PERSPECTIVE

Dental X-rays and Risk of Meningioma: Anatomy of a Case-Control Study

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"The purpose of computing is insight, not numbers."
(Hamming, 1973)

If there were a list of the most feared diseases, cancer would probably reside among the top positions. Thus, if a study postulates that a 'factor x' substantially increases the tumor risk (even if it is a benign one), a strong echo can be expected in the media. This happened when Claus *et al.* (2012) reported a significantly increased risk for meningioma induced by dental x-ray diagnostics. Even professional journals published the results without critical assessment.

There is strong evidence that ionizing radiation may cause cancer. This evidence is most thoroughly backed by epidemiological investigations on large collectives of survivors of the nuclear bombs dropped on Japan at the end of WW2 (Preston *et al.*, 2003). However, the question remains whether low-dose exposure to ionizing radiation (Appendix 1) leads to a *detectable* increase in risk of tumors.

There have been several similar studies investigating a possible association between cases of meningioma and various factors, including x-ray diagnostics and amalgam, the latest by Longstreth *et al.* (2004) and Ryan *et al.* (1992). They all have at least two things in common: Their design is that of a case-control study, and data acquisition is performed *via* interviews. Furthermore, most studies use the odds ratio as a measure of effect. However, the one presented by Claus *et al.* is the largest, and if any study could provide evidence for an association between dental x-ray diagnostics and intracranial meningioma, it should be this one. But does it?

The chosen case-control study design is the only reasonable approach for study, given the small incidence of this disease (around 2/100,000 annually). This means that a sample of patients (cases) is compared with a sample of healthy control individuals with respect to the relative frequencies of different types of exposures. In other words, the empirical probability of a patient having been subjected to a certain exposure is calculated, not the probability that an exposure is related to a disease. This is an inherent weakness of the case-control design besides the fact that it is prone to sampling and recall bias (Mann, 2003).

But let us look at the results. Central findings of the authors include (Appendix 2):

(1) "Over a lifetime, cases were more than twice as likely as controls [odds ratio (OR), 2.0 [...]] to report having ever had a bitewing examination."
(2) "...individuals who reported receiving such films [panorex] at ages < 10 years had a 4.9 times increased risk [...] of meningioma."
(3) "Risk estimates for full-mouth films, although not statistically significant, were consistently in the same direction as for the other 2 film types."

Finding #1 indicates a two-fold increase in risk, if the individual had at least one bitewing in his/her entire life. This is somewhat surprising, considering the small radiation dose associated with a bitewing, especially when compared with the other diagnostic methods. A look at the actual relative frequencies unveils the reason: Both cases and controls report this case with nearly the same (high) relative frequencies: 95.8% and 92.2%, respectively. As is demonstrated in the Appendix, the odds ratio may not simply be translated into a probability ratio (relative risk) if high probabilities are regarded (Davies *et al.*, 1998)—an important fact that is too often overlooked (Tetradis *et al.*, 2012).

Finding #2 postulates a nearly five-fold increase in risk for individuals who had at least one panorex film at an age < 10 yrs. In absolute numbers, this means that 22 out of 1,433 patients reported such examinations, while this was the case for five out of 1,350 control individuals. With this result, it should be kept in mind that case-control studies possess inherent uncertainties (Mann, 2003), amplified by the method of data collection, which is based on recall of treatments which, in this case, occurred, on average, five decades previously and is prone to personal bias (see also Jorgensen, 2013; White *et al.*, 2013). As is shown in Appendix 3, these ratios are very sensitive to even

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small errors. In the present case, an assumed error margin of ± 1% would suffice to reverse the ratio. It is highly questionable whether such accuracy can be assumed.

Finding #3 looks inconspicuous at first glance, but it unfolds a severe inconsistency of the results. The authors seem to be unaware of the fact that a full-mouth series consists of from 16 to 20 single films and thus exposes the patient to a dose which is larger by one order of magnitude than that with a single film and is still considerably larger than that obtained with a panorex. Nevertheless, in their findings, the authors suggest that a relatively large dose leads to no significant increase in risk, while much smaller doses do. A more plausible explanation would be (besides the fact that the OR in finding #1 overestimates the risk) that the figures simply lack reliability, especially when they are based on small absolute numbers, as with finding #2. Since finding #3 corresponds to a much larger radiation dose as well as to higher statistical reliability, this result alone would lead to the conclusion that there is no (observable) effect.

A remark should be made concerning the presentation of the results. Findings #1 and #2, which postulate an increased risk of meningioma, are prominently placed in the abstract (which is probably what most people will read). In contrast, finding #3, which describes a null result (with much larger biophysical and statistical impact), is somewhat hidden in the 'discussion' section. Thus, an impression is produced which does not stand a closer inspection.

A reliability analysis of the results in general reveals that the higher the reliability, the smaller the effect size (Appendix 4). This confirms our conclusion that the study provides little to no evidence of an increased risk of meningioma for individuals exposed to low-dose dental x-ray diagnostics. Future studies on this topic should pay more attention to dosimetry as well as to error analysis beyond standard confidence intervals.

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