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REVIEW ARTICLE

Risk factors for breast cancer: is ionizing radiation among them?

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Summary

All human beings are exposed to the influence of ionizing radiation from natural, medical and other artificial sources. Therefore, the influence of radiation as a risk factor for cancer development has been among the most studied external factors over the last 6 decades, particularly with respect to radiosensitive tissues and organs. It has been known that female breast tissue is highly sensitive to the carcinogenic effects of radiation, particularly when exposure takes place at younger age. All women are exposed to low doses of radiation for several common reasons (kind of occupation, medical diagnostic procedures, residence background radiation) whose effects on breast cancer development cannot be documented, and thus it is believed that ionizing radiation is not primary or major risk factor leading to development of breast cancer. Radiobiological studies revealed a specific event caused by radiation through recognition of the critical target in radiation-induced carcinogenesis. Accordingly, mutagenic and carcinogenic effects of ionizing radiation are evidenced both in vitro and in vivo, although the incidence of radiation-induced cancers is low. The highest risk of radiation-induced breast cancer is evidenced in the sub-population of female patients who have undergone radiotherapy for either malignant or non-malignant diseases, including benign breast diseases in their childhood or young age. Therefore, as a means of prevention in this group of population, indications for application of ionizing radiation, both diagnostic and therapeutic, should be highly selective, meaning that radiation should be applied only if the possible benefit outweighs the risk.

Key words: breast cancer, ionizing radiation, radiation-induced carcinogenesis

Introduction

All human beings are exposed to the influence of ionizing radiation from natural, medical and other artificial sources. Therefore, the influence of radiation as a risk factor for cancer development has been among the most studied external factors over the last 6 decades, particularly with respect to radiosensitive tissues and organs. It has been known that female breast tissue is highly susceptible to the carcinogenic effects of radiation, particularly when exposure takes place at younger age - before menopause.

Life on Earth is associated with exposure of all humans to low-level ionizing radiation from natural sources, including the radioactive gas radon which is inhaled, radioactive elements such as potassium-40 which is found in food (salt), uranium and thorium which are contained in the soil, as well as cosmic irradiation. In addition to natural sources, there are also numerous sources of ionizing radiation which have been introduced with the development of modern technologies: medical – used in diagnosis and treatment; industrial radioactive waste resulting from testing nuclear weapons or reactor accidents; radioactive emission associated with nuclear facilities, etc. In the light of fact that the whole population is exposed to ionizing radiation, the relevant literature reports the contribution of the natural sources to be the highest, followed by medical exposure. The radiation amount –a dose to be received by a woman over her lifetime– depends on the above-mentioned factors: type

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and number of radiological and radioisotopes-based diagnostic and therapeutic procedures, place of living, occupation and lifestyle. All women are exposed to low doses of radiation whose the carcinogenic effects cannot be documented, and thus it is believed that ionizing radiation is neither primary nor major risk factor leading to development of breast cancer. Although unnecessary exposures should be avoided, when application of certain diagnostic or therapeutic procedures are medically indicated, they should be performed regardless of the possible radiation risk. Radiobiological studies have revealed specific events. Studies on the carcinogenic potential of ionizing radiation have focused on initial DNA damage, which, if improperly repaired, can result in mutations or chromosomal damage. Also, cells surviving radiation can exhibit a persistent state of genomic instability. Although DNA damage can cause cell death and eliminate potentially dangerous cells, misrepaired damage may result in a mutation that can end up in the creation of a neoplastic cell. Consequently, DNA is commonly considered the major target of ionizing radiation damage. Nonmutagenic effects of ionizing radiation, however, can have persistent effects that perturb the multicellular system in a manner that clearly promotes, and may initiate, the neoplastic process caused by radiation through recognition of the critical target (DNA) in radiation-induced carcinogenesis [1-3]. Accordingly, mutagenic and carcinogenic effects of ionizing radiation are evidenced both *in vitro* and *in vivo*, although the incidence of radiation-induced cancers is low [4-8].

Radiation-induced breast cancer

What has been determined by the studies carried out so far on radiation-induced breast cancer and which factors influence or modify the carcinogenic effects of ionizing radiation?

The answer to the question that may be posed whether ionizing radiation is the cause of development of breast cancer is "yes". The association between radiation exposure and oncogenesis has been documented, particularly based on the epidemiological studies carried out on survivors of the atomic bombing in Japan during the World War II [9,10]. Moreover, the increased risk of malignant diseases has been evidenced among patients subjected to radiotherapy for both non-malignant and malignant diseases. Generally, the relative risk is higher in the Japan cohort in comparison to comparable groups exposed to radiation for medical reasons [11]. However, the absolute risk was proved to be higher in the majority of the radiotherapy groups [11]. The controversy may be explained by the significantly higher doses of radiation since the treatment is aimed at sterilization of the irradiated cells. On the other hand, one must also take into account the contribution of other factors, such as higher genetic-carcinogenic predisposition in most of the radiotherapy series in comparison to the Japanese series, as well as the effects of the level of the dose and the time of its absorption [10]. According to Little [11], the above-mentioned increase in risk should be precisely balanced, taking into account the higher spontaneous risk in these individuals and benefits that they may have from radiotherapy.

One of the studies carried out so far [12] has evidenced that sufficiently high ionizing radiation doses may be the cause of breast cancer in certain population groups: 1) women who had survived the atomic bombing in Japan during the World War II; 2) women treated by supradiaphragmatic radiotherapy for Hodgkin's disease, as well as both non-malignant and malignant breast diseases; 3) girls treated for non-malignant diseases, e.g. thymic enlargement; 4) female adolescents and young women subjected to a large number of radiological diagnostic chest exposures in the course of treatment of tuberculosis or severe scoliosis. It was also evidenced that female breast tissue is highly susceptible to ionizing radiation effects, as well as that the minimum latent period before onset of radiation-induced breast cancer is 5-10 years, and that higher levels of radiation exposure are associated with higher risk of onset of cancer. The presence of direct correlation between the absorbed dose and the carcinogenic effect, as well as that age of a woman at the time of exposure all are significant risk factors [12].

One of the first reports originating from 1960 evidenced increased incidence of breast cancer among women treated by artificial pneumothorax for pulmonary tuberculosis, who were thus exposed to frequent fluoroscopic examinations [13]. Due to the frequently repeated chest radioscopies the received doses reached even up to 12.5 Gy [14] with the equipment used at the time, which is now considered to be technically obsolete. Namely, due to the significantly lower quality of the x-ray images, the duration of the examination was prolonged and thus the absorbed radiation doses were significantly higher. Among a group of 271 female patients treated in a sanatorium, 13 cases of breast cancer were diagnosed, with disease-free interval ranging between 8 and 20 years (median 15). The calculated incidence of breast cancer in this population was statistically significant in comparison with the general population.

Both earlier and recent epidemiological studies carried out on survivors of the atomic bombing in

Japan have shown association between radiation exposure and carcinogenesis [9,10]. The studies on Japanese women who survived the bombing in Hiroshima and Nagasaki showed higher incidence of breast cancers in comparison to the general population [5,8,9]. Dose range during the atomic bombing was approximately 0-4 Gy, while the average doses to which radiation survivors were exposed were approximately 0.3 Gy [4]. Dose-response curves were rather similar, although the neutron component of the dose was predominant in Hiroshima and negligible in Nagasaki, which was suggestive of the same or highly similar mechanism of biological action in all radiation-induced cancers [15].

Higher incidence of breast cancers was evidenced among women subjected to radiation for different benign diseases. Concerning benign conditions, in a group of 1,037 women subjected to radiation for non-malignant diseases in Karolinska hospital in Stockholm in the period between 1927 and 1957, a 4-fold higher risk for breast cancer development was evidenced [16]. Radiotherapy indications included fibroadenomatosis, acute and chronic mastitis, unilateral hypertrophy of the breast in younger women, while the absorbed doses ranged between several dozens of cGy to 40 Gy. Some patients underwent repeated radiation series over a prolonged period of time. The studied period ranged between 6 and 42 years (median 31.5), while the mean disease-free interval before the onset of breast cancer was 24 years, being somewhat shorter in the group receiving higher doses. The highest incidence of breast cancer was recorded in the population subjected to repeated radiation series over the prolonged period of time of more than 5 years.

The risk of breast cancer development was also present after radiotherapy for malignant diseases if the radiation volume included a breast tissue portion with its associated anatomic region and depending on the radiation dose absorbed by the critical anatomic region. The majority of the studies [17-19] address the potential risk associated with the treatment of Hodgkin's disease. Since the treatment results of Hodgkin's disease have been significantly improved over the last 30 years, the number of cured female patients in whom the risk of development of second tumors may be assessed over a prolonged period of time is large. It has been documented that the risk of development of second solid tumors tends to increase along with the increase of the observation period, reaching the cumulative incidence of 10-13% after 15 years [17,18]. The risk is significantly increased in women under 30 years of age subjected to supradiaphragmatic radiotherapy, and particularly high in those under 15 years of age. Despite the fact that most of the breast tissue is protected during supradiaphragmatic radiotherapy, doses absorbed by unprotected breast tissue areas are calculated to range between 1.45 and 3.25 Gy. In a study from Stanford University hospital, among a group of 885 women treated for Hodgkin's disease in the period 1961-1989 at the department of radiation oncology, 25 invasive breast cancers were diagnosed during an average observation period of 10 years, which corresponds to a relative risk of 4.1%. The age of the patients at the time of radiation exposure ranged between 4 and 81 years (average 28). Most of the cancers (22 of 25) developed either within or on the radiation field margins, while histologically, all of them were invasive ductal cancers. The authors also recorded a significant increase of risk associated with increase of observation time, which indicated the need for regular follow-up over lifetime, aimed at early detection of breast cancer [19]. Gervais-Fagnou gave the following results in a group 427 female patients treated for Hodgkin's disease in the period from 1965 to 1990 [17]: 350 women were alive, 62 had died of Hodgkin's disease and 15 had died of other causes. Age ranged from 2 to 30 years (median 22 years) at the time of radiation treatment for Hodgkin's disease. The median follow-up time was 12.3 years (range 0.5-28.2). Of these 427 women, 15 subsequently developed breast cancer (Table 1). According to Program on Breast Cancer - Environmental Risk Factors from 2006 up to 50% of girls treated with supradiaphragmatic radiotherapy for Hodgkin's disease may develop breast cancer [12].

Improvements in the diagnosis and treatment of breast cancer have both contributed to significant increase in the number of treated female patients who have been in years-long complete remission. Patients whose therapeutic schedule included radiotherapy are of interest for the assessment of risk for radiation-induced second malignancies. One recently reported epidemiological study [20] included a cohort of 64,782 female patients with breast cancer treated in the period 1960-1985, out of whom 33,763 also underwent post-operative radiotherapy. Analysis of radiotherapy and non-radiotherapy cohorts revealed increased relative risk for the following second malignancies among the patients subjected to radiation: lung cancer 10-15^{+} years subsequent to the initial diagnosis of breast cancer; myeloid leukemia 1-5 years after diagnosis of breast cancer; second breast cancer 5-15^{+} years after diagnosis of the primary breast cancer; and esophageal carcinoma 15 and more years after the initial diagnosis of breast cancer (Table 2) [20]. However, the increased rate evidenced in the radiation cohort was low regardless of the statistical significance, i.e., in absolute numbers, out of 33,763 women second malignancy that might be the result of exposure to radiation was diagnosed

Table 1. Characteristics of patients treated for Hodgkin's disease (HD) and relationship to later development of breast cancer [17]

Characteristic	*Patients without breast carcinoma*	*Patients with breast carcinoma*
Patients (n)	412	15
Stage of HD, n (%)		
I or II	324 (80)	13 (87)
III or IV	83 (20)	2 (13)
Unknown	5	–
Age at radiation, years		
Median (range)	22 (2-30)	25 (19-30)
Treatment, n (%)		
Radiation alone	226 (55)	11 (73)
Radiation and chemotherapy	186 (45)	4 (27)
Time to breast cancer, years		
Median (range)	–	17 (9-25)
Deaths, n (%)	75 (18)	2 (13)
Cause of death		
HD	62	–
Breast cancer	–	2
Other cancer	4	–
Median follow-up, years (range)		
Alive	12.0 (0.5-28.2)	18.8 (13.5-28.1)
Dead	4.4 (0.1-24.4)	17.6 (13.3-22.0)

Table 2. Standardized incidence ratio and relative risk of developing second cancer for women who underwent surgery and radiotherapy for breast cancer, compared with those who underwent surgery only, tabulated by second cancer site and interval of follow-up [20]

		Non-RT cohort				*RT cohort*					
	Interval (years)	*Observed no. of tumors*	*Expected no. of tumors*	*SIR*	*95% CI*	*Observed no. of tumors*	*Expected no. of tumors*	*SIR*	*95% CI*	*RR*	*95% CI*
Lung	0–	27	22.8	1.18	0.78-1.72	10	21.1	0.47	0.23-0.87	0.40	0.17-0.85
	1–	50	79.4	0.63	0.47-0.83	50	77.4	0.65	0.48-0.85	1.03	0.68-1.55
	5–	60	77.5	0.77	0.59-1.00	69	81.6	0.85	0.66-1.07	1.09	0.76-1.57
	10–	34	56.0	0.61	0.42-0.85	62	63.0	0.98	0.75-1.26	1.62	1.05-2.54
	15+	55	55.9	0.98	0.74-1.28	80	54.5	1.47	1.16-1.83	1.49	1.05-2.14
Myeloid leukaemia	0–	2	2.0	1.02	0.11-3.67	2	1.8	1.13	0.13-4.08	1.11	0.08-15.3
	1–	6	6.8	0.89	0.32-1.93	17	6.4	2.66	1.55-4.25	2.99	1.13-9.33
	5–	7	6.5	1.08	0.43-2.23	8	6.7	1.19	0.51.2.35	1.10	0.35-3.59
	10–	5	4.6	1.09	0.35-2.55	3	5.1	0.59	0.12-1.72	0.54	0.08-2.78
	15+	2	4.5	0.45	0.05-1.62	9	4.3	2.09	0.95-3.96	4.66	0.97-44.8
Breast	0–	99	56.6	1.75	1.42-2.13	78	58.7	1.33	1.05-1.66	0.76	0.56-1.03
	1–	266	186.4	1.43	1.26-1.61	248	200.5	1.24	1.09-1.40	0.87	0.73-1.03
	5–	173	167.5	1.03	0.88-1.20	264	190.7	1.38	1.22-1.56	1.34	1.10-1.63
	10–	151	113.1	1.34	1.13-1.57	158	132.6	1.19	1.01-1.39	0-89	0.71-1.12
	15+	138	101.6	1.36	1.14-1.60	170	99.5	1.71	1.46-1.99	1.26	1.00-1.59
Oesophagus	0–	5	3.9	1.29	0.41-3.00	1	3.3	0.31	0.00-1.71	0.24	0.00-2.11
	1–	11	13.5	0.81	0.41-1.46	13	12.1	1.07	0.57-1.83	1.32	0.55-3.25
	5–	18	13.3	1.35	0.80-2.14	14	13.3	1.05	0.57-1.76	0.78	0.36-1.66
	10–	11	9.8	1.12	0.56-2.01	11	10.9	1.01	0.50-1.81	0.90	0.35-2.29
	15+	13	10.2	1.28	0.68-2.18	28	10.0	2.80	1.86-4.05	2.19	1.10-4.62

RT: radiotherapy, CI: confidence interval, SIR: standardized incidence ratio, RR: relative risk calculated by comparison of the SIR in the RT and non-RT cohorts in 160 individuals. Therefore, the authors of this study concluded that the benefits of radiotherapy in the treatment of breast cancer significantly outweigh the risk of development of second malignancies. As for the thyroid gland carcinoma, colon carcinoma and malignant melanoma, no statistically significant difference was observed between the two cohorts. Despite the documented evidence on the association between ionization exposure and radiation-induced oncogenesis, other risk factors that may have parallel roles cannot be neglected: genetic predisposition, reproductive factors, predisposition related to the environment, as well as unwanted effects of other therapeutic modalities. The same authors believe that both genetic and environmental factors are causes of general, permanent and unspecific increase in the incidence of second malignancies, while iatrogenic tumors developing as a result of known unwanted effects of the therapeutic manipulations for the primary malignancy are expected within certain, predictable time interval subsequent to the initial treatment. Boice et al. came to a similar conclusion arguing that radiation-induced cancers tend to develop after predictable time interval: in case of solid tumors after 10 years and within 5 years in case of leukemia [21].

Based on the literature, women treated for breast cancer are at the highest risk of onset of second breast cancer; such an event, however, must not be necessarily induced by radiation. Other non-radiation risk factors may also be the causes of development of a new breast cancer. Studies carried out on all female patients with breast cancer in Connecticut and Denmark showed absence of significant increase of radiation-induced secondary breast cancer risk. This could be due to the fact that most of the patients developed breast cancer after the age of 50, when the breasts are less vulnerable to the carcinogenic effects of ionizing radiation. However, increased risk that might be related to previous radiotherapy was determined in women subjected to radiation before the age of 45 [12].

Significant characteristics of radiation-induced breast cancer

According to the Cornell University report from 2006 “Program on Breast Cancer. Environmental Risk Factors” [12], radiation -induced breast cancer has 5 major characteristics:

1) Breast tissue of young women is a most sensitive tissue to the carcinogenic effects of ionizing radiation.
2) A minimal latent period of 5-10 years after the exposure is necessary, however it is usually considerably longer. The latent period is longer in young women and shorter in older ones. As for girls, the latent period is approximately 35-40 years. Radiation-induced breast cancer appears to occur later in life during the same age range when breast cancer rates, in general, begin to increase. It appears that only single exposure to sufficiently high dose in childhood will increase the risk of breast cancer 50 years later.
3) Regardless of the level of the absorbed dose, the risk of induced cancer is always present. Fortunately, in case of exposure to low doses the risk is negligible. Regardless of all the above-mentioned, all unnecessary exposures to ionizing radiation are to be avoided. The linear correlation between the radiation dose level and the risk of breast cancer is abandoned: the risk is lower in rather high doses. If the total radiation dose is divided to several smaller fractions the risk is approximately the same as in the case of application of the same dose within the same session, although opposite conclusions were reported in the most recent studies.
4) Age at the time of exposure is one of the most significant determinants of the future risk of radiation-induced breast cancer. The risk is highest in young girls and lowest in women exposed to radiation during the perimenopausal or menopausal period [12]. It seems that there is no strong evidence that exposure to ionizing radiation after the age of 45 leads to increased risk. One of the possible explanations is that radiation-induced damage of the breast tissue leading to mutagenesis and carcinogenesis necessitates estrogen stimulation and tissue proliferation which is normally associated with monthly menstrual cycles. On entering menopause, tissue proliferation is increasingly reduced, as is the possibility of radiation-damaged cells to escape the control mechanisms and evolve into malignant cells. There is some evidence suggesting that exposure of the immature breast during the premenopausal period is associated with the highest risk of radiation-induced cancer. The extent of the risk during pregnancy has not been elucidated yet, but in women subjected to radiation during pregnancy for Hodgkin’s disease, it appears that pregnancy increases breast sensitivity to the carcinogenic effects of radiation [12].
5) Most of the women exposed to radiation do not develop radiation-induced breast cancer. Among approximately 25,000 women from Japan who survived the atomic bombing and were under continuous follow-up for more than 50 years, 173 lethal outcomes were recorded as a consequence of breast cancer with only 41 cases (24%) being associated with radiation exposure in 1945 [4,10,12].

The risk of radiation-induced breast cancer differs, depending on the age (the effects of the dose are modified with age) and the dose absorbed during exposure. How high is the risk after relatively high radiation doses of 100 cGy? Since the dose is approximately 1000 times as high as the dose absorbed by the individual from all natural sources of radiation (approximately 0.1 cGy) and 50 times as high as the maximum admissible dose in occupationally exposed individuals (2 cGy in most of the countries), it is not low and the risk of exposure to doses at this level has been defined only in a few studies [12,21]; as for the young women from Western countries, the risk is increased by 40% on average, with associated relative risk of 1.40. Accordingly, this level of exposure is insufficient for doubling the risk of onset of breast cancer later in life.

Other breast cancer risk factors

Genetic and endocrine factors, certain external environmental factors and physiological immune mechanisms play certain roles in breast cancer etiology. It has been definitively confirmed that ionizing radiation may be a cause of breast cancer, however radiation exposure is neither the only nor the major risk factor. It has been evidenced that less than 1% of all breast cancers belong to the group of radiation-induced cancers. A number of internal and external breast cancer risk factors has been defied so far as capable to increase the risk even by 40%: menarche before the age of 11, late menopause, no pregnancies and nulliparity, positive family history of breast cancer, particularly among first-degree relatives, personal history of previously diagnosed breast cancer (development of second cancer is at least partially dependent on risk factors associated with onset of the initial breast cancer).

An interesting epidemiological study is related to the investigation of non-radiation breast cancer risk factors in a female population cohort who had survived the atomic bombing in Japan [22]. The cohort comprised 22,200 women residents of Hiroshima and Nagasaki and according to population-based records, a total of 161 cases of primary breast cancer was identified. Inverse relationship with age of menarche was determined, as well as poorly positive relationship related to the age of onset of menopause and inverse relationship with successfully completed pregnancies, although the number of pregnancies after the first one had no influence on the breast cancer rate in the complete cohort. In that study breast cancer risk was lower in women who successfully completed their first pregnancy before the age of 30 in comparison to older women, though without statistical significance. Moreover, a positive but non-significant risk trend was recorded in cases of increased body weight and mass. As for women receiving estrogens and having diabetes, the obtained risk rates were 1.64 and 2.06, respectively. The authors concluded that non-radiation induced risks for breast cancer were the same in the cohort of the atomic bombing survivors and the general population, although the prevalence of the general and common risk factors was low. Reproductive factors and hormone administration are separate breast cancer risk factors, independent of radiation exposure in the studied cohort [22].

Spectacular advances in molecular biology over the last 10 years have led to the identification of certain individuals with genetic predisposition to breast cancer, such as lesions and mutations of certain genes: BRCA1 and BRCA2, ATM heterozygosity, i.e. the genes that participate in the repair of DNA lesions and the control of the cell cycle. Molecular biology investigations in the field of radiation-induced breast cancer have focused on the determination and definition of the cancer-sensitive genes influence on the development of radiation-induced breast cancer [23,24].

The most recent biochemical and cell biology investigations are addressing the possible role of the lysosomal enzymes in breast cancer initiation, since it has been shown that lysosomes with their approximately 40 hydrolytic enzymes are included in the process of carcinogenesis. Since most of breast cancers start to grow in the mammary ducts, it is supposed that lysosomal enzymes pass from the secretory cells into the canals to produce cellular damages, leading to initiation of carcinogenesis. The risk factors for release and activation of the lysosomal enzymes may include ionizing radiation, oxidative stress, estrogens, certain food ingredients and exogenous toxins [25].

Mammography and risk of radiation-induced breast cancer

Having in mind the fact that ionizing radiation is applied with mammographic examinations, carcinogenic effects may be expected, particularly with repeated examinations using obsolete equipment necessitating higher doses in order to acquire quality images. However, modern radiological equipment has eliminated to a maximum degree the risk of inducing breast cancer after mammographic examinations. Contemporary apparatuses emit x-rays at an energy level compatible with the breast tissue and the dose absorbed by the breast is reduced to approximately 0.3 cGy upon two exposures, and thus, each hypothetic risk is insignificant and outweighed by the benefits of mammography [26,27]. Mammography has been introduced more than 50 years ago and is still considered the best routine method for the detection of breast cancer. As early as 1977 US National Cancer Institute held the first consensus conference with its major topic dealing with screening mammography [12]. Currently, controversial attitudes related to screening of healthy women are not related to the potential hazard of radiation exposure during mammography, but rather to the issue whether women under 50 years of age may benefit from these examinations. In randomized clinical trials, screening mammography has reduced breast cancer mortality by 30% in women above 50 years of age. The conclusions concerning the benefits that may be achieved in younger women are less clear, however the mortality rate is undoubtedly lower in this age group as well, and thus screening has been introduced in most of the developed countries as a mandatory procedure, particularly for sub-populations of younger females being at high risk of getting breast cancer. Periodic mammographic follow-up of younger women may result in the absorption of cumulative doses of e.g. 3 cGy, which increases the risk by approximately 1.2%, relative risk being 1.012, and such low risks have not been detected in human studies [11].

Conclusion

Based on literature data, one of the most significant factors in the development of radiation-induced breast cancer is the age of patients at the time of exposure to radiation. The influence of age is associated with hormonal factors determining the highest sensitivity to radiation carcinogenesis immediately before and during menarche, and most probably also during pregnancy. The younger the patient the higher the risk. However, the risk is always present, regardless of age.

The correlation between the absorbed doses and cancer development is suggested in most of the relevant studies. Time distribution of the total dose does not reduce the risk.

The relation of the absorbed dose and the development of the induced cancer is direct and constant.

The minimal latent period between radiation exposure and the onset of cancer is 5-15 years. The latent period is longer in women exposed to radiation before 30 years of age. Increase of time interval after exposure does not reduce the risk. Conversely, prolongation of the observation period may be associated with higher risk and breast cancer may be manifested even 45 years after the exposure.

The duration of the time interval between exposure and the onset of breast cancer may be influenced by factors such as hormonal status and genetic predisposition. However, the disease-free interval is not dependent on the absorbed doses, although some data are suggestive of such possible relations (genetic predisposition to radiation-induced carcinogenesis).

The maximum reduction of risk associated with mammography would need dose adjustment to values below 0.2 cGy upon each individual examination.

The highest risk of radiation-induced breast cancer is encountered in the sub-population of women who have undergone radiotherapy for either malignant or non-malignant diseases, including non-malignant breast diseases in their childhood or adolescence.

Undoubtedly, ionizing radiation may induce breast cancer. Women aged 30 years or less subjected to radiation are exposed to the highest risk. Therefore, as a means of prevention in this group of population, indications for application of ionizing radiation, both diagnostic and therapeutic, should be highly selective, meaning that radiation should be applied only if the possible benefit outweighs the risks.

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