

Case Report



Assessment of risks for breast cancer in a flight attendant exposed to night shift work and cosmic ionizing radiation: a case report

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Abbreviations

CI: confidence interval; CT: computed

tomography; IARC: International Agency for

ABSTRACT

Background: Some epidemiological studies have estimated exposure among flight attendants with and without breast cancer. However, it is difficult to find a quantitative evaluation of occupational exposure factors related to cancer development individually in the case of breast cancer in flight attendants. That is, most, if not all, epidemiological studies of breast cancer in flight attendants with quantitative exposure estimates have estimated exposure in the absence of individual flight history data.

Case presentation: A 41-year-old woman visited the hospital due to a left breast mass after a regular check-up. Breast cancer was suspected on ultrasonography. Following core biopsy, she underwent various imaging modalities. She was diagnosed invasive ductal carcinoma of no special type (estrogen receptor positive in 90%, progesterone receptor positive in 3%, human epidermal growth factor receptor 2/neu equivocal) with histologic grade 3 and nuclear grade 3 in the left breast. Neoadjuvant chemotherapy was administered to reduce the tumor size before surgery. However, due to serious chemotherapy side effects, the patient opted for alternative and integrative therapies. She joined the airline in January, 1996. Out of all flights, international flights and night flights accounted for 94.9% and 26.2, respectively. Night flights were conducted at least four times per month. Moreover, based on the virtual computer program CARI-6M, the estimated dose of cosmic radiation exposure was 78.81 mSv. There were no other personal triggers or family history of breast cancer.

Conclusions: This case report shows that the potentially causal relationship between occupational harmful factors and the incidence of breast cancer may become more pronounced when night shift workers who work continuously are exposed to cosmic ionizing radiation. Therefore, close attention and efforts are needed to adjust night shift work schedules and regulate cosmic ionizing radiation exposure.

Keywords: Breast neoplasms; Ionizing radiation exposure; Occupational exposure; Aviation

BACKGROUND

Breast cancer is a malignant tumor that usually develops in the epithelium lining the lobules and milk ducts of the breast,¹ except for some rare forms of breast cancer including

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Research on Cancer; IRB: Institutional Review Board; KOSHA: Korea Occupational Safety and Health Agency; OSHRI: Occupational Safety and Health Research Institute; PC: probability of causation; PEPC ver2.0: Program for Estimating the Probability of Causation for cancer after exposure to ionizing radiation version 2.0; SIR: standardized incidence ratio.

Competing interests

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Park DJ, Lee SG; Data curation: Park DJ, Lee KE; Formal analysis: Park DJ, Lee KE; Investigation: Park DJ, Park S, Ma SW, Seo H, Lee SG, Lee KE; Visualization: Park DJ, Lee KE; Writing - original draft: Park DJ, Lee KE; Writing - review & editing: Park DJ, Lee KE.

breast sarcoma, which is the most common cancer among all diagnosed cancers in Korean women.² It is an endocrine-related cancer and is simultaneously affected by occupational and environmental factors such as night shift work³⁻⁵ or ionizing radiation exposure.^{6,7} The International Agency for Research on Cancer (IARC) reported sufficient evidence of the carcinogenic effects of X-ray and gamma-ray in breast cancer. Although the mechanism of the relationship between night shift work and breast cancer is not fully understood, the IARC has also reported that there is limited evidence of the risk of breast cancer due to night shift work⁸⁻¹⁰ based on evidence in humans and experimental animals, and mechanistic evidence.

Flight attendants are frequently exposed to cosmic radiation consisting of high-energy charged particles, x-rays, and gamma-rays as well as night shift work. Moreover, they often cross multiple time zones, especially during international flights.

Compared to the incidence of other cancer types among female flight attendants, several previous studies have reported high incidence rates of breast cancer among this population.^{11,12} It is assumed that the special working environment of airplanes poses some adverse health risks, including a frequent crossing of multiple time zones, irregular night shift work schedules, and exposure to cosmic ionizing radiation.^{13,14} Therefore, we quantitatively assessed the estimated dose of cosmic radiation and nighttime flight in an international flight attendant with breast cancer. Finally, we reported the first breast cancer recognized for work relevance in a flight attendant determined by comprehensively examining the various risk factors.

CASE PRESENTATION

Patient information

The patient was a 41-year-old woman with a body mass index of 17.93 kg/m² (167 cm, 50 kg).

Chief complaints

Incidental mass on the left breast

Present illness

A hyperdense mass was found on the outer lower quadrant of the left breast with distributed calcification when mammograms were performed at a regular check-up on January 19, 2016. A suspicious multilobulated hypoechoic mass (1.78 × 0.994 × 2 cm) was also found on ultrasonography. After referring to a university hospital, a core biopsy, chest computed tomography (CT), positron emission tomography/CT, and bone scan were performed. On January 27, 2016, the patient was diagnosed with invasive ductal carcinoma of no special type (estrogen receptor positive in 90%, progesterone receptor positive in 3%, human epidermal growth factor receptor 2/neu equivocal) with histologic grade 3 and nuclear grade 3 in the left breast. The patient was treated with the neoadjuvant combination of five cycles of pertuzumab, trastuzumab, docetaxel, carboplatin, and pegfilgrastim (TCHP). TCHP followed by surgical operation including axillary lymph node dissection and breast-conserving surgery were planned. However, the patient refused surgical enucleation and opted for alternative and integrative therapies.

Past medical & obstetrical history

The patient, para 0-0-0-0, did not use any contraceptives and had a normal menstrual cycle. Her annual health check-up conducted from 2009 to 2015 indicated no specific findings other than being underweight. No significant medical or cancer histories were found according to her records from the National Health Insurance Service.

Social history

The patient was a non-smoker. Her alcohol consumption was an average of two beers less than twice per week.

Risk assessment

Personal risk

In general, age at first birth (parity), high family income, and heredity are well-known non-occupational risk factors for breast cancer. The patient was nulliparous, and had no family history in the first or second degree of benign or malignant breast cancer.

Occupational risk

The patient worked for about two months as a librarian after graduating from college in 2016. The patient worked as an airline flight attendant from January 15, 1996, to March 1, 2016, before taking sick leave due to breast cancer. Excluding for the first 3 months after employment, she mainly took a role in an international flight.

1) Assessment of night shift work

The Ministry of Employment and Labor defines night shift work as working from 22:00 to 6:00 in Korea.^{5,9} The working hours of flight attendants fluctuate according to flight schedules; thus, their working hours and shift times are mostly irregular.¹⁵ We could collect the records of the flight time using the routes the patient visited since 2005 from the airline's computerized log database. The patient's flight schedules with working hours between 22:00 PM and 06:00 AM based on the departure time were defined as night flights.

About 12,156 hours on 2,671 times flights accounted for the total flight time, of which 11,541 hours (94.9%) were spent on international flights with 10,469 hours (81.6%) crossing the time transitional zone (**Table 1, Supplementary Table 1**). Regarding international flights, 36.0% of the routes involved time gap ≥ 12 hours between departure and arrival of the total flight time (4,373 hours, **Table 1**). Flight time of specific schedules by the countries the patient visited is presented in **Supplementary Table 1**. The total time of night flight based on departure time, corresponding to night work was 3,190 hours, accounting for 26.2% of the total flight time, and was found to occur more than four times a month.

2) Assessment of cosmic ionizing radiation exposure and probability of causation (PC)

In Korea, the Ambient Radiation Safety Control Act came into effect in July 2012, and the airline where the patient was employed launched to record the radiation dose using CARI-6M for flight crews since 2008.¹⁶ The CARI-6M, a software developed by the US federal aviation administration, calculates the effective dose of cosmic radiation exposure to an individual on an aircraft flying a user-specified route. However, the routes beyond the Korean domestic area are also considered when calculating cosmic radiation with CARI-6M.

Based on the patient's flight log records between 2008 and 2016, the cumulative dose of cosmic radiation exposure was 29.05 mSv on CARI-6M (**Supplementary Table 2**). The annual

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Table 1. The patient's working hours on flight according to the types of flight schedules from June 2005 to March 2016

Time gap between departure and arrival ^c	Number of flights	Total flight time (hours) ^a			Night time flight (hours) ^b		
		Mean ± SD	Median (range)	Cumulative flight	Mean ± SD	Median (range)	Cumulative flight
International flight							
< 1 hour	564	3.31 ± 0.57	1.91 (0.55–5.08)	1,076.97	0.03 ± 0.22	0.00 (0.00–3.73)	16.40
1 hour ≤ and < 6 hours	964	5.98 ± 2.46	3.79 (1.05–12.38)	4,227.05	1.41 ± 2.18	0.00 (0.00–8.00)	1,362.14
6 hours ≤ and < 12 hours	171	10.40 ± 1.01	10.97 (8.22–13.80)	1,862.55	3.75 ± 3.19	3.53 (0.00–8.00)	641.73
12 hours ≤	354	10.29 ± 1.93	12.77 (6.02–16.20)	4,373.67	3.30 ± 2.82	2.92 (0.00–8.00)	1,168.65
Subtotal	2,053	5.62 ± 4.28	3.73 (0.55–16.2)	11,540.23	1.55 ± 2.46	0.00 (0.00–8.00)	3,188.92
Domestic flight							
	618	1.00 ± 0.14	0.98 (0.57–1.48)	615.70	0.00 ± 0.03	0.00 (0.00–0.68)	1.49

^aFlight time was calculated using the log histories of flight schedules recorded by Kalman filter navigation based on local time; ^bThe sum of hours spent on flight between 10:00 PM and 6:00 AM was defined as a night flight; ^cTime differences between departure and arrival were calculated outside of daylight saving time, and there is no time difference in a domestic flight

Table 2. Dose of cosmic radiation in the patient calculated by CARI-6M between 2008 and 2016

Year	Annual cumulative dose (mSv)	Number of flight ^{a,b}	Exposure dose of cosmic radiation per flight (mSv)							
			Mean ± SD	50th	75th	90th	95th	99th	Min	Max
2008	3.9469	164	0.0241 ± 0.0269	0.0110	0.0417	0.0736	0.0773	0.0856	0.0001	0.0909
2009	3.6170	193	0.0187 ± 0.0230	0.0084	0.0242	0.0617	0.0713	0.0780	0.0006	0.0836
2010	4.1470	200	0.0207 ± 0.0248	0.0083	0.0323	0.0644	0.0741	0.0911	0.0006	0.0922
2011	3.8150	185	0.0206 ± 0.0233	0.0086	0.0286	0.0600	0.0679	0.0840	0.0001	0.0929
2012	3.7129	157	0.0236 ± 0.0239	0.0104	0.0460	0.0615	0.0683	0.0779	0.0008	0.0791
2013	2.9907	168	0.0178 ± 0.0231	0.0073	0.0163	0.0561	0.0690	0.0847	0.0001	0.0890
2014	2.9953	216	0.0139 ± 0.0192	0.0057	0.0120	0.0493	0.0601	0.0760	0.0001	0.0805
2015	3.2920	202	0.0163 ± 0.0213	0.0069	0.0162	0.0546	0.0628	0.0813	0.0001	0.0852
2016	0.5315	36	0.0148 ± 0.0206	0.0067	0.0112	0.0521	0.0666	0.0716	0.0001	0.0717
2008–2016	29.0483	1,521	0.0191 ± 0.0232	0.0077	0.0267	0.0601	0.0708	0.0826	0.0001	0.0929

^aThe flight records that landed after take-off was calculated as one flight for regardless of the departure and arrival location; ^bDomestic flights were excluded to estimate the exposure dose of cosmic radiation.

Table 3. Probability of causation by the estimated dose of cosmic radiation from 1996–2016

Scenarios under annual radiation exposure on board between 1996–2008	Estimated cumulative doses of cosmic radiation from 1996 to 2016	Distribution of probability of causation (KOSHA-PEPC ver2.0)			
		Median	90th	95th	99th
4.15 mSv	78.85 mSv	4.0886%	7.6197%	8.8441%	11.8915%
3.66 mSv	43.92 mSv	3.6595%	6.8705%	7.9962%	10.8103%
3.56 mSv	42.72 mSv	3.5750%	6.7223%	7.8282%	10.5954%
2.99 mSv	35.88 mSv	3.0752%	5.8179%	6.7672%	9.2159%

KOSHA: Korea Occupational Safety and Health Agency; PEPC ver2.0: Program for Estimating the Probability of Causation for cancer after exposure to ionizing radiation version 2.0.

dose of cosmic radiation was the highest in 2010 with 4.15 mSv accounting for 200 times of international flights. However, the mean dose of cosmic radiation exposure per international flight was the highest in 2008 with 0.0241 mSv (Table 2). The cumulative dose of radiation exposure over the 12-year period of 1996 to 2007 was calculated under four scenarios of annual exposure of 4.17, 3.66, 3.56, and 2.99 mSv. These are equivalent to the maximum, median, mean, and minimum values, respectively from the estimated annual doses from 2008 to 2016. The cumulative dose of the cosmic radiation during the patient's working period was 78.85, 43.92, 42.72, and 35.88 mSv respectively (Table 3).

PC developed by the Occupational Safety and Health Research Institute (OSHRI) and Radiation Health Research Institute was used to assess the causal relationship between radiation exposure and disease under four scenarios.¹⁷ It is recommended that the International Atomic Energy Agency, International Labor Organization, World Health Organization, and the United States of America jointly use the PC method as a compensation criterion for cancer occurrence.¹⁸ In Korea, the Notification No. 2014-78 of the Nuclear Safety and Security Commission recommends using the PC to determine radiation-related

occupational cancer in radiation workers.¹⁹ The PC reflects the unique characteristics of Koreans and has been well developed.¹⁷ If the PC is greater than 50% for solid cancer, the cancer is considered to be due to radiation exposure generally at the significance level of 95th percentile in Korea. The PC for the 95th percentile implies the probability of the fifth person with the highest radiation contribution to cancer development when 100 people are listed under the same condition of radiation exposure. The result of the PC for the 95th percentile was 8.84%, 8.00%, 7.83%, and 6.77% respectively against 78.85, 43.92, 42.72, and 35.88 mSv of cumulative dose of cosmic radiation between 1996 and 2016 (Table 3). The results of the PC for the 95th percentile were 8.84%, 8.00%, 7.83%, and 6.77% respectively against 78.85, 43.92, 42.72, and 35.88 mSv of cumulative dose of cosmic radiation between 1996 and 2016 (Table 3).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of the Occupational Safety and Health Research Institute IRB (IRB No. OSHRI-202108-HR-019), and written informed consent was obtained from the patient for the publication of this report and any accompanying data.

DISCUSSION AND CONCLUSION

The patient worked for 20 years as an international flight attendant since April 1996, and this case was commissioned in July 24, 2018 to Korea Occupational Safety and Health Agency for assessing the work relatedness of cancer development. Despite the slightly short duration of night-shift work and the cumulative dose of cosmic radiation under 100 mSv, the work-relatedness between flight attendants and breast cancer was approved by the Epidemiological Investigation and Evaluation Committee for this case in May 21, 2021. The committee determined considering the case specific circumstances in terms of the increasing risk of biological circadian disruption owing to international flight schedules, spending more time in working at night, and crossing time transition more frequently than regular night workers along with concurrent exposure to cosmic radiation.

In breast cancer, the cause of a mutation in a cell gene in the breast, which causes the cells to proliferate indefinitely, is unknown. Age, breast cancer history in first- and second-degree relative, age at menarche, age at menopause, nulliparity, previous benign breast disease, hormone-replacement therapy, presence of susceptibility genes such as BRCA1 and BRCA2, high-fat diet, alcohol intake, smoking, and environmental hormones have been reported as risk factors for breast cancer.^{3,20,21}

IARC also reported that there is limited evidence regarding the risk of breast cancer due to night-shift work^{8,10} based on evidence in humans and experimental animals and mechanistic evidence. In this case report, we calculated the cumulative hours of flight by locations and time for the recent 12 years of the patient. In the schedules from 2005–2016, 3,188.2 hours accounting for 27.6% of total flight hours, were during nighttime. Additionally, 25.6% (n = 525) of flights in 2005–2016 included six or more time-transition zones on each one-way flight. The Epidemiological Investigation and Evaluation Committee believed that this patient should have been classified and managed as a night-shift worker, considering that the IARC defines night-shift work as working during the usual sleeping hours of the general population, which includes trans-meridian air travel.²²

Night-shift work is known cause breast cancer development owing to circadian rhythm disturbances.²³ It is also known that the synthesis of melatonin, which has an anti-proliferative effect and a reducing effect on human cancer cells, including metastatic properties, is inhibited by light.²⁴ It is hypothesized that these factors may be related to the development of breast cancer. IARC maintained night-shift work as carcinogenic class 2A in 2019 as well as in 2007.⁹ The flight attendant crossed multiple time zones during international flights. Jet lag is known as a sleep-wake disorder caused by crossing time zones so quickly that the circadian clock cannot not keep pace.²⁵ This happens when crossing at least two time zones.²⁶ There is a difference in the degree to which flight attendants are exposed to jet lag. Grajewski et al.²⁷ reported that the number of time zones a flight attendant crosses determines the severity of circadian rhythm disturbances such as sleep displacement or melatonin desynchronization. It should also be noted that these occupational environments basically exist at high altitudes, which is reported as a risk factor of circadian rhythms disturbances.²⁸ He et al.²⁹ also reported high risk (1.56; 95% confidence interval [CI]: 1.10–2.21) of breast cancer owing to circadian rhythm disturbances in flight attendants.

Although the dose-response standard for identifying the number of night shifts related to the incidence of breast cancer is still unclear, breast cancer development among flight attendants was reported consistently. Pukkala et al.³⁰ established a cohort of airline crew members from several Nordic countries and reported their standardized incidence ratio (SIR). SIR for breast cancer in the crew members was 1.50 (95% CI: 1.32–1.69). In this cohort study, the average follow-up time of the participants was 23.6 years, like that of the present patient.³⁰ Several meta-analysis studies including female flight attendants were conducted. Buja et al.³¹ reported that breast cancer meta-SIR in female flight attendants was 1.4 (posterior index: 1.19–1.65) by analyzing seven previously published studies. Tokumaru et al.³² conducted a meta-analysis study including female attendants using a bibliographical computer search. The combined relative risk calculated through data analysis for about 41 years was 1.41 (95% CI: 1.22–1.62).³² Liu et al.³³ performed a meta-analysis of breast cancer-related studies recruiting flight attendants; after analyzing ten eligible studies, the SIR of flight attendants' breast cancer was 1.40 (95% CI: 1.30–1.50). Large meta-studies consistently reported an association, and one study explained that breast cancer development among flight attendants was attributed to night-shifts. In the study, the relative risk was 1.79 (95% CI: 1.25–2.57) for international flights of short time-duration and 2.26 (95% CI: 1.08–4.75) for overnight shifts.³⁴

Ionizing radiation is known to cause breast cancer by affecting hormonal regulation, oxidative stress, DNA damage, inflammation reaction, and genomic variation.³⁵ The IARC reported that there was sufficient evidence of the carcinogenic effect of ionizing radiation in patients with breast cancer,⁸ even though the association between cancer development and exposure to low-dose radiation remains controversial.³⁶ In this case, it was assessed that the patient was exposed to 2.99–4.17 mSv of cosmic radiation annually on her occupational flight. According to the estimated natural radiation exposure dose of the Spanish population, the annual dose was reported to be about 1.6 mSv.³⁷ Compared to the patient's occupation period of about 20 years, the net occupational radiation exposure excluding natural exposure is about two times higher than that of the general population.

Considering the result of PC (8.84% at maximal estimates), additional exposure to cosmic radiation itself did not contribute significantly to increased risk of breast cancer. However, it is recently reported (by analyzing blood samples from 150 nurses) that ionizing radiation exposure during shift work and working at night elevates levels of circulating redox and inflammatory cytokines, which are known to induce cell mutation and cancer development.³⁸

In this patient, the nulliparity might also contribute to the progression of carcinogenesis in the breast. Schubauer-Berigan et al.³⁹ explained that the higher incidence of breast cancer among flight attendants was due to age at first birth and parity in the US. Other studies reported that occupational factors such as circadian disruption and cosmic radiation were independently associated with the high risk of breast cancer irrespective of the existence of obstetric risk factors.³⁹⁻⁴¹ Airline and railroad flight attendants are considered representative occupations in Korea that are prone to career interruption due to childbirth and childcare; thus, considering social perspectives rather than individual factors, nulliparity could be regarded a risk factor of breast cancer among individuals in these occupations.

There are several limitations in this case report. First, the exposure during the clinically undiagnosed period was not excluded when calculating the exposure period; the flight-time and cumulative dose of cosmic radiation could be overestimated. However, the result of PC applying the cumulative dose of cosmic radiation would not be largely affected. The PC program we used is designed to include the date of diagnosis and the type of the disease; it automatically calculates the probability by weighing the exposure considering the latent period of the disease based on domestic epidemiology. Second, the patient's actual flight schedules could only be used partly because the airline did not keep the record before 2005. When the Ambient Radiation Safety Control Act was enacted, the estimates of cosmic radiation for each route were recorded in the airlines after 2008 using CARI-6M for flight crews. Considering that the dose of cosmic radiation was not regulated by individual tracking before 2018, the actual cosmic radiation exposure of the patient could be higher than our estimate. Therefore, we provided the estimates under four scenarios of annual exposure: the maximum, median, mean, and minimum values from the estimated annual doses between 2008 and 2016. Third, the nighttime flight was calculated based on departure time; thus, there might be cases where the amount of sunlight at arrival does not affect the circadian rhythm although the flight was classified as a nighttime flight.

This report is the first to quantitatively assess the flight time considering nighttime flights and cosmic radiation exposure in an international flight attendant for 20 years. Despite several limitations, this report provides several suggestions regarding health protection among flight attendants. We found that 27.6% of total flight hours were in the nighttime with 25.6% of international flights crossing six or more time-transition zones during 20 years. We also showed that the international flight attendant was annually exposed to 2.99–4.17 mSv of cosmic radiation, which was twice that of the general population exposure.³⁷ However, many flight attendants in Korea do not undergo health checkups as nighttime and radiation workers, because nighttime work in the enforcement regulations of the Occupational Safety and Health Act is defined only by the chronological period without considering the trans-meridian air travel. Moreover, the cabin crews are not yet classified as radiation workers and are not strictly managed through health checkups for radiation exposure in the enforcement decree of the Act on Protective Action Guidelines against Radiation in the Natural Environment nor in the Aviation Act. Under these circumstances, regular health monitoring of flight attendants is required to prevent health problems attributed to the occupational exposure. Further, the regulatory amendments in health management for workers covering the flight attendants should be prepared.

This report also provided the statistics of flight time and radiation exposure dose by location in the appendices; they can be used for occupational exposure assessment of other flight attendants. These data are expected to be useful for other occupational medical specialists evaluating the occupational exposure level of workers with flight crew history.

This report supported the committee to apply the epidemiologic evidence of higher incidence of the breast cancer among attendants. The committee determined that about 20 years of irregular flight schedules with jetlag and additional cosmic radiation exposure twice as high compared with the general population might be attributed to breast cancer in a flight attendant.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Summary of patient's flight schedules based on the time spending on flights based on the departure time by the airport spot (2005–2016)

[Click here to view](#)

Supplementary Table 2

Patient's international flight histories and estimated dose of cosmic radiation by Cari-6M based on the airport spot between departure and arrival (2008–2016)

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