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Age and sex bias in radiation research – and how to overcome it

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Editorial

Basic research is the driving force behind medical progress. As successful as this relation has been, an intrinsic dilemma persists to this day: each study design frames reality–yet the conclusions seek general validity. This dilemma crystallizes into major bias when conclusions are based on selected groups that do not represent the reality of biological diversity. Ironically, while striving for a future of highly-personalized treatments, we have overlooked the obvious features that make an individual, stratify a cohort, and influence outcome: age and sex.

A current example of this issue are molecular biomarkers that may bring the next quantum leap in clinical practice. Biomarkers such as transcripts, proteins, or metabolites, can easily be sampled from blood, quantified, and used for biological dosimetry, risk estimation for post-radiation therapy p diseases, or screening in radiation hazard events. Still, most studies that use novel 'omics' or 'next-gen' methods for screening harbor similar pitfalls as previous methodologies and neglect age and sex as important factors. This can compromise the sensitivity, specificity, and accuracy of biomarkers, leading to erroneous diagnosis and treatment planning.

Sex bias in biomedical research is not a new revelation (Beery & Zucker, 2011). Surprisingly, it stems not only from the use of single-sex cohorts, but also from omitting sex as a factor altogether. While other fields such as neuroscience research have started to tackle this issue (Will *et al*., 2017), it remains largely unaddressed and under-represented in radiation biology and related medical fields. For instance, sex-specific radiation sensitivity is known in principle, yet rarely considered in study designs beyond this particular research question. The bias in our knowledge base becomes even more worrisome when considering the non-linearity of age between humans and mice (Dutta & Sengupta, 2016). Do we relate age according to sexual maturity, onset of senescence, or total life span? It is reasonable to assume that the answer is 'depending on the research question and biological endpoint'. However, this issue is usually neglected altogether and the age of the animal is chosen for purely practical reasons. Recently, research on age and sex bias has shown that radiation responses can differ largely between male and female mice, as well as between adolescent and adult specimen (Langen *et al*., 2017). If only one group had been used in the proteomic screening for blood-based biomarkers, the conclusions on dose-response would differ and poorly represent radiobiological effects for other sex and age groups. Most importantly: if neglected, the bias would remain unknown and create large uncertainties that ultimately lead to avoidable risks for patients in radiotherapy and nuclear medicine.

It will be difficult to update our knowledge base to consider these basic factors systematically; in the end, a large body of evidence will still include age and sex biases. Nevertheless, the sooner we start taking action to overcome age and sex bias in our field, the less misleading information will contaminate the knowledge base. Each of us can partake in this effort according to our opportunities:

- Researchers can plan studies with male and female cohorts, and PIs should establish it as group standard. Our manuscripts and grant applications should address these possible biases and highlight measures on how to control them.
- Reviewers can identify age and sex bias and consider it methodological limitations, and editors should establish submission forms that require disclosure of age and sex as preclinical study parameters.
- Lecturers can inform about these potential biases in research and raise awareness when working with source material.
- Finally, students and PhD candidates can take initiative and address age and sex as important factors if presented with biased data or methodologies.

Undoubtedly, using both male and female cohorts and different age groups in research is resource-intensive. It is paramount that funding agencies support these efforts by rewarding points for rigorous research designs that consider age and sex as essential factors. Some large international funding agencies have already started to include dedicated sections on the ‘age and sex dimension’ in grant applications, but this change needs to be consistent across all funding bodies on the national and regional levels.

By committing to a higher methodological standard we can reduce critical bias in our field and in radiation research as a whole. Ultimately, our effort will increase the quality of diagnosis and treatment and improve the odds for therapeutic success for every patient.

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