0.51–4.90 |
| Larynx | 6 | 1.95 | 3.08 | 1.12–6.70 | 1 | 0.26 | 3.86 | 0.05–21.5 | 5 | 1.69 | 2.96 | 0.95–6.90 |
| Lung | 31 | 36.4 | 0.85 | 0.56–1.21 | 2 | 4.34 | 0.46 | 0.05–1.67 | 29 | 32.1 | 0.90 | 0.61–1.30 |
| Breast | 263 | 176.0 | 1.49 | 1.32–1.69 | 66 | 50.8 | 1.30 | 1.01–1.65 | 197 | 125.3 | 1.57 | 1.36–1.81 |
| Cervix uteri | 26 | 31.7 | 0.82 | 0.54–1.20 | 19 | 21.1 | 0.90 | 0.54–1.40 | 7 | 10.6 | 0.66 | 0.27–1.37 |
| Prostate | 24 | 21.7 | 1.11 | 0.71–1.65 | 1 | 0.23 | 4.38 | 0.06–24.4 | 23 | 21.4 | 1.07 | 0.68–1.61 |
| Kidney | 5 | 12.4 | 0.40 | 0.13–0.94 | 0 | 2.20 | 0 | 0.00–1.67 | 5 | 10.2 | 0.49 | 0.16–1.14 |
| Bladder | 15 | 13.7 | 1.09 | 0.61–1.81 | 3 | 1.78 | 1.68 | 0.34–4.92 | 12 | 11.9 | 1.01 | 0.52–1.76 |
| Skin melanoma | 77 | 37.9 | 2.03 | 1.60–2.54 | 37 | 18.3 | 2.02 | 1.42–2.79 | 40 | 19.7 | 2.04 | 1.45–2.77 |
| Head and neck[2] | 5 | 3.19 | 1.57 | 0.51–3.66 | 3 | 1.33 | 2.25 | 0.45–6.58 | 2 | 1.85 | 1.08 | 0.12–3.91 |
| Trunk[2] | 43 | 13.6 | 3.16 | 2.29–4.26 | 17 | 6.54 | 2.60 | 1.51–4.16 | 26 | 7.05 | 3.69 | 2.41–5.40 |
| Limbs[2] | 28 | 18.9 | 1.48 | 0.98–2.14 | 16 | 9.45 | 1.69 | 0.97–2.75 | 12 | 9.49 | 1.26 | 0.65–2.21 |
| Other skin[1] | 23 | 11.7 | 1.97 | 1.25–2.96 | 4 | 2.07 | 1.93 | 0.52–4.95 | 19 | 9.60 | 1.98 | 1.19–3.09 |
| Kaposi sarcoma | 10 | 0.25 | 40.8 | 19.5–75.0 | 8 | 0.09 | 84.7 | 36.5–167.0 | 2 | 0.14 | 14.2 | 1.60–51.3 |
| Brain/nervous system | 26 | 28.3 | 0.92 | 0.60–1.34 | 10 | 12.1 | 0.82 | 0.39–1.51 | 16 | 16.2 | 0.99 | 0.56–1.60 |
| Thyroid | 17 | 17.7 | 0.96 | 0.56–1.54 | 9 | 10.4 | 0.86 | 0.39–1.64 | 8 | 7.32 | 1.09 | 0.47–2.15 |
| Leukemia | 18 | 9.97 | 1.81 | 1.07–2.85 | 6 | 3.65 | 1.64 | 0.60–3.58 | 12 | 6.31 | 1.90 | 0.98–3.32 |
| Chronic lymphatic (CLL)[2] | 4 | 2.70 | 1.48 | 0.40–3.79 | 0 | 0.31 | 0 | 0.00–11.9 | 4 | 2.41 | 1.66 | 0.45–4.26 |
| Non-CLL[2] | 14 | 7.27 | 1.93 | 1.05–3.23 | 6 | 3.34 | 1.79 | 0.66–3.91 | 8 | 3.90 | 2.05 | 0.88–4.04 |
| Acute myeloid (AML)[2] | 8 | 4.17 | 1.92 | 0.83–3.78 | 5 | 2.30 | 2.18 | 0.70–5.08 | 3 | 1.87 | 1.60 | 0.32–4.68 |
| Not included above: | | | | | | | | | | | | |
| Basal cell carcinoma of the skin[3] | 58 | 24.9 | 2.33 | 1.77–3.01 | 12 | 6.08 | 1.97 | 1.02–3.45 | 46 | 18.8 | 2.45 | 1.79–3.27 |

Women and men combined.
[1]Excludes basal cell carcinoma; [2]Subcategory also included in the main category; [3]Only Finland (1953–2005) and Iceland (1955–2001).

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Table 6. Odds ratios (OR) among female airline cabin crew members in Finland, Iceland and Sweden, derived from case-control analyses by conditional logistic regression model, with 95% confidence intervals (CI), for continuous and categorical estimated cumulative dose

| | Breast[1] | | Skin melanoma | | Other skin[2] | | Basal cell carcinoma[3] | | Leukemia, non-CLL | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cumulative dose | OR | 95%CI | OR | 95%CI | OR | 95%CI | OR | 95%CI | OR | 95%CI |
| Continuous per 10 mSv | 0.98 | 0.80–1.20 | 0.99 | 0.59–1.66 | 0.67 | 0.31–1.45 | 0.95 | 0.72–1.25 | 1.66 | 0.77–3.55 |
| | 152\6375 | | 34\1590 | | 6\166 | | 53\1762 | | 9\295 | |
| Categorical < 5 mSv | 1.00 | (ref.) | 1.00 | (ref.) | 1.00 | (ref.) | 1.00 | (ref.) | 1.00 | (ref.) |
| | 52\1907 | | 19\935 | | 2\31 | | 25\694 | | 3\177 | |
| 5–14.9 mSv | 1.08 | 0.70–1.67 | 0.98 | 0.35–2.75 | 0.62 | 0.06–6.46 | 0.62 | 0.27–1.43 | 3.61 | 0.34–38.1 |
| | 60\2432 | | 8\358 | | 2\29 | | 9\396 | | 4\94 | |
| 15–34.9 mSv | 0.71 | 0.42–1.18 | 0.80 | 0.24–2.72 | 0.41 | 0.05–3.55 | 1.00 | 0.45–2.20 | 3.29 | 0.14–75.2 |
| | 33\1876 | | 6\292 | | 2\79 | | 17\569 | | 1\21 | |
| ≥ 35 mSv | 1.52 | 0.56–4.13 | 5.38 | 0.37–77.5 | – | – | 0.46 | 0.10–2.19 | 8.04 | 0.31–207.8 |
| | 7\160 | | 1\5 | | 0\27 | | 2\103 | | 1\4 | |

Lag 10 years, no adjustments was made (except for parity for breast cancer). Numbers of cases\controls in each exposure category are given below the respective OR.
[1]ORs for breast cancer adjusted for parity (dichotomous variable: parous, nulliparous); [2]Excludes melanoma and basal cell carcinoma; [3]Only Finland (1953–2005) and Iceland (1955–2001).

disturbances are more frequent after long-haul flights than after short-haul ones,[24] and lead to marked changes in several aspects of the immune system and in biological processes related to the risk of breast cancer.[25] Further, disruption of menstrual cycle due to jet lag showed some association with breast cancer risk in a case-control analysis of Finnish cabin crew.[20] Other previous studies showed that changes in molecular signaling pathways were already detected after a single night of partial sleep deprivation,[26] and hormonal changes become manifest after a single or several nights of partial sleep deprivation.[27,28] Lack of data on work at night is a limitation of our study.

Another problem in the evaluation of the impact of shift work and transmeridian flights is circadian-infradian interactions. In experimental studies on different animal species, not all shift schedules led to harmful health effects.[29] SAS in Sweden compared the impact of transmeridian flights in crews who had a rapid turnaround with crews who had a prolonged stay over and found significant differences in sleep disturbances.[30]

Empirically, a 6-hr time difference may be a logical limit for assuming a significant disruption of the circadian system with subjective symptomatology in the majority of subjects. If sleep deprivation plays a role as an associated outcome, as anticipated, a shorter flight associated with a 4-hr sleep deprivation may already be biologically important. In our study, change of the criterion of jet lag from ≥6 time zones to ≥5 or ≥4 did not markedly change the results.

### Breast cancer

The largest number of excess cases was in breast cancer. There were 87 cases more than the 176 cases that would have been expected based on the average national cancer incidence rates. Of the main risk factors of breast cancer, we were able to adjust for age at first birth and number of children. Long-term hormonal therapy and obesity are risk factors for breast cancer among postmenopausal women, but as the majority of the crew members were younger than the normal perimenopausal age (50–55 years) these are not likely to be major confounders. Furthermore, the physical activity at work for cabin crew might be higher than in most other occupations, which should decrease the breast cancer risk.[16]

Breast cancer is one of the alcohol-related cancers, with a measurable risk increase starting from one daily drink.[31] In a pooled analysis,[32] the multivariate relative risk for a 10 g per day (one unit) in alcohol was 1.09 (95% CI 1.04–1.13). In our study of female cabin crew members, we observed a tendency of decreased relative risk of strongly alcohol-related cancers of the oral cavity, pharynx, esophagus, liver and larynx.[33] This suggests that alcohol is not a positive confounder for breast cancer. Thus, none of the known risk factors seems to explain the excess risk of breast cancer.

### Leukemia

Leukemia (excluding CLL) is a malignancy suitable as an indicator of health effects of ionizing radiation due to the high relative excess risk and few other risk factors. The effects of occupational exposure to ionizing radiation on developing leukemia have been studied primarily among cohorts of nuclear industry workers. A pooled analysis of mortality among nuclear workers from 15 countries demonstrated an excess rate ratio of 0.19 for non-CLL leukemia for a cumulative protracted dose of 100 mSv compared with zero dose.[34] In our cohort, the estimated cumulative doses, however, only exceeded 20 mSv for 26% of the follow-up time, that is, the expected excess risk derived from the nuclear worker study would not exceed 1.05.

Cosmic radiation in flight altitudes consists of gamma and neutron radiation. Neutron radiation is more effective in inducing biological damage than gamma radiation. No human studies on carcinogenicity of neutron radiation have been published. We estimated exposure as effective doses, calculated using a radiation weighting factor (determined by radiation type and energy) of 5–20 for neutrons, depending on neutron energy, that is, presuming that the effectiveness of neutrons is 1–30 times that of gamma radiation. Accordingly, the absorbed (physical) dose from neutrons is multiplied by 1–30 to obtain the effective dose. Radiation doses in our study are so low that we would not have sufficient statistical power to detect an effect on leukemia, unless the weighting factors are too low by at least one order of magnitude. An increased frequency of chromosomal aberrations that may predict cancer risk[35,36] has also been reported among airline personnel.[37,38] Deletion or loss of chromosome 7 has been found increased among cases with myelodysplasia and acute myeloid leukemia (AML), the cases originating from cohorts of aircrews.[39]

The excess OR of 1.66 per 10 mSv for non-CLL leukemia in our study, based on nine cases, was not statistically significant. A Danish study in pilots[40] found suggestive evidence of an increase in the risk of AML with increasing flight hours in jets, however based on only three observed cases. The SIR for AML in our study was 1.83, based on six observed cases and thus nonsignificant.

### Skin cancers

This observations on the excess risk of skin cancers are in line with previously published findings. An increased incidence of cutaneous malignant melanoma among cabin crew was reported earlier in the Finnish, Norwegian, Icelandic, U.S. and Swedish studies.[3,6–9] A significantly increased incidence of squamous cell carcinoma was observed in the Norwegian, Icelandic and Swedish studies.[6,7,9] A meta-analysis suggested a pooled meta-SIR of 2.15 (95% CI 1.56–2.88) for malignant melanoma and a meta-SIR of 1.91 (95% CI 0.71–3.73) for squamous cell carcinoma for female cabin crew.[41]

Exposure to ultraviolet radiation (UVR) is by default the most likely explanation for the increased risk of skin cancers, as up to 90% of all skin cancers are thought to be attributable to UVR.[42] The major risk factors for malignant melanoma of the skin include intermittent sun exposure, sunburn at early age and host factors related to skin color and nevi.

There is no exposure to UVR in the aircraft cabin.[43] One study reported that the aircrews spend more time in sun resorts and use more frequently sunscreen than the general population. However, there was basically no difference in frequency of nonoccupational risk factors for skin cancer including excessive exposure to sun in a study from Iceland, and nonoccupational risk factors did not seem to explain the excess risk of malignant melanoma among aircrews in our study.[44] The risk in the head and neck area seems to be similar irrespective of whether the person is regularly outdoors or not, while skin melanoma of the trunk and limbs is more common among indoor workers probably owing to intermittent recreational UVR exposure combined with propensity to sunburn.[16]

There has been little indication of an association between ionizing radiation and malignant melanoma in earlier studies in various other settings, but the data are sparse.[10] Other skin cancers have been associated with radiotherapy among children, and an excess of BCC has been found among A-bomb survivors.[10]

It has been suggested that night shift work may also be associated with an increased risk of melanomas,[45] but a recent large prospective cohort study observed a significant decreased risk related to light-at-night.[46] We conclude that despite the nonsignificantly increased melanoma risk with exposure to cosmic ionizing radiation in our case-control study, the excess risk of skin cancer may be attributable to UVR.

We observed 10 cases of the rare Kaposi sarcoma, a sentinel cancer for AIDS, among male cabin crew. In California, male cabin crew had an 8- to 9-fold increased risk of Kaposi sarcoma.[8] This cancer type is not related to work exposures.

### Non-Hodgkin lymphoma

The only cancer type with a significantly elevated SMR among male cabin crews in the eight-country study[47] was non-Hodgkin lymphoma (9 cases, SMR 2.28 and 95% CI 1.04–4.56), while there was no excess mortality from non-Hodgkin lymphoma among the 33,000 female cabin crew members in the same study. The authors concluded that some of the deaths from non-Hodgkin lymphoma could have been related to AIDS. The SIR for non-Hodgkin lymphoma among cabin crew members in the present study was 1.89 (95% CI 0.81–3.72) in men and 1.12 (95% CI 0.30–2.88) in women. There are some data to suggest that NHL may also be related to circadian rhythm disruption but this evidence is not strong.[48]

### Cancers of the mouth, pharynx and liver

Excess risks of cancers of the mouth, pharynx and liver have been demonstrated among persons infected with human immunodeficiency virus (HIV).[49] In theory, it is possible the up to four-fold excess risk of alcohol-related cancers after retirement age in men could be associated with HIV infection.

### Detection bias

The cabin crew members are subject to regular medical control surveillance, which may affect their cancer risk pattern. An increased incidence of BCC might indicate higher diagnostic activity among cabin crew members than among the average population, but the similarity of the risk of BCC and other skin cancers (for which diagnostic activity should not play an equally important role) suggests that the excess is real. Cancers of the prostate and thyroid represent other examples of cancers where active case finding increases the incidence. The incidence of these cancers among cabin crew members did not differ from the national averages. Therefore, it appears that diagnostic activity does not have a major effect on our results.

Mammography tests may have been more frequent among cabin crew than in the reference population, but the difference should have been decreasing when the organized whole-population screening programs started (in Finland 1986, Iceland 1987 and Sweden 1997). In Norway, the organized breast cancer screening started in mid-1990s in four counties (40% of population) and was stepwise introduced until national coverage in 2004. For instance, in Finland, all women in age range 50–59 years are invited to mammography screening every 2 years, and the participation rate has been close to 90%. The SIR for breast cancer has not changed over decades, which suggests that the excess risk is not an artefact due to high diagnostic activity.

### Final remarks and conclusions

There are few areas outside the Nordic countries with several decades of population-based registration of cancer. Because our study cohort included most of the cabin crew ever certified in the four Nordic countries, our study can be considered as having the maximal potential world-wide to evaluate cancer incidence among cabin crew. Some of the results based on the national cohorts have been published earlier.[3,6,7,9] For this article, new data have been added, both in terms of additional cohort members and of increased follow-up time for those included in the national analyses. The larger material allowed analyses of more detailed classifications of exposure and subcategories of cancers than in the national settings.

Due to the accurate population registration systems in all Nordic countries, the follow-up for deaths and emigration is complete and the person-year calculations are precise. Cancer registration systems in Finland, Iceland, Norway and Sweden are also virtually complete and the computerized record linkage procedure precise.[16] Therefore, the SIR estimates of our study are not affected by bias attributable to incomplete follow-up or failures in record linkages. The use of systematically registered cancer incidence data (instead of mortality data) avoids bias caused by better cancer survival between population with a relatively high educational level such as cabin crew and the reference population,[50] as well as sometimes problematic definitions of the underlying cause of death. Furthermore, the use of incident cancers as outcome events instead of cancer deaths increases the study power due to a larger number of events and allows evaluation of risks for cancers that are rarely lethal, such as skin cancer.

Our study included a novel approach to compare cancer risk by levels of estimated exposure to cosmic ionizing radiation and of circadian disruption. There was a statistically nonsignificant indication of an increased risk of leukemia (excluding CLL) in the very highest dose levels of estimated radiation accumulated in cabin crews, and no other factors than radiation are evident that could explain the excess risk.

No association was observed for any metric of estimated cosmic radiation or the estimated circadian disruption and risk of breast cancer. For certain known risk factors of breast cancer, we did not find evidence to imply an explanation for our main results. These findings indicate a need of detailed studies focusing on more precise estimates of repeated jet lags, irregular night shift work and sleep deprivation, possible work-related factors involved in the increased breast cancer risk and the suggestive dose-response pattern in non-CLL. More information on the role of occupational exposure versus nonoccupational risk factors in the observed excess may potentially be obtained by collecting some data by questionnaire.

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