Journal of BUON **13:** 377-384, 2008

ORIGINAL ARTICLE

The incidence of malignant neoplasms in individuals working in areas of ionizing radiation in hospitals

S. Milacic
University of Belgrade, Faculty of Medicine, Institute of Occupational Medicine and Radiological Protection, Belgrade, Serbia

Summary

Purpose: *To assess the radiation risk of carcinogenesis in individuals professionally exposed to low-level ionizing radiation in a longitudinal cohort study.*

Materials and methods: *Analysed were the incidence and mortality induced by malignant neoplasms in a cohort of 1,560 occupationally exposed individuals (OEI) working in areas of ionizing radiation during 1992-2002 (study group). Assessment of exposure to radiation was recorded by personal thermoluminescent dosimeters (TLD), regular periodic health checkups, and bio-dosimetric data (chromosomal aberrations). Incidence and mortality were calculated using conventional epidemiological methods. The same methodology was applied in 5,480,408 individuals from the general population of central Serbia (PCS), not professionally exposed to ionizing radiation (control group).*

Results: *The annual incidence rate of malignancies was 163 for males and 282 for females, per 100,000 OEI and mortality 44 for males and 11 for females. For general PCS the annual incidence rate of malignancies was 374 for males and 347 for females per 100,000, while mortality was 267 for males and 191 for females. Solid malignant neoplasms prevailed in OEI.*

The frequency of chromosomal aberrations in the group of OEI with malignant neoplasms was 0.33%, compared with 0.20-0.50% of the general population. The incidence of pharyngeal carcinomas in the group of occupationally exposed males was 5-fold higher than in males of the general PCS. In females of OEI the risk of malignant neoplasms such as uterus, ovary, bone marrow, lymphomas, thyroid, larynx and breast was increased compared with the general PCS.

Conclusion: *The incidence rate of malignancies in the group of OEI to low-level ionizing radiation was not significantly different from the incidence rates of malignant diseases in the general PCS. The same applied for mortality. Differences were observed between the OEI and the general PCS in the localization of malignant neoplasms and sex.*

Key words: carcinogenesis, incidence, malignant neoplasm, low-level ionizing radiation

Introduction

Any substance in a working place is considered to be occupational carcinogen if it is capable to increase the incidence of malignant diseases among the exposed workers. Ionizing radiation causes stochastic effects in the cell which are not linearly correlated to the absorbed dose. Exposure to ionizing irradiation itself is a risk sufficient for carcinogenesis and the probability of clinical manifestation of cancer is correlated to the absorbed dose as its exponential function. Development of malignant tumors may be simultaneously influenced by numerous factors, both external and hereditary, as well as constitutional ones. Cohort studies select a study group (cohort) based on the information on the presence or absence of certain exposure and they assess the risk of onset of diverse diseases in the exposed cohort in comparison to the non-exposed one [1]. These studies are most commonly used for investigation of chronic diseases with prolonged latency, such as occupational cancer. The epidemiological studies aimed at investigating the occupational cancers are intended at identifying

Correspondence to: Snezana Milacic, MD. Faculty of Medicine, University of Belgrade, Institute of Occupational Medicine and Radiological Protection. Deligradska 29, 11000 Belgrade, Serbia. Tel: + 381 11 3674 515, Fax: + 381 11 643 675, E-mail: m.masha@beotel.net

Received 21-12-2007; Accepted 02-02-2008

of the working environments and occupations associated with increased risk of cancer among a group of workers [2]. Health care professionals working in ionizing irradiation zones are subjected to medical supervision pursuant to the Law on ionizing radiation protection [3], although no influence of low doses on increased tumor-associated mortality has been verified. Malignant tumors are caused by increased exposure in industrial [4] and nuclear plants, in the course of accident management or after decontamination of the terrain or they may be caused by years-long radionuclide intake on the contaminated terrains [5,6].

Leukemia is the most commonly described malignant disease associated with exposure to radiation of both children from contaminated regions and occupationally exposed adults. Solid tumors account for only 0.4% of all malignant diseases caused by ionizing radiation, with thyroid carcinoma being the most frequent one [5-7].

Investigation of the consequences of accidental and wartime radioactive contaminations evidenced significant increase of the incidence of colon and lung carcinomas in males and breast carcinomas in females, as well as increased number of solid tumors, regardless of their localization. It has been notorious that ionizing radiation primarily results in damaging of the most radiosensitive tissues. Therefore, diagnostic procedures involving these tissues are included in the program of the preventive, periodic medical checkups of the exposed health care professionals. Even the slightest disorders necessitate decrease of exposure, i.e., removal of a worker from the radiation zone, which enables repair in the phase when the changes are reversible. The most sensitive tissues are at the same time the most reparable. In this way, the onset of disease is postponed or prevented [6].

However, the probability of onset of solid tumors in exposed workers has been neglected. It may be assumed that in the group of sensitive individuals, ionizing radiation acts as cofactor for the development of different tumors even on the relatively radioresistant tissues. As for the radiosensitive individuals, even small doses may suffice for initiation of carcinogenesis [7,8].

This study aimed at investigating the incidence of different tumors of diverse localizations influenced by occupational exposure to ionizing radiation, in comparison to the occupationally non-exposed adult population in Serbia.

Materials and methods

Epidemiological methods of this retrospective longitudinal cohort study were used for comparison of the incidence and mortality due to malignant tumors between health care professionals working in ionizing radiation zones (OEI) and the general adult population in central Serbia over the specific time period, from 1992 to 2002.

The cohort comprised 1,560 health care workers in ionizing radiation zones in central Serbia (study group) who had been subjected to regular checkups in the period 1992-2202, based on the program of radiological protection of individuals occupationally exposed to radiation [3].

The annual equivalent ionizing radiation doses absorbed by the cohort subjects were measured using personal TLD and expressed in millisiverts (mSv) [4, 9,10]. The exposure was also assessed based on the absorbed dose and the incidence of chromosomal aberrations counted on 200 mitoses of peripheral blood lymphocytes [6].

The occupational structure of the study group is presented in Table 1. Out of 1,560 subjects, with their age ranging from 20 to 65 years (median 41), the group aged 40-50 years was the most predominant (approximately 40%) with male to female ratio of 43 vs. 57% (675 vs. 887 persons, respectively).

Standard epidemiological procedures [2] were used for the calculation of incidence and mortality rates for the given cohort over the specific 10-year period.

General incidence and mortality rates of OEI and specific rates according to sex were calculated as follows:

Incidence rate formula

$Ir = [\Sigma MNC: (\Sigma OEI \times TP)] \times 100{,}000$

Ir - Incidence rate
MNC - Malignant neoplasm cases
OEI - Occupationally exposed individuals
TP - Time period

Specific incidence rate formula for females

$SIrf = [\Sigma FMNC: (\Sigma FOEI \times TP)] \times 100{,}000$

SIrf - Specific incidence rate of females
FMNC - Female malignant neoplasm cases
FOE - Females occupationally exposed
TP - Time period

Specific incidence rate formula for males

$SIrm = [\Sigma MMNC: (\Sigma MOEI \times TP)] \times 100{,}000$

SIrm - Specific incidence rate of males
MMNC - Male malignant neoplasm cases

Table 1. Medical workers of different occupations exposed to ionizing radiations (study group, n=1,560)

No.	*Occupation*	*Sex*				*Total*	
		Male		*Female*			
		n	*%*	*n*	*%*	*n*	*%*
1	Roentgen technicians	233	34.5	435	49.0	668	42.8
2	Senior Roentgen technicians	130	19.3	101	11.4	231	14.8
3	Pneumonologists / T.B. specialists	32	4.7	28	3.2	60	3.8
4	Specialists in nuclear medicine	4	0.6	14	1.6	18	1.2
5	Radiologists*	110	16.3	81	9.1	191	12.2
6	Dental technicians	1	0.1	9	1.0	10	0.6
7	Anesthesiologists	0	0.0	1	0.1	1	0.1
8	Dentists	21	3.1	9	1.0	30	1.9
9	Surgeons	8	1.2	1	0.1	9	0.6
10	Cardiologists	4	0.6	13	1.5	17	1.1
11	Gynecologists	0	0.0	1	0.1	1	0.1
12	Photo-laboratory technicians	7	1.0	14	1.6	21	1.3
13	Medical technicians	2	0.3	68	7.7	70	4.5
14	Laboratory technicians	12	1.8	26	2.9	38	2.4
15	Other workers in zone	110	16.3	86	9.7	196	12.6
	Total	675	100.0	887	100.0	1560	100.0

*Both diagnostic and therapist doctors

MOE - Males occupationally exposed
TP - Time period

Mortality rate formula

Mr = [(ΣDMNC: TP): (ΣOEI × TP)] × 100,000
Mr - Mortality rate
DMNC - Deceased from malignant neoplasm cases
OEI - Occupationally exposed individuals
TP - Time period

Specific mortality rate formula for females

SMrf = [ΣFMNC: (ΣFOEI × TP)] × 100,000
SMrf - Specific mortality rate of females
FMNC - Females deceased from malignant neoplasm cases
FOE - Females occupationally exposed
TP - Time period

Specific mortality rate formula for males

SMrm = [ΣMMNC: (ΣMOEI × TP)] × 100.000
SMrm - Specific mortality rate of males
MMNC - Males deceased from malignant neoplasm cases
MOE - Males occupationally exposed
TP - Time period

Standardized incidence and mortality rates represent fictive values reached by a certain technique, introducing standard population of central Serbia. They are used to eliminate differences (mostly gender and age) existing in different populations and are, therefore, convenient for comparison.

The same methodology was applied in the control group of 5,480,408 individuals from the general PCS, not professionally exposed to ionizing radiation.

Parameters of OEI to ionizing radiation were compared with the corresponding rates in the PCS exposed only to the natural radiation [10]. The average annual rates per 100,000 individuals non-occupationally exposed to ionizing radiation (raw rates) were adopted from the Cancer Register of Central Serbia [11].

The impact of other factors, except ionizing radiation, such as duration of exposure and years of service, smoking habits and family history of cancer were also analyzed for the OEI. The data were retrieved from periodical examination forms of exposed workers and presented as relative numbers (%).

The results are presented in relative numbers, percentages and rates. The significance of difference between incidences is presented as relative risk (RR).

Results

Malignant neoplasms occurred in 36 out of 1,560 OEI (study group). Intervals of equivalent doses received by the 36 subjects were approximately similar to the absorbed doses in the other subjects of the study group, as well as in the general PCS due to natural radiation (1-2 mSv (average 1.5, range 1-2 mSv; Table 2).

The incidence of chromosomal aberrations as a

Table 2. Annual average of equivalent doses measured with TLD of diseased workers*

mSv/year	*n*	*%*
0.50 - 1.00	9	25.00
1.01 - 1.50	15	41.70
1.51 - 2.00	11	30.60
2.01 - 2.50	1	2.80
Total	36	100

*For non-diseased workers the average was 2.5 (range 1-5); for general PCS the range was 1-2

specific element of the periodic checkups induced by the absorbed dose was 0.33% (a total of 24 per 7,200 mitoses), which was not significant, as it was less than 1% (Table 3).

The incidence of malignant tumors in the study group was lower than the incidence recorded in the general PCS of both sexes (Table 4). Also in the study group sex distribution was significantly different, with higher incidence among females, while in the general PCS the incidence did not differ significantly between sexes.

The average annual mortality was also significantly lower in the study group (Table 5).

In the same group the highest incidence of tumors was evidenced among those working with x-ray apparatus, particularly x-ray technicians, followed by radiologists (both diagnostic and therapist doctors) (Table 6).

The incidence of tumors developing in the course of occupational exposure was compared to the one evidenced in the general PCS (raw incidence rate) per 100,000 (Tables 7 and 8).

The group of male subjects developed the following malignant tumors (Table 7): lung, skin, hypopharynx, larynx and colon. The incidence of hypopharyngeal carcinoma was 5-fold higher in the study group compared with the control group. Occupational exposure to ionizing radiation significantly increased the risk of onset of carcinoma in this localization. Malignant tumors of the lung were the most frequent malignancies in males (Table 9), including the occupationally exposed workers as well (Table 7). The difference in incidence was not significant and the RR was not increased due to the occupational exposure, being 0.9. The incidence of tumors of other localizations was also non-significantly increased as a result of work in a radiation zone (RR <1; Table 7).

Breast was the most frequent tumor localization in the group of female subjects (Tables 8 and 9). Comparison of incidence rates of the malignant tumors according to their localization in the exposed women and raw incidence rate in the general PCS per 100,000 subjects revealed higher incidence rates of malignant

Table 3. Frequency of chromosomal aberrations in the study group

Chromosomal aberrations - characteristic						*Chromosomal lesions- non characteristic*		*Total*	
Dicentric		*Acentric fragment*		*Ring*		*Breaks and exchanges*			
n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
3	0.04	14	0.20	–	–	7	0.09	24	0.33

Table 4. Average annual incidence and relative risk (RR) of malignant neoplasms per 100,000 individuals in males and females

Population	*Incidence on 100,000 individuals per year*					
	Males	*%*	*RR*	*Females*	*%*	*RR*
Exposed population	163,00	0.16	0.43	281,80	0.28	0.81
Population of central Serbia	374,00	0.37		347,00	0.34	

Table 5. Average annual mortality and relative risk (RR) of malignant neoplasms per 100,000 individuals in males and females

Population	*Mortality on 100,000 individuals per year*					
	Males	*%*	*RR*	*Females*	*%*	*RR*
Exposed population	44	0.044	0.16	11	0.01	0.05
Population of central Serbia	267	0.267		191	0.19	

Table 6. Malignant neoplasms' frequency according to occupation

Occupation	*Malignant neoplasm* *n*	*%*
Roentgen technicians	15	41.40
Senior Roentgen technicians	7	19.50
Radiologists*	7	19.50
Medical technicians	3	8.40
Laboratory technicians	1	2.80
Dentists	1	2.80
Pneumonologists / T.B. specialists	1	2.80
Other workers in zone	1	2.80
Total	36	100.00

*Both diagnostic and therapist doctors

breast tumors in the group of the exposed women in comparison to the general population. However, the difference was not significant and the relative risk was only slightly increased (RR=1.05).

The incidence of the uterine (RR=2.1) and ovarian (RR=1.3) cancer was significantly higher ($p<0.05$) in the group of OEI (Table 8). The incidence of malignant tumors of the larynx (RR=5.5), thyroid gland (RR=3.6), bone marrow (RR=5.5) and lymphomas (RR=11) were also significantly higher ($p<0.01$) and thus, the risk of malignant diseases at these localizations was significantly higher in the female population.

The rank of the most common malignant tumors in individuals from the ionizing radiation zones was

Table 7. Average annual incidence of malignant neoplasms in males according to localization

Localization	*Average annual incidence per 100,000 OEI*	*Average annual incidence per 100,000 individuals of PCS*	*RR*
Lung	89	97	0.91
Skin	30	46	0.65
Pharynx	15	3	5.00
Larynx	15	20	0.75
Large bowel	15	22	0.68

OEI: occupationally exposed individuals, PCS: general population of central Serbia, RR: relative risk

Table 8. Average annual incidence of malignant neoplasms in females according to localization

Localization	*Average annual incidence per 100,000 exposed persons*	*Average annual incidence per 100,000 individuals of population in central Serbia*	*RR*
Breast	101	96	1.05
Uterine corpus	45	21	2.14
Uterine cervix	45	35	1.29
Skin	23	38	0.60
Ovary	23	17	1.35
Bone marrow	11	2	5.50
Thyroid gland	11	3	3.66
Larynx	11	2	5.50
Lymphoma (non-Hodgkin's)	11	1	11.00

RR: relative risk

Table 9. Rank of the most frequent malignant neoplasms in central Serbia according to localization and sex

Rank	*Males*	*Average annual incidence* *PCS*	*EI*	*Females*	*Average annual incidence* *PCS*	*EI*
1	Lung	97	89	Breast	96	101
2	Prostate	30	0	Uterine cervix	35	45
3	Urinary bladder	26	0	Lung	27	0
4	Large bowel	22	15	Uterine corpus	21	45
5	Stomach	22	0	Ovary	17	23

PCS: population of central Serbia, EI: exposed individuals almost identical to the rank found in the general PCS (Table 9). In females, the most common was breast cancer and in males lung cancer. Out of 11 males affected with malignant tumors, 6 (54.5%) were diagnosed with lung cancer (Table 10), while out of 25 females with malignant tumors, 9 (36%) were affected by breast cancer (Table 11).

Skin cancer (Tables 10 and 11) ranked 2nd and 4th in occupationally exposed male and female workers, respectively, while in the general PCS they were not among the first 5 localizations (Table 9). However, the RR of developing skin cancer was not increased in the study group (RR=0.6).

Development of systemic hematopoietic and lymphatic system malignancies was evidenced in females, while in males only solid tumors were found (Table 10). Leukemia and non-Hodgkin's lymphoma (Table 11) accounted for 8% of female cancers, while the remaining 92% were solid tumors.

The highest incidence of malignant tumors (41.4%) was found between 21 and 30 total years of service. Concerning 11 and 20 years of occupational exposure to ionizing radiation the incidence of malignant tumors was 36.2%, while it was only 14% after 30 years.

Family history of cancer was identified in 12 (33.4%) of the affected OEI (Table 12). Out of the total number of cancer patients, 25 (69.4%) were smokers (Table 13). Family history of cancer and tobacco smoking was similar to the general PCS [11].

Table 10. Malignancies in exposed males in the period 1992-2002 ranked by frequency

Rank	*Cancer type*	*n*	*%*
1	Lung	6	54.5
2	Skin	2	18.2
3	Larynx	1	9.1
4	Rectum	1	9.1
5	Hypopharynx	1	9.1
	Total	11	100.0

Table 11. Malignancies in exposed females in the period 1992-2002 ranked by frequency

Rank	*Cancer type*	*n*	*%*
1	Breast	9	36
2	Uterine cervix	4	16
3	Uterine corpus	4	16
4	Skin	2	8
5	Ovary	2	8
6	Larynx	1	4
7	Thyroid	1	4
8	Leukemia	1	4
9	Non-Hodgkin's lymphoma	1	4
	Total	25	100

Discussion

No absolute radiation risk of carcinogenesis due to occupational exposure of health care professionals to low-dose ionizing radiation has been documented. The increased relative radiation risk was detected on certain localizations after prolonged latency.

Based on TLD and the frequencies of chromosomal aberrations, radiation-induced damages were not expected in the studied cohort. However, in conditions of chronic occupational exposure, radiation risk cannot be ruled out [6,7]. Epidemiological studies [9,11] evidenced lower average annual incidence (raw rate/100,000) of malignant tumors in males in the exposed population in comparison to the average annual incidence (raw rate/100,000) of malignant tumors in males and females in the general PCS. The radiation risk was not increased, being almost the same as in the occupationally unexposed population. Most of the subjects in whom the increased dose (mSv measured by TLD) or those with higher frequencies of chromosomal aberrations (positive biodosimetric test) were removed timely from the zone of exposure and they were not in the group of the affected individuals.

As for the subjects affected with cancer, most of them were not exposed to excessive doses, and had not increased incidence of chromosomal aberrations, and therefore, they continued to work in ionizing radiation zones. It is not possible to estimate the number of workers

Table 12. Family history of cancer of occupationally exposed individuals

Family history of cancer	*Malignant neoplasm*	
	n	*%*
Yes	12	33.4
No	24	66.6
Total	36	100.0

Table 13. Tobacco smoking impact of occupationally exposed individuals

Smoking	*Malignant neoplasm*	
	n	*%*
Yes	25	69.4
No	11	30.6
Total	36	100.0

that wouldn't develop malignant diseases if they were removed from ionizing radiation zones. In addition, mandatory periodical checkups enable earlier detection of precancerous lesions and timely treatment. Thus, survival is also prolonged and the mortality of the exposed subjects is significantly lower. Control of exposure has influenced significantly the development of cancer [7,8,11].

The maximum admissible dose (MAD) for the occupationally exposed individuals is 100 mSv/5 years (or 20 mSv/year), while the lowest dose for the initial, dose-dependent, radiation-induced damages of the radiosensitive tissues is 150 mSv [8-10]. However, biological consequences of the low radiation doses with low linear energy transfer (LET) (x or gamma rays) below 0.1 Gy (absorbed doses), i.e., 100 mSv (equivalent dose), are possible [10].

Significant biological changes are also possible in the absence of direct nuclear damage, i.e., in the absence of obvious mutation(s) but with onset of gene expression, DNA repair and cell metabolism disorders [9,10]. Genomic instability developed in this way in the metabolically and functionally altered cell with reduced antioxidant reserve is in linear correlation with induction of carcinogenesis [12,13].

Detection of gene radiosensitivity as a genetic instability marker in the population may be used in epidemiological studies for the determination of the way by which molecular changes can influence the radiation risk [13,14].

In our study the incidence of cancer was higher in the exposed women. Sex distribution in the study group was uneven and was not analogous to the sex distribution in the general population. The distribution of women working in the radiation zones was higher, and consequently the distribution of patients affected with cancer was higher. We have found that the incidence of malignant tumors was higher in the group of occupationally exposed women in comparison to the incidence in the group of occupationally exposed men. It is possible that women are more extensively exposed and susceptible, or the disease is diagnosed earlier due to an easy-to-diagnose localization (e.g. breast). However, the number of the deceased women is significantly lower since both prevention and prophylaxis are more effective in women [14-16].

Breast cancer is the first most common malignancy in women in Serbia. Its incidence is slightly higher in women working in radiation zones, and thus the influence of small doses of ionizing radiation cannot be ruled out, in addition to hormonal, constitutional, age-related and other factors, such as habits of alcohol consumption and cigarette smoking [15-18]. Epidemiological cohort studies carried out in 2003 in the USA suggested that the breast is radiation-sensitive since rather low doses (2 mGy/year) absorbed over a 15-year period increased the incidence of tumors [16-18]. Breast cancer is the most common malignancy in women in America, and in addition to skin cancer, it is also an occupational disease in women working in nuclear plants [15]. The minimal period of latency is 10 years, while the risk is highest 20 years after the initial exposure. Breast cancers that are proved to be a consequence of radiation tended to develop in earlier age, 15 years earlier on average than in the non-exposed women [6,16,17].

Comparison of the incidence rates of malignant tumors of the respiratory system (lung, hypopharynx, larynx) has shown higher rates in the exposed males [17-20]. Under the influence of low LET radiation below 100 mSv, no significant increase of lung cancer morbidity was evidenced. Significantly higher incidence of lung cancer was described only in miners and uranium and radon-exposed industrial workers due to inhalation of the high LET radioactive particles (alpha) [5]. Higher incidence of the respiratory malignant tumors influenced by low LET radiation (gamma - cesium-Cs137) was found in workers engaged in the management of the nuclear accident in Ukraine, however only after 12-15 years after the Chernobyl accident, with insignificant increase of RR (RR: 1.28) [5,18,20]. RR for lung carcinoma in our subjects was 0.9, with hypopharyngeal carcinoma RR being 5.

In our study malignant tumors of the respiratory system were the most common in males, both exposed and unexposed. The contribution of smoking was high, present in 2/3 of the cohort subjects. On the other hand, smoking is also widespread in the general population. Cigarette smoke is a documented carcinogenic substance, it belongs to the group one of the environmental carcinogens and is the most responsible for lung malignancies, which are equally distributed in both exposed and unexposed subjects [18,19]. Nevertheless, the incidence of some respiratory tumors, such as laryngeal carcinoma, was significantly higher in x-ray technicians and radiologist doctors [20].

In the present study malignant tumors of the skin tended to develop in the occupationally exposed workers; however, the RR was not increased. The incidence rates of these tumors are lower, both in males and females, due to roentgen x and gamma rays. Low LET radiation (x and gamma) penetrates the whole body, thus inducing less extensive radiological effects on the surface. Ionization density in the skin is minimal [11,20].

It is generally known that in addition to skin cancer, acute and chronic leukemia are the most common consequences of ionizing radiation. However, neither our nor previous studies [17-19] evidenced that. In our study, leukemia and lymphomas developed only in women, contrary to other studies [15,17,20], while solid tumors affecting airways, head & neck sites and female reproductive organs were present in the majority of the patients.

The average annual mortality of OEI in the 10-year period of this study was significantly lower than the mortality from malignant tumors in central Serbia in the year 2000.

Malignant tumors characterized by prolonged latency, slower evolution, rare metastases and prolonged survival in comparison to other tumors developing in the general population are found in the OEI [11,18,19]. Thus, mortality rates are rather low in the OEI, even in the presence of increased incidence [2,15]. The cumulative effect of low doses leads to 2-3-fold increase of the radiation risk [1,18]. Increased mortality from cancers resulting from exposure to low chronically absorbed environmental doses is described in individuals over 45 years of age, still only after prolonged latency [18].

Solid tumors in less radiosensitive organs are predominant. The morbidity is higher among females while the mortality is higher among males. X-ray technicians are more frequently affected than other individuals in radiation zones. Long-term occupational exposure to low doses of ionizing radiation has caused increased risk of malignant diseases because of the cumulative effects of radiation.

Control of the exposure and radiological protection of the occupationally exposed individuals have reduced the risk of developing malignant diseases. Chronic exposure to radiation is one of the co-factors which, along with other factors, contributes to initiation of carcinogenesis.

Acknowledgement

We are grateful to Dr. Tanja Dasić for the collected data, Prof. Dr. Tanja Pekmezović for her assistance in data processing using the conventional epidemiological methods and Mr. Jadranko Simic for the final preparation of the text.

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