Assisted reproduction and cancer risk: how useful are national databases?

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This issue of Human Reproduction presents an impressively large population-based study that evaluated the risk of developing cancer after assisted reproductive treatment (ART) in parous women (Reigstad et al., 2015a). The study included 806,248 women that gave birth in Norway between 1 January 1984 and 31 December 2010. These data were coupled to a cancer registry. All study subjects started follow-up at the starting date of their first pregnancy as registered in the Medical Birth Registry of Norway between 1 January 1984 and 31 December 2010.

In the ART group 2.0% of women developed a cancer over an average period of 7.3 years. In the non-ART group 2.9% of women developed a cancer over an average period of 16 years. Controlling for some basic confounders resulted in a hazard rate of 1.16 (95% confidence intervals (CI) 1.04–1.29) for the ART group versus the non-ART group. This suggests a 16% increase in cancer development rate over time in the women in the ART group. The large difference in follow-up time between the two groups is a little problematic; the hazard rate assumes the hazard or event rate in one group is a constant proportion of the hazard in the other group and there is no way to know whether this assumption holds. Stratified analysis per cancer group suggested that women in the ART group have a higher hazard rate for developing breast cancer — strangely enough not reported in the present study — and central nervous system (CNS) cancer (Reigstad et al., 2015a,b). This was even more pronounced in women that had undergone IVF. However, these excess risks were statistically non-significant after correction for multiple analyses. For all other cancers results seemed reassuring as no evidence for further differences in hazard rate were observed.

Breast cancer is the most highly prevailing cancer in women in general but also in women during the fertile age period. Breast cancer accounts for > 40% of all cancers in women below 40 years of age (Anders et al., 2009). In the Reigstad study database breast cancer accounted for almost 40% of all cancers. CNS cancer is rarer in these relatively young women. In the general population CNS cancers account for 4% of all cancers (Cancer Research UK — original data sources are available from http://www.cancerresearchuk.org). In the Reigstad study, CNS cancer occurred at a somewhat higher rate and accounted for 9% of cancers in the ART group and for 7% in the non-ART group. As the investigators suggest in their discussion, CNS cancer in women in the ART group might have been caused by fertility specific factors. Certain tumors of the pituitary gland are for instance known to be associated with infertility (Fourman and Fazeli, 2015).

I am actually quite reassured in reading these data for two reasons. First, although the population data were very large and likely to be complete it was not collected for this analysis. As a result many well-established risk factors for cancer rates could not be accounted for as they are simply not known. Well-known risk factors for many cancers are BMI, cigarette smoking, use of alcohol, physical activity, socioeconomic status and ethnicity. A high BMI is also a risk factor for infertility. If obesity was more prevalent in the ART group, this risk factor for cancer could potentially explain (part) of the excess risk. However, imagine that some important adjustments for risk factors had been made and that an excess risk was still there. Would that prove that parous women after ART have a higher risk to develop cancer than women that did not undergo ART? Not necessarily as there is at least a second possible explanation for the observed higher incidence of cancer in women in the ART group — an earlier detection. Before undergoing ART, women undergo a fertility work-up. The family history, hormonal measurements and ultrasound scans can alert physicians at a much earlier stage. Though the investigators ruled out a large early detection effect by doing subanalyses excluding the first year of treatment, this earlier detection bias cannot completely be ruled out. Familiarity with the hospital and association with a successful ART might render women in the ART group more inclined to seek medical help when the first signs of their developing cancer appeared. Thus cancers may have been detected that would never have caused symptoms, or would have caused symptoms only many years later. Furthermore, women in the ART group that have been noticed in previous studies to have a relatively high social-economic status might also visit a specialist at an earlier stage. If true, the resulting earlier detection of the cancer would make a higher incidence rate of cancer in the ART group a logical finding. A longer follow-up time...
could maybe make such early detection bias visible. Another option would be to compare the ART group to a non-ART group visiting the hospital for other, non-cancer-related, reasons, preferably in a prospective study design, allowing better control for confounding, effect modifiers and bias.

Future epidemiological studies on cancer following ART should be aware of early detection bias and aim at large prospective databases with a long follow-up time that include all risk factors.

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**References**


