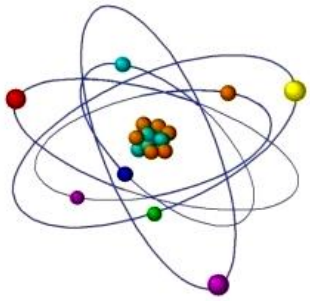
RADIOGENIC BREAST CANCER RISK PROJECTION FOR THE GEORGIAN FEMALE POPULATION



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ABSTRACT**:** *This paper presents the results of the initial stage of the research cycle, aimed at adapting the methodology for assessing radiogenic risk to the specifics of the Georgian population. This adaptation aims to equip practicing radiologists, medical workers, and nuclear and radiation safety regulators with appropriate theoretical and methodological bases. Data from the National Center for Disease Control and Public Health of Georgia for 2017-2019, regarding the age structure of breast cancer incidence among the female population of Georgia, and demographic data from the National Statistical Office of Georgia for 2017-2019, were used. Comparative analysis utilized data from The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the USA and Cancer Statistics in Korea. Competing risk methodology was employed to estimate the age-conditional and lifetime baseline risk (LBR) of developing breast cancer. The US National Cancer Institute's DevCan 6.9.0 software was used for computation.*

The methodology described in the 2006 report of the National Academies of Sciences' BEIR VII Committee was used to estimate the age-conditional and Lifetime Attributable Risk (LAR) of radiogenic breast cancer. US National Cancer Institute software RadRat (version 4.3.1) and the R package for lifetime attributable risk estimation (LARisk) were used for computation. Monte Carlo simulation techniques were applied to estimate uncertainties in risk and subjective uncertainties under various assumptions. It was revealed that the lifetime baseline cancer risk for the hypothetical population of Georgia is 6.5% (95% CI: 6.2%-6.9%), for the US white non-Hispanic female population is 14.1% (95% CI: 13.99%-14.23%), and for the Korean female population, it is approximately 4.2%. For women in Georgia, the United States, and Korea irradiated with a dose of 10 mGy, the lifetime attributable risk is approximately the same, varying between 120-140 cases per 100,000 persons. The Lifetime Fractional Risk (LFR), defined as the ratio of lifetime attributable risk to lifetime baseline risk, is 3.5 times higher in the American white non-Hispanic female population than in Korea, and 2 times higher than in the female population of Georgia.

Key words*:* Radiogenic breast cancer risk, Georgian female population, Radiation Protection

INTRODUCTION

Implementing the scientific support system (risk management) for decision-making in the health sector is the main priority of the 2022-2030 national strategy in the healthcare field (Resolution #230 of the Government of Georgia dated May 2, 2022). The strategy's implementation in the medical exposure field started in 2022 [1].

The International Commission on Radiological Protection stated that the intended effective dose should be used as a principal protection quantity for establishing radiological protection guidance. However, it should not be used to assess risks of stochastic effects in retrospective situations for exposures in identified individuals and epidemiological evaluations of human exposure [2,3]. In these cases, an age- and sex-specific radiogenic carcinogenic risk assessment methodology should be used. The population-specific, age- and sex-dependent radiogenic risk assessment methodology was initially developed by the National Research Council (US) Committee on the Biological Effects of Ionizing Radiation (BEIR) of the National Academy of Sciences of the United States of America [4]. This methodology is based on a study of long-term radiation-related health effects in Japanese atomic bomb survivors and US demographic and health data. At the modern stage, different modifications of this methodology have been developed under various assumptions and approximations for the populations of the USA, Great Britain, France, South Korea, Japan, and others [2,5,6,7]. To fulfill its mandate to provide consultations and assistance to public health during radiation emergencies, the medical consequences of the Fukushima nuclear incident were evaluated using this methodology by the expert group of the World Health Organization [9]. This paper presents the results of the initial stage of the research cycle, aimed at adapting the methodology for assessing radiogenic risk to the specifics of the Georgian population. This adaptation aims to equip practicing radiologists, medical workers, and nuclear and radiation safety regulators with appropriate theoretical and methodological bases.

MATERIALS AND METHODS

Data from the National Center for Disease Control and Public Health of Georgia for 2017-2019 on the age structure of breast cancer incidence among the female population of Georgia, and demographic data of the population of Georgia for 2017-2019 from the National Statistical Office of Georgia, were used. Data from The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the USA and Cancer Statistics in Korea [15] were used for comparative analysis. Competing risk methodology was used to estimate the age-conditional and lifetime baseline risk (LBR) of developing breast cancer. The US National Cancer Institute's DevCan 6.9.0 software was used for computation. The methodology described in the 2006 report of the National Academies of Sciences' BEIR VII Committee was used to estimate the age-conditional and lifetime attributable risk (LAR) of radiogenic breast cancer. US National Cancer Institute software RadRat (version 4.3.1) and the R package for lifetime attributable risk estimation (LARisk) were used for computation. Monte Carlo simulation techniques were used to estimate uncertainties in risk and subjective uncertainties under a range of assumptions.

Results: First, let's consider the basic provisions of the BEIR VII approach to make clear all the assumptions and approximations that the methodology is based on. In general, in the direct assessment of health risk in the exposed population, two models are considered: excess absolute risk - EAR(t) = $\lambda_E(t) - \lambda_U(t)$, which is a difference in cancer incidence rates of the exposed and unexposed populations, and excess relative risk, which is defined as: - ERR(t) = $[(\lambda_E(t)/ \lambda_U(t)) -1]$; The incidence rates of the exposed and unexposed population in this case are related by the equation

$$\lambda_E(t) = \lambda_U(t) \{1 + ERR(t)\}$$

In terms of the mechanisms of radiation carcinogenesis, the first model reflects the nature of radiation as a cancer initiator, and the second as a cancer promoter.

BEIR VII methodology is based on statistical approximation of existing experimental and epidemiological data with classes of functions based on the most general regularities of radiation carcinogenesis. Based on Radiobiological considerations, it is postulated that for low doses of radiation with low LET (linear energy transfer), the risk of disease for a person exposed to dose d depends on a linear or linear-quadratic function of the form: $f(d) = \alpha_1 * d + \alpha_2 * d^2$ where α1 and α2 are parameters to be estimated from the epidemiological data. In linear approximations, the dose-effect function of cancer incidence in the experimental population is described by the expressions:

$$\lambda(s,a,d) = \lambda(s,a) + [1 + \beta_S^{ERR} * ERR(e,a) * d]$$

$$\lambda(s,a,d) = \lambda(s,a) + \beta_S^{EAR} * EAR(e,a) * d$$

where λ(s, a) - sex-dependent baseline cancer incidence rate, βs - sex-dependent coefficient determining dose-effect dependence. The influence of dose-effect modifying factors - age at irradiation (e) and attained age (a) is described by the expressions:

$$ERR(e,a) \; or \; EAR(e,a) = \exp(\gamma e) * a^{\eta}$$

Coefficients γ and η are empirical and based on epidemiological and statistical principles [18]. In BEIR VII approach the lifetime attributive risk (LAR), for each cancer sites, is the main measure of risk.

$$LAR^J(d,e) = \int_{e+L}^{100} M^J(d,e,a) * {S(a)}/{S(e)} * da$$

where *S(a)* is the probability of surviving to age a, and L is the minimum latency period of developing cancer. Index J-corresponds to either the EAR or ERR model, and accordingly:

$$M^{EAR}(d,e,a) = \beta_S^{EAR} * EAR(e,a) * d$$

$$M^{ERR}(d,e,a) = \beta_S^{ERR} * ERR(e,a) * d * \lambda(s,a)$$

Coefficients βs, γ, and η for each individual sex and each individual cancer site were calculated from health data of Japanese atomic bomb survivors. [18].

The key issue in risk assessment is the legality of applying the estimates obtained based on the study of a specific population, to other populations that may have different genetic characteristics and lifestyles, as well as different baseline cancer risks. In this regard, it should

be noted that the BEIR VII methodology does not take into account the interpopulation radiosensitivity factor and the possible causal relationship between radiogenic and baseline carcinogenesis mechanisms, and adapting the results obtained in Japanese atomic bomb survivors to the specificity of the United States population (risk transport) performs by combining EAR and ERR models with appropriate weighting coefficients (w):

$$LAR(d,e) = w * LAR^{ERR}(d,e) + (1-w) * LAR^{EAR}(d,e)$$

From the positions above, for the assessment of LAR and age-conditional risk for the population of Georgia, it is necessary to bring the demographic data of the population of Georgia and the *cancer statistics* under the requirements of the methodology.

Demographic data

As it was clear from the above discussion, for population-specific risk assessment, the degree of detailing of demographic data and population morbidity is of principal importance, this primarily concerns the age-dependent intensity of population mortality, according to which life tables are calculated. As it was clear from the above discussion, for population-specific risk assessment, the degree of detailing of demographic data and population morbidity is of principal importance, this primarily concerns the age-dependent intensity of population mortality, according to which life tables are calculated. Life tables are currently constructed using age-specific central mortality rates derived from vital statistics and census data. Over the age of 85, the reliability of mortality rates is compromised by incorrect age reporting and lack of birth records for extremely elderly people.

The life tables of the population published by the National Statistical Service of Georgia, as well as the life tables of many other countries, closed with the category 85 years, while in Georgia approximately 30-35% of the female population survives beyond the age of 85 years. Consequently, a life table inadequately describes the mortality structure of a significant proportion of the population. To expand the open age interval of the life table of the Georgian population to 100 years, we used the procedure developed by Coale and Kisker [10], which predicts mortality by extrapolating mortality in a range close to 85 years. The developed model has a well-founded theoretical basis [13,14] and has been verified on the populations of the United States and Canada [11,12]. The procedure relies upon a function called the age-specific rate of mortality change with age (k_x). By definition,

$$k_x = ln(m_x) - l\,n(m_{x-1}) \quad (1)$$

m_x - central death rate by x age interval.

The first important assumption is that k above 85 years should be linear,

$$k_x = k_{85} + (x-85) * s \quad (2)$$

Where s denotes the slope of the change in k_x.

By combining these formulas, we get the expression:

$$m_x = m_{84} * exp\left[\sum_{y=85}^{x} (k_{85} + (y-85) * s)\right] \quad (3)$$

through which it is possible to calculate m_x for any x>85 age interval if k_{85} and s are known. k_{85} is calculated from the central mortality rate in age intervals close to x=85

$$k_{85} = \left({}^{1}/_{4}\right) * log\left[{}^{m_{86}}/_{m_{82}}\right] \quad (4)$$

s - Calculated from the expression (3),

$$s = \left(-{}^{1}/_{325}\right) * \left[\log\left({}^{m_{84}}/_{m_{110}}\right) + 26 * k_{85}\right] \quad (5)$$

where m_{110} denotes the cut-off age for the given population. According to the assumption of Coale and Kisker, the cut-off age is determined to be about 110 years, while m_{110} is considered equal to 1 for men and 0.8 for women.

For the 2017-2019 population of Georgian women, the parameters estimated by the above procedure have the following values: k_{85} = 0.1; m_{84} = 0.1132; s=-0.002. It should be noted that the values of s for US White end US Black Females, estimated based on demographic data and verified by Medicare Data are equal respectively −0.00243 and −0.00151 [11],

Figure 1. and Figure 2**.** presents the age structure of the central mortality rate of the female populations of Georgia, the United States, and South Korea, and the survival rate estimated by the method of [10].

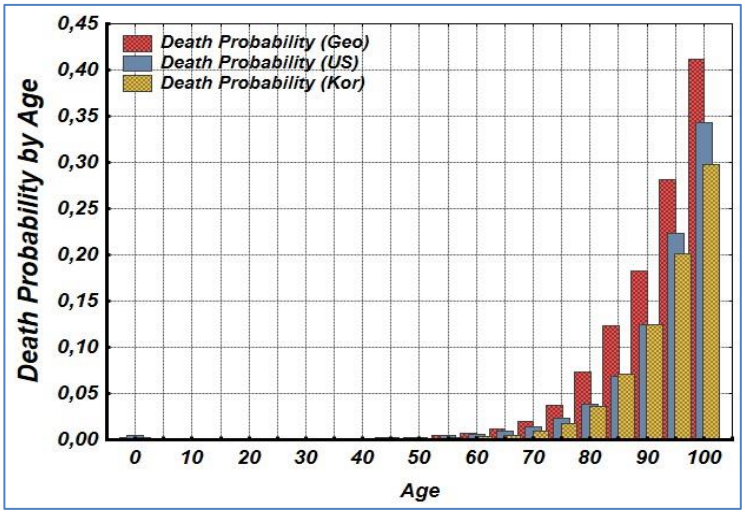

Figure 1. Mortality probability of the female populations of Georgia, the United States, and South Korea. (2015-2019 US white non-Hispanic women, Georgian 2015-2019 women's populations, and South Korea 2010 women's populations.)

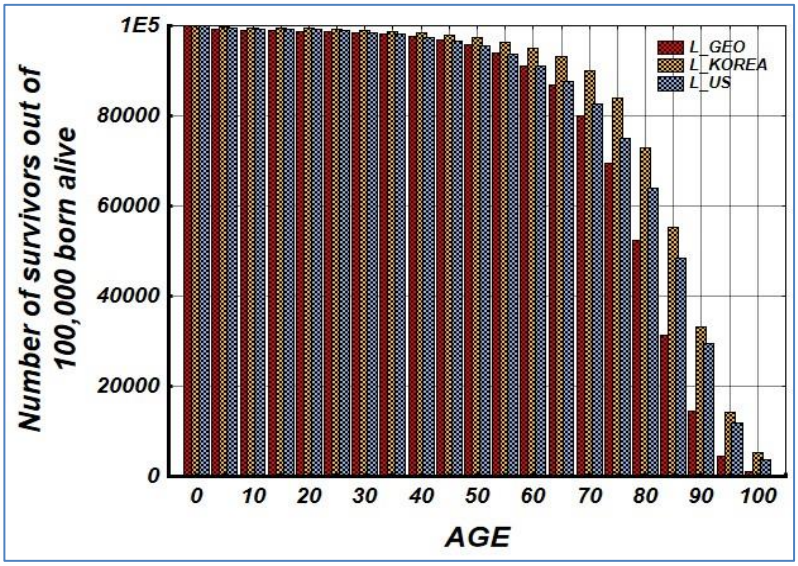

Figure 2. The survival rate of the female populations of Georgia, the United States, and South Korea. (2015-2019 US white non-Hispanic women, Georgian 2015-2019 women's populations, and South Korea 2010 women's populations.)

As can be seen from the graph, the central mortality rate in the female population of Georgia is significantly higher than in the female population of the United States and especially South Korea, this is reflected in the survival rate as well. The threshold age of the female population of Georgia is about 100 years, this allows the use of the last closed interval in the calculations, which significantly simplifies the calculations and reduces the level of uncertainty in the estimates.

Baseline Breast Cancer Risk

The baseline breast cancer risk is not directly factored into the formulas for lifetime and age-conditional radiogenic cancer risk. However, it is important to examine how these indicators vary between different populations concerning radiation-related cancer risk. This analysis helps clarify the mechanisms of radiation-induced carcinogenesis and the population-based predisposition of cancer. To estimate lifetime and age-conditional probabilities of developing breast cancer in a hypothetical cohort for the Georgian population, we use methodology [19] which is currently used by the US National Cancer Institute to review cancer statistics from the Surveillance, Epidemiology, and End Results (SEER) program [https://seer.cancer.gov/];

In this approach the probability of getting a first cancer in the age interval $[t_0, t]$ given alive and cancer-free until just before t_0 is:

$$\boldsymbol{P(t_0,t) = \int_{t_0}^{t} \lambda_c(u) S(u) du \Big/ S(t_0)} \quad \textbf{(6)}$$

Where $\boldsymbol{S(u) = exp\{-\int_0^u [\lambda_c(a) + \lambda_o(a)]da\}}$

$\boldsymbol{\lambda_c}$ **(a)** is the rate of first cancer per person-years alive and cancer-free at age **a** and $\boldsymbol{\lambda_o}$ **(a)** is the rate of deaths per person-years alive *and cancer free* at age **a.** If we take into account that $\boldsymbol{exp\{-\int_0^u [\lambda_c(a)]da\} \approx 1}$ and to a crude approximation ignore it, then S(u) essentially coincides with survival rate and the meaning of the probability functions $P(t_0,t)$ becomes clear. Figure 3**.** and Figure 4**.** present the distributions of Baseline age-conditional and lifetime baseline breast cancer risk (LBR) *.

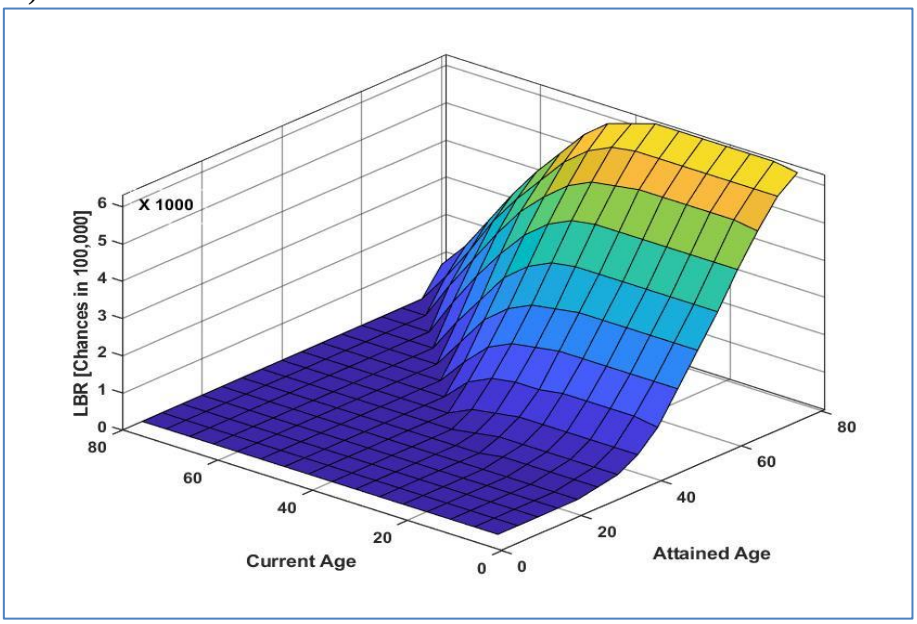

Figure 3. Age-conditional probabilities of developing breast cancer in the hypothetical cohortfor Georgian population

**** Number of individuals in the hypothetical cohort, diagnosed with cancer to the end of the expected lifetime (100 years), given nndiagnosed at current Age.***

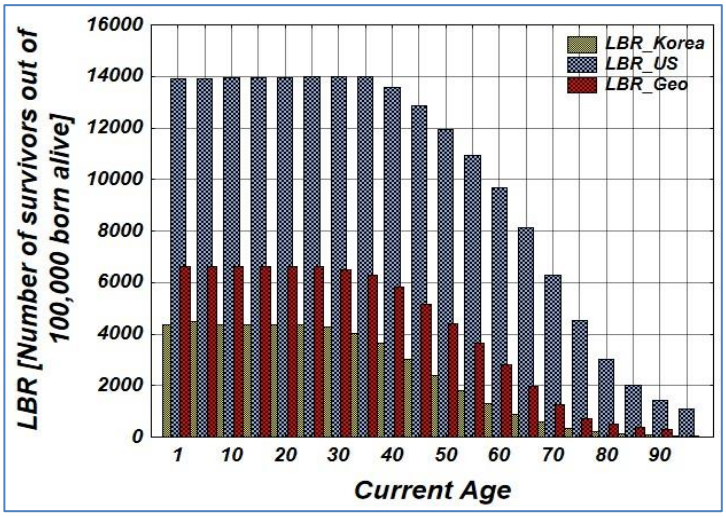

Figure 4. Lifetime baseline risk in 2015-2019 US white non-Hispanic women, Georgian 2015-2019 women's populations, and South Korea 2010 women's populations.

As can be seen from the distribution, lifetame baseline cancer risk for the hypothetical population of Georgia is equal to 6.5%, 95%CI (6.2%-6.9%) , and for the population of American women is equal to 14.1% 95%CI (13.99%-14.23%), lifetame baseline cancer risk for the Korean female population is smaller and equal to about 4.2%.

As can be seen from the expression (6), lifetime baseline risk depends on both the survival rate and the level of cancer incidence in a specific population, although the main determining factor is the incidence, which can be easily confirmed by a joint analysis of lifetime baseline risk (Figure 4.), Survival rate and Age-conditional cancer incidence rate in populations (Figure 5). From these positions, the identification of the factors that determine the level of cancer incidence in the population acquires both theoretical and practical relevance. A comparative analysis of the patterns of oncology in the American and Korean populations can give us some insight into the factors responsible for the practically two-fold difference in the risk of developing breast cancer in the Georgian and American women's populations;

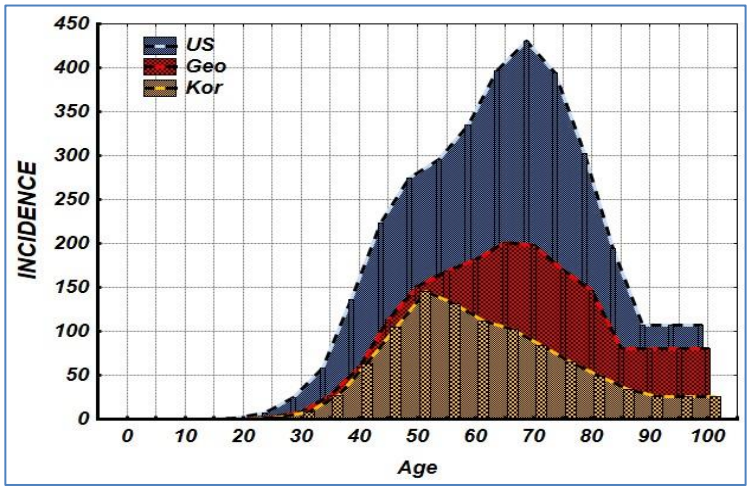

Figure 5. Age-conditional cancer incidence rate in 2015-2019 white non-Hispanic women, Georgia 2015-2019, and South Korea 2010 female populations

The incidence of cancer has been studied in white and black Americans, Korean immigrants, and native Koreans [15,16,17]. Data from the Surveillance, Epidemiology, and End Results (SEER) program and the International Agency for Research on Cancer were used. It was revealed: that in men the risk of stomach, liver, gallbladder, larynx, and esophageal cancer has sharply declined in Korean-American men compared with their native counterparts while prostate, colon, and rectum cancer risk has increased. In women, there was a decrease in stomach, liver, gallbladder, and cervical cancers, and breast, lung, colon, rectum, and endometrial cancers increased. It is worth noting that the incidence of breast cancer among Korean immigrant women, although increasing, remains at a much lower level than among white Americans; Age-adjusted cancer rates in Koreans are equal to 50.7, while in white Americans their value reaches 152.9 [16,17]. These studies highlight the leading role of nutritional diet and environment, as well as social factors in the risk of several cancer site, although the role of genetic factors in breast localization is also clearly defined.

Radiogenic Breast Cancer Risk

For breast cancer, the BEIR VII Committee used only an EAR model to quantify risk. The model was based on a pooled analysis of eight cohorts, including the LSS cohorts [18]. The parameterized function of EAR has the following form:

$$EAR(d,e,a) = \beta * d * exp\left[\frac{\gamma(e-25)}{10}\right]\left(\frac{a}{50}\right)^{\eta}$$

where $\beta = 10$; $\gamma = -0.50$; $\eta = 3.5$ for $a < 50$ and 1.1 for $a \geq 50$.

For the irradiated population, the dependence of lifetime attributable risk on age-at-exposure and radiation dose was calculated using the following expression:

$$LAR^{Breast}(d,e) = \beta * d * \int_{e+L}^{100} exp\left[\frac{\gamma(e-25)}{10}\right]\left(\frac{a}{50}\right)^{\eta} * S(a)\Big/S(e) * da$$

The latency period L was assumed as 5 years.
For the populations of women in Georgia, the United States, and Korea irradiated with a dose of 10 mGy, the lifetime attributable risk is approximately the same within the margin of error and varies between 120-140 cases in a cohort of 100,000 persons. Small inter-population differences in lifetime attributable risk estimates are explained by differences in inter-population survival rates [20] (Figure 6.)

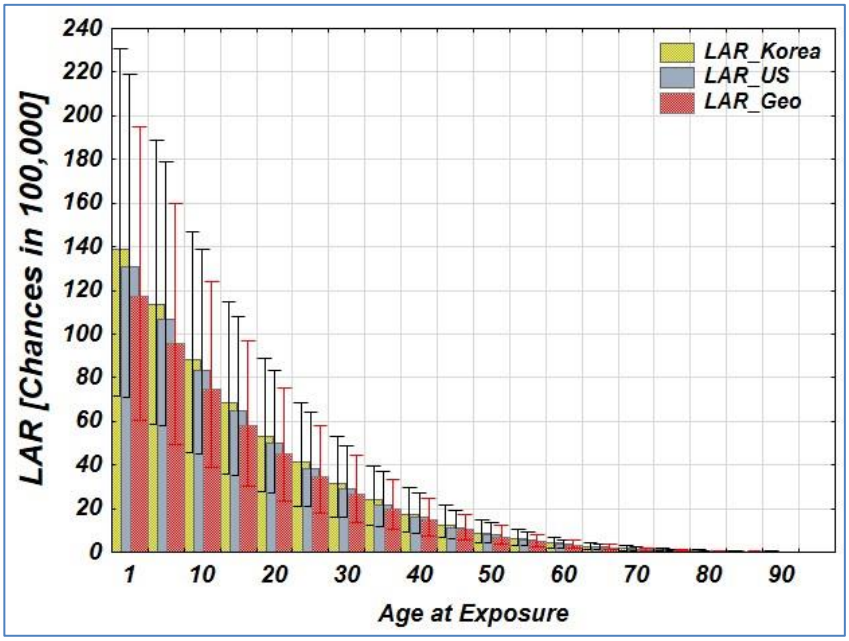

Figure 6. Distributions of lifetime attributable risk for female populations of Georgia, the United States, and Korea irradiated at a dose of 10 mGy. Whiskers - uncertainty range (95% CI)

We get a completely different picture if we consider the Lifetime Fractional Risk (LFR), which is defined as the ratio of lifetime attributable risk and lifetime baseline risk [21] – in the American white non-Hispanic female population is 3.5 times higher than that of Korea, and 2 - times higher than in the female population of Georgia (Figure 7.).

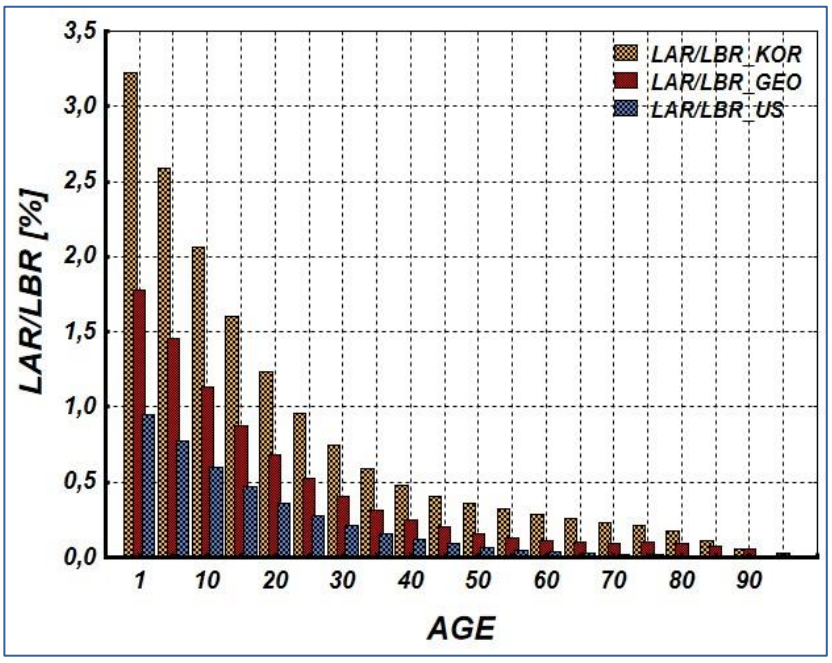

Figure 7. Distributions of lifetime fractional risk (LFR) for female populations of Georgia, the United States, and Korea irradiated at a dose of 10 mGy.

DISCUSSION

We will discuss those assumptions and approximations that can modify the results, uncertainties related to them, and possible ways to minimize these uncertainties for the population of Georgia. First of all, it should be noted that the main sources of uncertainties considered in the BEIR VII methodology, and its various modifications include:

1. Coefficients of ERR and EAR models
2. Dose and dose rate factor (DDREF)
3. The latent period of cancer development in the post-radiation period
4. Radiation dose and dose power
5. Factors related to the quality of medical statistics and demographic data
6. Risk transport coefficient

The algorithmic base and software used in this work for uncertainty estimation use the Monte Carlo method and values of parameter variability obtained at the modern stage in radiation epidemiology.

- The main dose-effect factor β - 10.00 (7.00–14.20) is considered with its variability ranges, while the corresponding coefficients of the modifying factors; $\gamma = -0.50$ (irradiation age) and $\eta = 3.50$ (attained age) are considered as fixed quantities and therefore do not contribute to the uncertainty.
- The distribution of DDREF is described by log-normal distribution (mean= 1.5, std=1.35)
- The latent period of breast cancer development usually represents an S-shaped curve with a parameter in the center of the S-shaped function and a range of variability from 2.5 to 7.6 years.
- Radiation dose uncertainty can be applied to a fixed value
- Uncertainties related to demographic data and medical statistics: the software we use does not provide for the analysis of uncertainties related to medical statistics and demographic data, especially the analysis of time trends of these data, which is especially important in the case of long-term prognosis. From this point of view, it is appropriate to develop new software that ensures the consideration of the uncertainties related to the demographic and medical statistics of Georgia in the risk assessment.

The subject of detailed consideration is the analysis of the uncertainty associated with the weight coefficient (w) of the ERR and EAR models, which are used for interpopulation risk transfer., and determine the contribution of age-dependent and age-independent members of risk to LAR. As mentioned above, the conceptual basis of the BEIR VII methodology is the assumption that the sex-specific main component of the dose-effect (β) is invariant for different populations, which implies that the inter-population difference in radiosensitivity is leveled in the dose-effect relationship, although it is somewhat reflected in the high range of its uncertainty, but as it is known, populations differ in the basic (background) level of cancers of

different sites, therefore, the generalizability of radio-epidemiological- data obtained in Japanese LSS cohorts to other populations depends on**:**

1) Are there correlations between background and radiogenic carcinogenesis risks, that is, if we formulate it differently, is there a causal relationship between genetic predisposition to cancer and genetic susceptibility to radiogenic cancer;

2) What is the share of endogenous (genetics, age, sex) and exogenous (chemical factors, diet, lifestyle, etc.) factors in the background level of cancer incidence and its age structure in a specific population? The latter has an independent scientific and practical value in terms of developing a national cancer prevention strategy for any country [22-25]

The issue is particularly relevant in terms of the prognosis of radiogenic breast cancer because it is modeled only based on the EAR model (WEAR=1), which completely excludes the contribution of the population-specific factor of onco-incidence and therefore a certain correction of the risk according to the population specificity. This assumption was mainly based on the study of Preston and colleagues [18], where the age structure of radiogenic breast cancer in the American and Japanese populations was comprehensively analyzed (it should be noted that the background level of breast cancer in the American population almost twice as high as in the Japanese population). It was revealed that the β estimated by the ERR model was equal to 1.44 for the LSS cohorts, and 0.51 for the American cohorts, and the level of the LAR estimated by the EAR model was identical for all four studied cohorts. Based on the opinion that the increase in cancer incidence in different populations irradiated with the same doses should be identical, the use of the EAR model was considered more correct. At that time, this argument was considered sufficient, however, the study of genetic susceptibility to radiation tumorigenesis is ongoing and is still the subject of intensive research. Based on these studies, the recommendations of the International Commission on Radiological Protection #103 of 2007 conclude that; "Although the Commission recognizes that weakly expressing variant cancer genes may, in principle, be sufficiently common to impact upon population-based estimates of radiation cancer risk, the information available is not sufficient to provide a meaningful quantitative judgment on this issue".

The same position is shared by The Advisory Group on Ionising Radiation (UK), of the AGIR report (AGIR, 2013, www.gov.uk)), „Although theoretical and empirical considerations suggest that individuals differ in their response to radiation exposure, no strong and consistently validated biomarkers of either tissue or stochastic effects have been identified to date. Studies of functional assays and candidate SNPs have been largely inconclusive"

The United Nations Scientific Committee on the Effects of Atomic Radiation 2020/2021 report [26] indicates that such modifiers of low dose effects as Genomic instability, bystander effects, adaptive response, which can be considered as possible mechanisms of individual radiosensitivity in the range of small doses, are still not clear and are insufficiently coherent to adopt for risk assessment purposes.

On the other hand, in the last period, solid evidence has been obtained that questions the correctness of using the EAR model for breast cancer risk assessment [21], in particular, the incidence of breast cancer among the Japanese population is constantly increasing. As a result, in the Life Span Study (LSS) of Japanese atomic bomb survivors, the ERR model currently

predicts similar dose-dependent increases among different birth cohorts, whereas the EAR model predicts different dose-dependent increases among different birth cohorts. This contradicts the findings of Preston and colleagues [18]. These circumstances point to the need for further elaboration and development of radiogenic carcinogenic risk models.

CONCLUSION

Considering the level of uncertainty in modern concepts of individual and interpopulational radiosensitivity mechanisms, as well as the problems that have recently been revealed in methodological approaches to interpopulational transport of radiogenic breast cancer risk, we consider it appropriate to consider the issue of using Lifetime fractional risk as an additional criterion for decision-making and regulatory control in medical exposure, understanding the problems related to the ethical aspects of the issue.

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