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Post-Chernobyl Renal Cancers vs. Control from Spain and Colombia: A Comment

Sergei V Jargin

Peoples Friendship University of Russia, 117198 Moscow, Russia

Abstract

International differences in the average histological grade of cancers may reflect the diagnostic quality and population coverage by medical examinations. A series of studies of post-Chernobyl renal cancers with a control from Spain and Colombia is discussed here compared to another research. Suppositions about enhanced aggressiveness of cancers from the areas previously contaminated by the Chernobyl fallout are unproven and can have unfavorable consequences for the therapy: a decision to perform nephrectomy may be taken more frequently than clinically indicated instead of a kidney-preserving procedure. Results of some studies of Chernobyl-related malignancy are valuable; but conclusions should be revaluated taking into account that some cases, classified as aggressive radiogenic cancers, were in fact late-stage neglected malignancies.

Keywords: Renal cell carcinoma; Cancer grading; Ionizing radiation; Chernobyl

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Correspondance: *Sergei V Jargin, Peoples Friendship University of Russia, 117198 Moscow, Russian Federation, Russia. Phone: +7 4959516788; E-mail: sjargin@mail.ru*

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Introduction

The letter [1] with references to the papers [2-6] has not been cited in the subsequent article [7]. However, the concerns are remaining. The worldwide exposures to natural background radiation are generally expected to be within the range 1-10 millisievert per year (mSv a^{-1}), the global average being 2.4 mSv a^{-1}. Some national averages exceed 10 mSv a^{-1}, while in certain populated areas individual doses exceed 100 mSv a^{-1} [8], which is not known to be associated with any increase in health risks. The cumulated average individual effective dose to 6 million residents of contaminated areas after the Chernobyl accident for the period 1986-2005 was ~9 mSv [9]. Admittedly, doses to the thyroid from ^{131}I were higher; but the thyroid is a separate topic discussed previously [10,11]. Annual average doses from the natural background should be indicated in studies with international controls; otherwise exposures in a control group may be not significantly lower than in the "exposed" population e.g. in patients with Renal Cell Carcinoma (RCC) from Spain *vs.* those from Kiev [4,12]. The average individual dose from the natural background in Spain is ~5 mSv a^{-1}[13,14]. External and internal doses received by residents of Kiev in the first year after the Chernobyl accident were reportedly ~3 mSv and 1.1 mSv respectively [15]. According to another assessment, the average whole-body individual effective dose to the residents of Kiev from all sources was ≤10 mSv in 1986, decreasing thereafter [16]. Moreover, comparisons with controls from Western Europe should take into account dose estimates for diagnostic radiology more extensively used in the West. For example, a Computed Tomographic (CT) scan produces a dose 2-20 mSv, while doses from interventional CT procedures usually produce doses 5-70 mSv [17].

Apart from Thyroid Cancer (TC) in people exposed as children or adolescents, no significant cancer incidence increase has been proven to have resulted from Chernobyl exposures [9]. The discussed incidence elevation of RCC in Ukraine [2,6,7] was probably caused by improved diagnostics and population coverage after the accident [10]. It was assumed that a radiation exposure leads to an increase in the micro-vessel density in RCC, which is known to be associated with a higher histological grade [6]. In general, RCC from Ukraine has been less differentiated than the controls from Spain [2,4,6,7]. The RCC from Ukraine more frequently contained the sarcomatoid i.e. poorly differentiated histological pattern compared to Spanish controls. "Comparative analysis between all Ukrainian and Spanish groups showed more frequent incidences of high grade RCC in Ukrainian patients with the significant differences" [2]. Apparently, the differences in the histological grade have been caused by the averagely earlier cancer detection in Spain than in the former Soviet Union (SU). The same considerations pertain also Colombia *vs.* former SU, considering the results of [7]. Analogous mechanisms have been discussed also in regard to thyroid and urinary bladder lesions [10,11,18]. According to the UNSCEAR, among causes of the registered incidence increase of TC was the screening, improved medical surveillance and reporting after the Chernobyl accident [9]. The screening detected not only early tumors but also advanced cases, neglected because of the incomplete coverage by medical checkups prior to the accident [10,11]. Furthermore, some people were striving to be recognized as Chernobyl victims to gain access to health care provisions and compensations [19], so that some non-exposed patients were counted among radiation-exposed cases [10]. Cancers from non-contaminated areas were probably averagely more advanced because there was no regular screening outside the contaminated territories. The following citations are explicative: "The tumors were randomly selected (successive cases) from the laboratories of Kiev and Valencia... [The cancers were] clearly more aggressive in the Ukrainian population in comparison with the Valencian cases" [5]; "The dramatic increase of aggressivity and proliferative activity" was found in RCC from Ukraine [2], while "the majority of the high grade tumors occurred in the Ukrainian (rather than in the Spanish) groups" [3].

It can be reasonably assumed that the reiteration of "aggressivity" [2] of post-Chernobyl RCC might have consequences for the therapy. Based on the information from respected journals that cancers from contaminated areas tend to be more aggressive than usual, whereas the surrounding renal parenchyma harbors "proliferative atypical nephropathy with tubular epithelial nuclear atypia and *carcinoma in situ*" [3], some surgeons might decide to perform nephrectomy more frequently instead of kidney-preserving procedures. By analogy, the misinterpretation of advanced TC as aggressive radiogenic malignancies had consequences for the therapy. "Practically all nodular thyroid lesions, independently of their size, were regarded at that time in children as potentially malignant tumors, requiring an urgent surgical operation"[20]. In the 1990s, the thyroid surgery in some institutions of the former SU became more radical compared to the international practice [11].

Certain results of the study [12], where molecular-genetic features of RCC from Ukraine were compared with the Spanish controls, are significant: "These findings do not allow us to consider the immunohistochemical expression of ubiquitylation and sumoylation as valuable markers for discriminating the effects of long-term, low-dose ionizing radiation exposure in conventional RCC carcinogenesis" [12]. Considering that the cancers from Ukraine tended to be more advanced, these results indicate that the ubiquitylation and sumoylation do not correlate with the progression of RCC. On the contrary, the RET/PTC3 chromosomal rearrangements are apparently associated with the progression of papillary TC [11,21]. An association was found of RET/PTC3 with a more aggressive phenotype, large tumor size and advanced stage at the diagnosis [22]. With time passing after the Chernobyl accident, the prevalence of RET/PTC3 declined [23,24] apparently because advanced cases were found and sorted out by the screening [21]. The cohort of pediatric PTC after the Chernobyl accident with the predominance of RET/PTC3 was deemed unique: in sporadic papillary TC the RET/PTC1 rearrangement is more frequent [25]. In fact, it is unique not worldwide but for more developed countries where cancer is diagnosed relatively early. RET/PTC3 was the most frequent RET rearrangement type in the studies from the Indian Subcontinent [26,27]. On the other hand, RET/PTC3 was infrequent in papillary TC from France [28]. Pediatric papillary TC from Japan was higher differentiated than that from Ukraine and Belorussia [29]. The frequency of RET/PTC3 among Japanese papillary TC cases has been low [30], which certifies the efficient and early tumor diagnostics in Japan. Analogously, more mutations were found in thyroid tumors from Russia compared to controls from the United States [31,32].

Conclusion

Results of some studies of Chernobyl-related cancer are valuable; but conclusions should be revaluated considering that some cases classified as aggressive radiogenic cancers were in fact late-stage neglected malignancies [10]. The well-known example is the RET/PTC3 chromosomal rearrangement in papillary TC, supposedly associated with a relatively late step of the tumor progression [11,21]. Furthermore, an association with the tumor progression and disease duration can exist for some markers of RCC, where differences between Ukrainian and Spanish cohorts were found [2,4]. The authors should think about a re-interpretation of their valuable results.

The monitoring of populations exposed to low-dose radiation is important but will hardly add much insightful information about cancer risks. It can be reasonably assumed that the screening effect, biased research and increased attention of exposed people to their health will result in new reports on the elevated risks, which would prove no causality [33]. Dose-response dependencies for low-rate ionizing radiation should be studied in large-scale animal experiments. The life duration is a sensitive endpoint attributable to radiation exposures [34]. Such non-invasive experiments are simple and ethically acceptable. To enable extrapolations to humans, the doses and dose rates in experiments must be comparable to the doses and rates in human populations.

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