

Systematic review and Meta-analysis on Iron and cancer risk - Reply

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We thank Garmendia and cols. (1) for the attention given to our paper “Iron and Cancer Risk – A Systematic review and Meta-analysis of the Epidemiological Evidence” (2), in spite of its

conclusion that we “failed to synthesize available research into a coherent body of evidence that informs practice”. Indeed, given the topic being discussed, we aimed to synthesize available research, but our goal was to inform research itself, not practice. Beyond this, there are other issues argued by Garmendia and cols. on which we would like to comment.

First, they claim that we included only cohort and case-control studies without explanation, while experimental studies have the highest methodological rigor. As we clearly stated that studies in animal models were left out, we guess that by ‘experimental’ studies they refer to randomized clinical trials (RCT). Since increased iron intake and/or iron overload involve potential risk, such studies simply cannot be carried out in human populations because exposing subjects to harmful factors is unethical. Furthermore, as we were interested in the etiological role of iron on cancer risk, only studies addressing causal relationships were considered, thus excluding cross-sectional designs, case series, studies using existing databases or historical controls, often included under the overall term of observational studies (3). We thought that this was quite obvious to the intended audience of the journal, with an epidemiological background, so we did not provide further details.

We did not use PubMed as the only source of publications, but as the single primary source; we also explored all references in the retrieved articles. Besides it must be recalled that PubMed remains the most widely used resource for medical literature available online and freely accessible around the world. The double recall rate for Google Scholar as compared to PubMed (4) is deceptive, as it refers to the first 40 citations, a condition not used in systematic reviews. While using PubMed as the only source may reduce sensitivity to 66-82%, it remains the database with the highest sensitivity and specificity out of the nine databases compared (5). Garmendia and cols. found in EMBASE 8 additional eligible studies, about 10% of the 88 studies identified in our search. However, the relevant issue here is not the figure itself, but whether or not including these articles would have substantially modified the major conclusions of the review.

The assertion that we did not address the important failing in meta-analysis of including studies with important heterogeneity is wrong and misleading. In fact, our paper was primarily a review, and meta-analysis was just provided as supplementary information. The reason for that, quoting ourselves (2), was that providing a combined measure of effect by means of a meta-analysis “assumes there is a common assessment of such an effect across all studies, whereas in many instances, the studies reflect a huge variability of results. In this case, trying to explain the observed differences may be more interesting than just providing an overall estimate that could prove difficult to interpret. This is particularly important when heterogeneity does not only reflect underlying differences in populations but also rather methodological differences in the study design”. Further, we decided not to mix (as is often done) different tumor sites, different metrics of exposure, or study design (prospective versus case-control). Moreover, in the four meta-analyses presented in the paper, heterogeneity was tested and measured by the quantity I^2 as suggested (6).

Finally, application of the MOOSE checklist (2) may be considered a recommendation, but it has not been incorporated universally in epidemiological reviews of observational studies. To what extent we adhered to these guidelines is meaningless to us since they were not taken into account when we designed our review. Although medical decision-making can benefit from high quality systematic reviews, meta-analyses are but one of the many elements used in the process of decision making. When the subject, as here with the relationship between iron and cancer, is complex and the data at hand do not allow a clear conclusion yet, we find gathering the available evidence in an organized way, with a focus on the details of the studies and a summary of main results (2) more

useful for the scientific community than a summary figure of effect estimate. In this way, we provide the interested reader with a lot of already elaborated and organized data, but then it is the informed reader who is responsible for making a judgment and taking a decision.

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