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Reply To The Letter

Reply to the Comments on "Radiation induced breast cancer risk in BRCA mutation carriers from low-dose radiological exposures: a systematic review"

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In response

First, we would like to thank the authors of the Letter for their comments on our article. This response gives us the opportunity to further explain our points and to reinforce the impact of our review (Colin *et al.*, 2017). The authors basically raise four points to which we respond.

1 Comparison between DNA damage caused by endogenous causes and DNA damage caused by medical radiological exposure

The statement that "*DNA damage due to endogenous causes*" are more numerous "*than the DNA damage caused by low levels of radiation such as from diagnostic X-ray exposures*" is questionable because the authors compared the effect of natural radiation background with that of acute doses. In fact, they omitted the impact of the dose rate. In addition, they did not consider the DNA damage repair as a function of time in their comparison. They only took into account the absolute numerical values without integrating them on a same period of time. Indeed, X-ray exposure for a mammographic view is delivered in less than 5 s while natural radiation background is delivered continuously. Hence, we proposed two examples of comparison by considering induced DNA double strand breaks (DSBs) and effective dose:

– it is generally considered that each human cell is subjected to about 8 induced DSBs per day, which represents the major DNA damage induced by endogenous causes (Lieber and Karanjawala, 2004). It is well documented that a dose of 1 Gy of X-rays induces 40 DSBs per human diploid cell independently of dose range and cellular radiosensitivity (Foray *et al.*, 2016). A mean glandular dose of 2 mGy per mammographic view corresponds therefore to the induction of 0.08 DSBs per cell, but induced in 5 s. In comparison, endogenous causes induce 0.00046 DSBs, *i.e.*, 172 times less in the same period of time;
– natural radiation background is expressed as effective dose (*e.g.*, 2.4 mSv y^{-1} is the average natural radiation background in Europe). In the case of mammography, a mean glandular dose of 2 mGy for each breast corresponds to an effective dose of 2×0.12 mSv = 0.24 mSv (taking into account the weighting factor for the breast $W_T = 0.12$). But, again, this effective dose is delivered in 5 s while natural radiation background effective dose is 0.315 nSv in the same period of time. In this case, the ratio is about 762.

Hence, these two methods of calculations contradict the opinion of the authors in their letter.

2 Boosting of immune system and DNA repair

The authors of the letter argued that "*the increased damage from low-dose radiation would boost defenses such as antioxidants and DNA repair enzymes... and the immune system... and so would reduce DNA damage from endogenous causes... and eliminate the cancer cells more effectively, reducing the cancer risk*". This statement does not hold if we take in consideration several issues from epidemiology, radiation biology and immunology.

Epidemiological data show that ionizing radiations constitute a risk of cancer which increases with dose (Preston

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et al., 2002; Wakeford 2004). These data establish an increase of the breast cancer risk linked to the increase of cumulated doses (Ronckers *et al.*, 2005), especially at young age at exposure (Hoffman *et al.*, 1989; Miller *et al.*, 1989; Howe and McLaughlin, 1996; Doody *et al.*, 2000). This is the case even for very low cumulated doses in BRCA mutation carriers (Pijpe *et al.*, 2012). Furthermore, even if we introduce the notion of dose threshold below which the immune system, anti-oxidants, and DNA repair enzyme contribution are significant to reduce cancer incidence, it would include the natural radiation background. However, there is no significant difference between cancer incidence in the regions of low natural radiation background (*e.g.*, Japan) and of high natural radiation background (*e.g.*, Ramsar, Iran) while the ratio between the corresponding natural radiation backgrounds is about 100.

Radiation biology data certainly show that DNA repair enzymes are mobilized after exposure to ionizing radiation above a significant dose to trigger signalization of DNA damage. However, this does not last very long, indeed a few days at most. Therefore, a mammography examination every two years cannot produce a significant long lasting level of intracellular defenses able to confer radioresistance to protect from breast cancer. Furthermore, one cannot even imagine that an eventual boosting of DNA repair enzymes would improve the poor functioning of genetically altered BRCA proteins in these mutated patients.

The hypothesis that the immune system would better eliminate irradiated precancerous cells than non-precancerous cells generally originates from a biased interpretation of the hypersensitivity to low doses (HRS) phenomenon (Tubiana, 2005). However, it was clearly showed that: i) the HRS phenomenon is limited to 25% excess of cell death and would therefore not concern all the irradiated cells (Thomas *et al.*, 2013); ii) the HRS phenomenon is also observed in primary fibroblasts and therefore not specifically in precancerous cells (Slonina *et al.*, 2007); iii) the HRS phenomenon is not limited to cell death and can be associated with excess of cell mutations, in complete disagreement with the hypotheses of the authors of the letter (Xue *et al.*, 2009).

Finally, there is no evidence that ionizing radiation boosts the immune system but there is evidence that ionizing radiation induces ageing of immunocompetent cells (UNSCEAR, 2006).

3 Consistency of epidemiological data

It must be stressed that, despite of all the biases due to the variety of the diagnostic procedures (Tab. 3 of our review), the great majority of epidemiological studies show the same trend, suggesting a radiation-induced cancer risk linked to the BRCA mutational status, whatever the design of the epidemiological study. Besides, in our review, there is only one study taking into account the cumulated doses of all the radiological breast exposures (Pijpe *et al.*, 2012) and this study is in agreement with the majority of the others (Fig. 1 of our review). Notably, this is a major point for clinical practice: avoiding thoracic computed tomography in BRCA (or P53) mutation carrier should be considered a must for clinicians. Therefore, the argument of the authors of the letter concerning the inconsistency and the weakness of the epidemiological data gathered in our review does not stand.

4 Radiation-induced mutations and radiation-induced cancer risk

The authors present the following syllogism: "*The number of natural mutations is significantly larger than those created by low-dose ionizing radiation. If low-dose radiation is a hazard, one would expect that the natural mutations would propagate cancer at a rate larger than observed. Since this does not occur, the DNA repair mechanisms and human immune system must function efficiently to remove both naturally occurring abnormalities and those caused by low-doses of ionizing radiation.*" The first sentence is not in agreement with the very documented observation that mutation frequency increases with dose and, as stated above, omits the dose rate effect that refers to the point 1 of our reply. The incidence of heterozygous mutations of genes of DNA damage signaling and repair pathways that all confer cancer-proneness may represent together 5–20% of the whole population, which is not negligible. Interestingly, all these gene mutations are not necessarily associated with immuno-deficiency. Finally, if *DNA repair mechanisms and human immune system must function efficiently to remove both naturally occurring abnormalities and those caused by low-doses of ionizing radiation,* how to explain that 5–20% of the whole female population is at high increased risk of breast cancer?

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