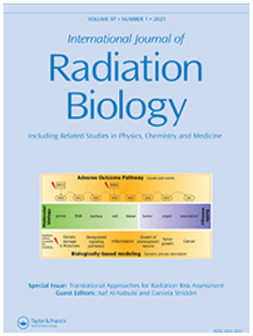

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REVIEW

Utility of gene expression studies in relation to radiation exposure and clinical outcomes: thyroid cancer in the Ukrainian-American cohort and late health effects in a MAYAK worker cohort

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ABSTRACT

Purpose: We herein report on changes in gene expression after radiation exposure to iodine-131 from the Chernobyl accident in the Ukrainian-American thyroid cohort and to external gamma ray or internal plutonium exposure in the Mayak Production Association radiation workers.

Materials and methods: Taking advantage of access to tissue samples from the thyroid cancer cases in the Ukrainian-American cohort, our group tried to identify candidate genes to discriminate spontaneously occurring thyroid cancers from thyroid cancers caused by radiation exposure. We also examined gene expression changes in normal and cancerous thyroid tissue in relation to iodine-131 dose separately. Gene expression changes in the peripheral blood of radiation exposed Mayak workers were examined to elucidate the dose-to-gene and gene-to-health (e.g. cardiovascular disease) relationships.

Conclusions: Results of both projects are discussed under the aspect of dose-response relationships (dose-to-gene) and clinical outcome relationships (gene-to-effect) in light of how mechanistic data can be translated into actionable knowledge for radiation protection or clinical purposes.

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Introduction

Within the TARRA workshop (Translational Approaches for Radiation Risk Assessment), we were asked to present our recent studies to provide examples in which mechanistic data have the potential of translating into actionable knowledge for radiation protection or clinical purposes. In this manuscript, we provide two examples and briefly describe the associated studies.

In previous work, we examined changes in gene expression following radiation exposure in two different cohorts, namely the Ukrainian-American cohort (UkrAm) of residents exposed to the Chernobyl fallout during childhood (Abend et al. 2012, 2013) and the Mayak production association (MPA) radiation workers cohort (Abend et al. 2014a, 2014b; Abendm, Azizova, et al. 2015). The average iodine-131 (I-131) thyroid dose received from the Chernobyl accident by thyroid cancer patients in the UkrAm cohort was 1.25 Gy ± 1.68 (stdev), ranging from 0.008 to 8.6 Gy (Abend et al. 2012). Based on their exposure history, Mayak workers were categorized into two groups. The group working in the nuclear reactor facility on average received an external gamma ray dose to the red bone marrow of 1.3 Gy (range: 0.4–3.1 Gy). The other group employed in plutonium (Pu) manufacturing/processing facilities on average absorbed an external total gamma dose of $\geq$ 0.5 Gy as well as an internal Pu dose to the red bone marrow of 0.1 Gy (range: 0.03–1 Gy, Abend et al. 2014a).

Regarding the Chernobyl study, we aimed to contribute evidence to an unresolved question of whether radiation-related cancers can be discriminated from spontaneously occurring cancers based on certain molecular characteristics. The answer is important for understanding radiation carcinogenesis and may have practical applications. For example, if a disease could be attributed to occupational radiation exposure based on molecular characteristics, the worker would be financially compensated. Molecular biological examinations can be performed on a DNA-level searching for mutations or copy number alterations to name but a few examples. However, advancements in the field of radiation-induced epigenetic modifications of the transcriptome (RNA-level) have supported studies employing whole genome screening methods such as gene expression microarray analysis or, currently, next generation sequencing techniques (Goldberg et al. 2004, 2006; Torres-Roca et al. 2005;

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Albanese et al. 2007). Such examinations are challenged by the availability of appropriate material and models. Ideally, cancer incidence should be substantially higher in the radiation-exposed group relative to the spontaneous or baseline cancer incidence so that most cases in the radiation exposed group can be attributed to radiation. The strong association between childhood exposure to I-131 and incidence of thyroid cancer coupled with dose levels received by children following the Chernobyl accident (Tronko et al. 2006; Brenner et al. 2011; Likhtarov et al. 2014), make this cancer a promising study candidate. In 2011, Maenhaut et al. (2011) reviewed the literature on radiation-associated gene expression changes in post-Chernobyl thyroid cancers. Many different research groups reported having identified some gene expression pattern typical for the radiation-exposed group. However, the reported patterns differed considerably among the studies and only a minor overlap, if any, remained. Besides methodological difficulties related to the – at that time – new technology (microarrays and platform differences), including missing validation steps (e.g. using qRT-PCR), low sample sizes and inadequate control groups, it was the absence of high quality individual dose estimates which among other reasons were identified as causes of inconsistencies in the reported gene expression patterns. In this context, we wanted to contribute a more conceptual approach: If gene expression is altered by radiation exposure, it should follow a certain dose-response (dose-to-gene) relationship. This represents one of the strongest Bradford-Hill criteria implicating causality (Bradford Hill 1965). Hence, instead of comparing gene expression patterns between a radiation-exposed and an unexposed control group, we searched for significant dose-to-gene (expression) associations taking advantage of high quality individual dose estimates in the UkrAm cohort. We thus evaluated differential gene expression in thyroid tissue in relation to thyroid doses of I-131 received from the Chernobyl accident (Abend et al. 2012, 2013). Sixty three of 104 papillary thyroid cancers diagnosed between 1998 and 2008 in the UkrAm cohort with individual dose estimates had paired RNA specimens from fresh frozen tumor (T) and normal (N) tissue provided by the Chernobyl Tissue Bank. Corresponding gene expression changes in the normal tissue were used as the reference to adjust for individual variance. For screening of the whole transcriptome, we first hybridized 32 randomly allocated RNA specimen pairs (T/N) on 64 whole genome microarrays (Agilent, 4x44K). Associations of differential gene expression (T/N) with dose were assessed statistically. Candidate genes were independently validated by changing both the technology (employing quantitative RT-PCR/qRT-PCR) and cases (using the remaining 31 T/N RNA samples).

Regarding examinations in the Mayak cohort, we developed a strategy of searching for target genes for which transcription was altered following radiation and which were also associated with late health effects, namely the development of cardiovascular disease (Abend et al. 2014a, 2014b; Abend, Azizova, et al. 2015). The Mayak radiation workers were employed either in plutonium manufacturing/processing facilities or in a nuclear reactor facility. The plutonium workers, but not the reactor workers, were exposed to densely ionizing alpha particles as a consequence of plutonium inhalation (Anspaugh et al. 2002; Azizova et al. 2008).

The sections following the introduction will refer to our two studies and, in the very first section, we will compare conventional and molecular radio-epidemiological studies under the question: what incremental knowledge do we gain? We will report on the previous studies with a focus on scientific developments bearing the potential to provide 'Practical tools for the Decision-Maker', but will also refer to the associated challenges.

Conventional versus molecular radiation epidemiology – what do we gain?

Conventional radiation epidemiology studies are multidisciplinary in nature and challenging to conduct, because epidemiologists, dosimetrists, statisticians as well as pathologists have to work in concert and must have an understanding of the other fields involved (Figure 1, left side).

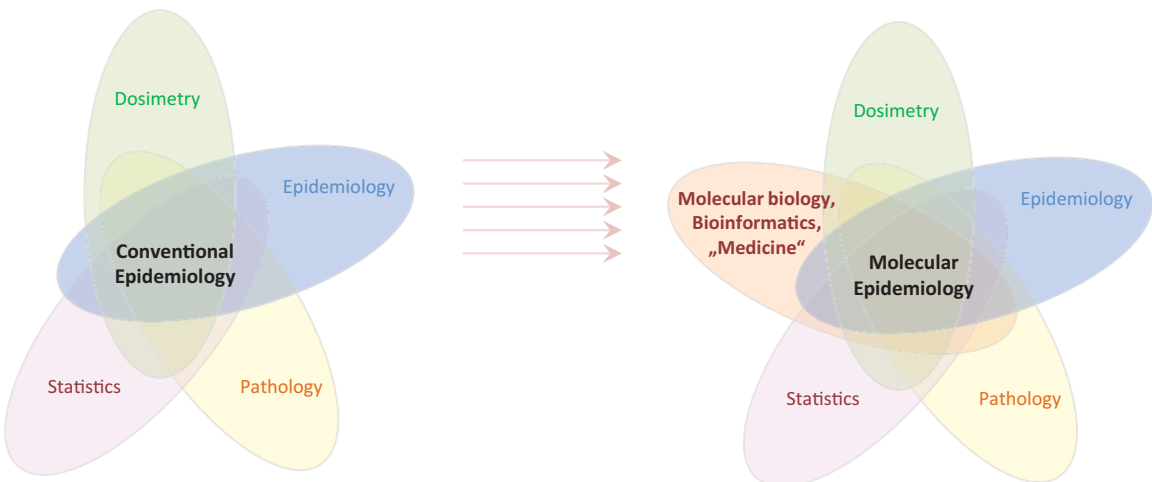

Figure 1. Shifting from conventional radiation epidemiological studies (left side) to molecular radiation epidemiological studies (right side) adds another degree of complexity (interface to molecular biology, bioinformatics and (often) medicine). Studies like this are rather expensive and challenging for the participants, but bear the potential for identification of new and clinically relevant diagnostic or therapeutic molecular targets.

When performing molecular radiation epidemiology studies an additional interface comes into place. It is the field covering molecular biology, bioinformatics and (often) medicine (Figure 1, right side). This enhances the complexity of the studies with regard to communication, understanding and finances – molecular biology is expensive. The question arises: How much do we gain scientifically? Conventional radiation epidemiology uses dose estimates for risk estimation, prediction, and transfer. However, combined with molecular biology, it could unravel mechanisms underlying health effects of radiation exposure. Once dose-dependent bioindicators are identified, in an extended approach, we can examine whether late health effects can be predicted based on these bioindicators. This approach might have potential for a more individualized risk assessment following the concept of adverse outcome pathways where molecular key events have to be identified. Moreover, the extended approach holds promise for improving clinical diagnostics and providing target molecules for potential individual therapeutic intervention (Abend and Port 2015) or in other words 'practical tools for the decision-maker'.

Discriminating radiation-induced from spontaneously occurring thyroid cancers – is that possible?

Using the whole genome gene expression approach, we identified and selected 75 genes with a priori evidence or significant dose-to-gene associations for validation by qRT-PCR on the remaining 31 RNA T/N specimen pairs (Abend et al. 2012). Eleven of 75 qRT-PCR assayed genes (*ACVR2A, AJAP1, CA12, CDK12, FAM38A, GALNT7, LMO3, MTA1, SLC19A1, SLC43A3, ZNF493*) were confirmed to have a statistically significant differential dose-expression relationship. Using individual I-131 dose estimates, we evaluated dose in three categories, not making assumptions about the dose-response shape and assuming a linear dose-response. Often curvilinear (non-linear) dose-to-gene associations were found. For instance, relative to the lowest dose category (Figure 2, upper panel), gene expression values for *CA12* were either similarly up- or about 3-fold down-regulated (for further examples, refer to Abend et al. 2012). Because different radiobiological effects might occur with increasing radiation doses, including cell killing and induction of persistent chromosomal rearrangements which themselves are known to follow a non-linear relationship (Romm and Stephan 2004; Caudill et al. 2005), we concluded in previous publications that a curvilinear relationship for differential gene expression is plausible (Abend et al. 2012). Hence, based on this analysis, we believe it should be possible to identify a radiation-associated gene expression signature(s) in tumors caused by radiation exposure. It is noteworthy that, in additional analyses of the same specimens, we searched for dose-related gene expression changes in histologically normal and cancerous tissues separately. Bioinformatic pathway analysis demonstrated significant overrepresentation of genes coding for nucleic acid binding in normal and tumor tissues and for p53, EGF, FGF signaling pathways in tumor tissue (Figure 2, lower panel). Our finding of dose-related gene expression found in normal and tumor thyroid tissue, coupled with additional changes found in the tumor tissue, suggests a multistep process of radiation carcinogenesis which may have already started in histologically normal tissue (Abend et al. 2013). This intriguing finding might bear the potential of improved surveillance during the follow-up, but require validation in future studies.

While discussing our results, we hypothesized that dose-dependent epigenetic modifications and copy-number alterations (CNA) could have shaped the tissue transcriptome and influenced gene expression (Ortiz-Estevez et al. 2011). To study CNA, we collaborated with another research group that identified significant overexpression of *CLIP2* gene among several genes examined within the gained 7q11.22-7q11.23 region in post-Chernobyl thyroid cancers (Hess et al. 2011). In further examination, the group confirmed exposure-related differences in *CLIP2* expression at the mRNA and protein level. The investigators successfully used CLIP2 measurements for mechanistic modeling of epidemiological data (Kaiser et al. 2016). This demonstrates potential usability of tissue markers in the context of the adverse outcome pathway (AOP) and even demonstrated the applicability on tissues using immunohistochemistry (Selmansberger, Feuchtinger, et al. 2015; Selmansberger, Kaiser, et al. 2015; Kaiser et al. 2016).

In another collaborative study with Dr. Nikiforovś group, the relationship between I-131 thyroid dose and frequency of gene mutations and gene fusions in post-Chernobyl thyroid cancers was evaluated (Efanov et al. 2018). In a recent publication, the investigators concluded that their findings provide support for a link between I-131 exposure and generation of carcinogenic gene fusions which, from their perspective, appear to be the predominant mechanism of thyroid cancer development following radiation exposure from the Chernobyl accident (Efanov et al. 2018). The same question was independently investigated by another group examining anaplastic lymphoma kinase (*ALK*) gene rearrangements in post-Chernobyl thyroid carcinomas (Arndt et al. 2018). *ALK* encodes for a membrane tyrosine kinase receptor, which is physiologically expressed in fetal neuronal progenitor cells and plays a key role in cell proliferation, survival, and differentiation (Werner et al. 2017). Aberrant non-neuronal expression of *ALK* caused by rearrangement events has been shown to drive the carcinogenesis of various malignancies, including anaplastic large cell lymphoma and, more recently, aggressive forms of thyroid cancer (Kelly et al. 2014; Pérot et al. 2014; Werner et al. 2017). Targeted therapy with ALK inhibitors like Crizotinib is used to treat ALK-rearranged anaplastic large cell lymphoma and offers a promising therapeutic option for other ALK-driven tumors (Kruczynski et al. 2012). The diagnosis of *ALK* rearrangements is required prior to ALK-inhibiting therapy and can be routinely performed using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). In a study by Arndt et al., FISH-detected ALK rearrangements in post-Chernobyl thyroid carcinomas were confirmed by IHC and dose-to-gene fusion relationship could be established. The authors concluded that IHC may represent an effective

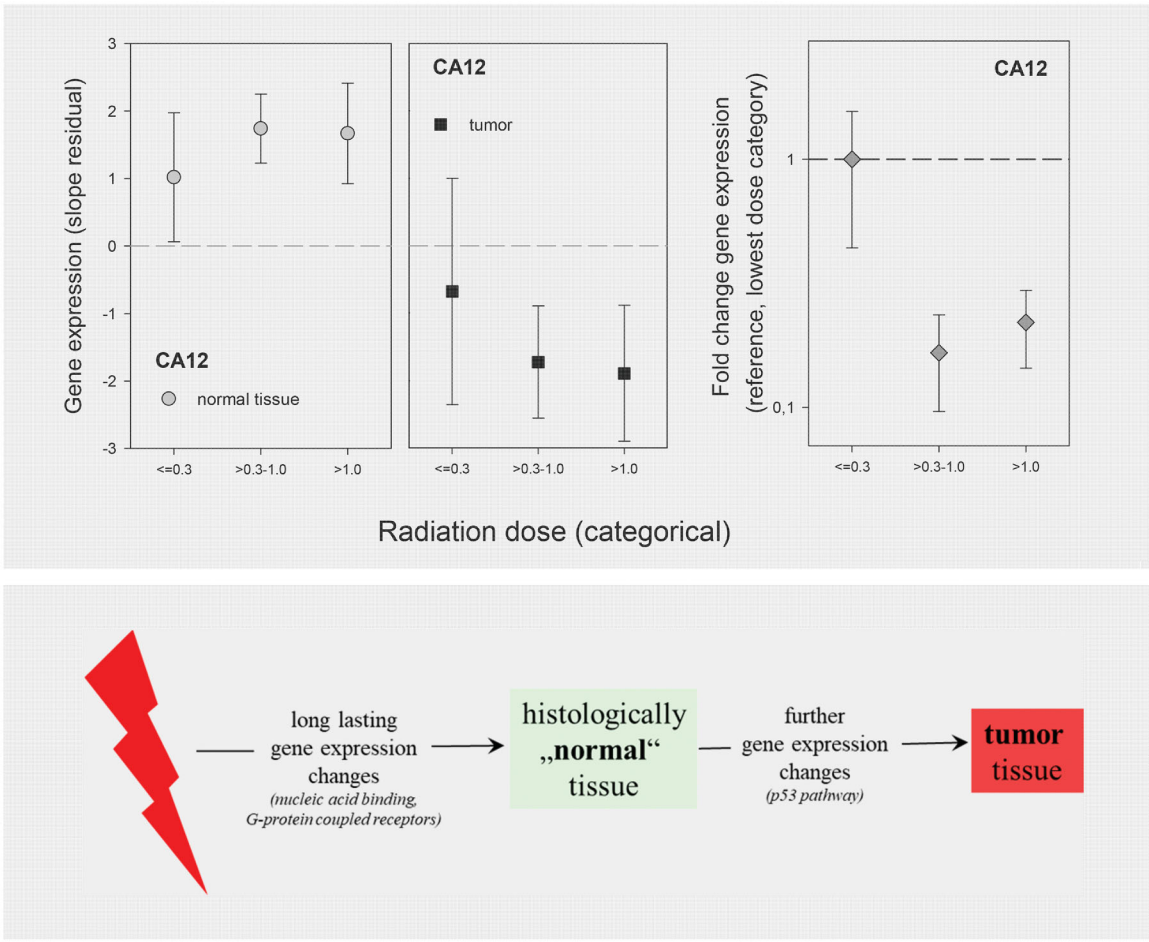

Figure 2. *Upper panel*. Residual gene expression by tissue type in relation to I-131 thyroid dose estimates and fold-differences among the tissues. *Note*. Mean of residual gene expression after removing the effects of age, oblast, and sex is plotted separately for normal tissue (left graph) and tumor tissue (middle graph) against three I-131 dose categories (<0.3 Gy, >0.3–1.0 Gy, and > 1 Gy). Circles with gray fills correspond to mean gene expression values for normal tissue (left graph) and squares with black fills correspond to mean gene expression values for tumor tissue (middle graph). A fold-difference (linear scale) was calculated among log2-transformed tumor expression values normalized by corresponding normal tissue values and the lowest dose category served as the reference and was arbitrarily set to one (right graph). By doing so, it is exemplified that CA12 RNA copy numbers appear about 0.2–0.3 –fold (or 3–5-fold) downregulated in the two higher exposure groups relative to the lowest exposure group set to one. Error bars represent 95% confidence intervals. *Lower panel*. A causal pathway of radiation exposure and later development of a tumor depicts assumed long lasting gene expression changes. These changes can be found already in histological 'normal' tissue (G-protein coupled receptors) and further gene expression changes (e.g. along the p53 signal transduction pathway) finally facilitate tumor development.

method for ALK-screening in thyroid cancers with known radiation etiology (diagnosis), which is (also) of clinical value since oncogenic *ALK* activation might represent a valuable target for small molecule inhibitors (Arndt et al. 2018).

Identifying molecular targets for potential diagnosis and/or therapy of radiation induced late health effects – how to do this?

In our recently published work, we performed a gene expression study on a group of Mayak workers who were exposed either to combined internal alpha particles due to incorporated Plutonium-239 (239Pu) and external gamma rays, or to external gamma rays only (Abend et al. 2014a, 2014b; Abend, Azizova, et al. 2015). Peripheral blood was taken from workers older than 70 years of age, suffering from 29 different chronic diseases such as atherosclerotic disease or diabetes. We conducted a two-phase study. For phase I, we screened the whole genome for radiation-associated candidate genes and identified 25 mRNAs and 20 miRNAs species. Within the following validation step, we employed another methodology (quantitative real time PCR, qRT-PCR), used 92 blood samples from different individuals, and adjusted each of the radiation-to-gene models for 26 potential confounders such as age at biosampling, lifestyle factors (smoking, alcohol), and health status indicators (diastolic/systolic blood pressure, body mass index, atherosclerosis, etc.). We then examined whether significant dose-to-gene relationships remained after considering all potential confounders. Ultimately, 15 mRNA and 15 miRNAs showed statistically significant dose-to-gene relationship following adjustments (Figure 3, upper panel). After identification of genes presumably related to radiation exposure (dose-to-gene associations), we wondered about the clinical significance of the genés altered gene expression (gene-to-disease associations). Hence, in the next phase of our study (phase II), we sought to determine the clinical significance of

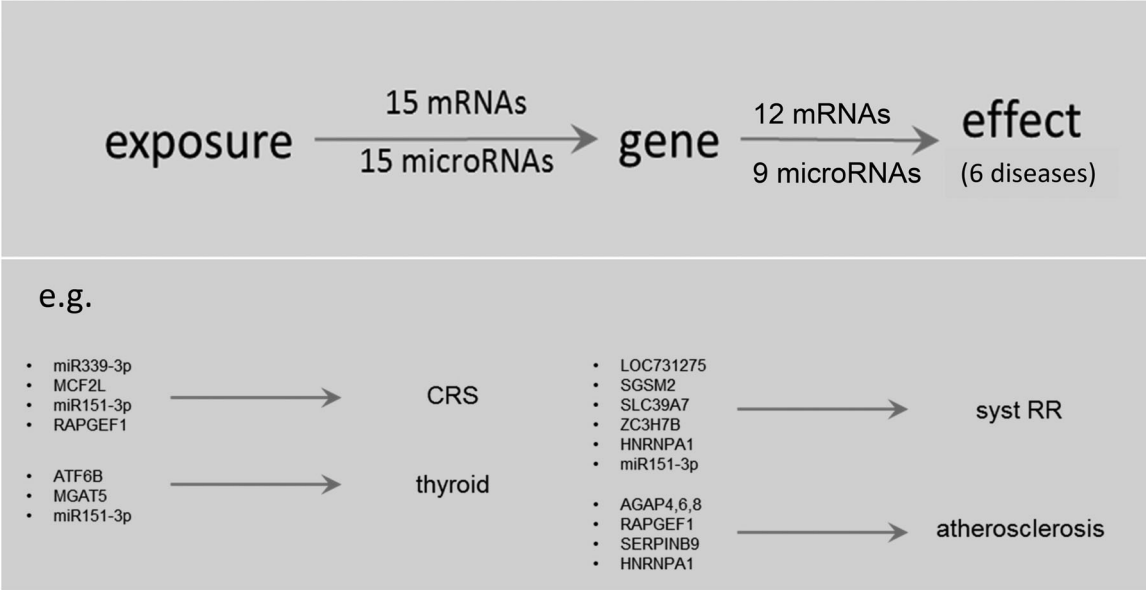

Figure 3. In *phase I* of a previous study employing a whole genome screening approach, we identified 15 mRNA and 15 microRNA species showing a significant radiation-to-gene (expression) association (upper panel). In *phase II* we examined which of these radiation-associated genes are also significantly associated with the presence of certain diseases (prevalence). Examples of mRNA and microRNA species and diseases are shown in the lower panel. Abbreviations: CRS, chronic radiation syndrome, systRR, systolic blood pressure, thyroid, thyroid diseases.

altered gene expression for 15 validated mRNAs and 15 miRNAs. Specifically, we tested the association between altered gene expression intensity and risk of chronic disease other than cancer employing more complex mathematical models. We examined the association of Phase I-identified radiation-associated genes with the 29 different chronic diseases from which the Mayak workers were suffering. Altogether, 12 mRNAs and 9 miRNAs appeared to be significantly associated with 6 diseases, including chronic radiation syndrome, thyroid disease, increased blood pressure, atherosclerotic disease and others (Figure 3, lower panel). In particular, *HNRNPA1, RAPGEF1* and *SERPINB9* appeared to be very promising molecular targets; these were further confirmed by a bioinformatic approach which emphasized their impact on the atherosclerotome (Abend, Azizova, et al. 2015). These findings are currently being validated in a prospective cohort study of the Ukrainian Chernobyl clean-up workers.

Again, combining a whole genome screening for radiation-to-gene associations in *phase I* with examining best *phase I* candidates for gene-to-disease associations in *phase II*, provides a successful strategy for identification of promising radiation-induced molecular targets for clinical diagnostic and/or therapeutic purposes.

Changes on the DNA level such as epigenetic modifications are considered complementary approaches with impact on the transcriptional (mRNA) and post-transcriptional (e.g. miRNA) level.

In summary, examples of two studies and the associated body of work demonstrate that performing molecular radiation epidemiological studies is more challenging and expensive than doing conventional epidemiological studies, but that it also bears the potential for improving our understanding of biological mechanisms underlying health effects of radiation and identification of new and clinically relevant molecular targets for diagnosis and/or therapeutic intervention.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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