Elsewhere in JAMA Network Open, Weng et al assessed the risk of childhood cancer in children born following fertility treatment, based on nationwide registry data from Taiwan using a nested case-control study design. They found that children born via assisted reproduction technology (ART) conception have a higher risk of any type of childhood cancer, as well as leukemia and hepatic tumors, compared with children born via either natural conception or parental subfertility. The increased risk was found not to be mediated by perinatal factors. The report by Weng et al is unique, as no other study based on registry data from a large Asian population has previously been published on the association between ART and childhood cancer. Furthermore, this work is important because the main limitations of studies to date include self-reported exposure data and small study sizes, leading to potential bias and imprecise risk estimates. Additionally, few studies have been able to consider the possibility of confounding by indication (ie, the underlying subfertility of the parents), which was done by Weng et al. According to the authors, the data completeness, validity, and possibility of individual-level data linkage of the Taiwan registry data rival those of the Nordic registries. If correct, this study significantly contributes to previously published literature.

The first child born via ART was born in 1978, and today, more than 8 million children have been born worldwide through the use of ART. Since that first birth, several studies have investigated possible health effects in the children, and studies have found ART to be associated with a number of adverse health outcomes, including an increased risk of congenital malformations and perinatal mortality. One of the most common causes of mortality in children is cancer, and although the etiology is largely unknown, the unexplained increase in childhood cancer incidence in recent decades points to a change in the prevalence of external risk factors.

One of the first studies linking fertility treatment with childhood cancer risk was a study by Michalek et al, wherein the use of hormones to treat infertility was found associated with a more than 10-fold increase in neuroblastoma risk in children (RR, 10.4; 95% CI, 1.2-89.9). Whereas earlier studies were based on self-reported data and a low number of participants, with evident methodological limitations, a number of more recent published studies have been based on high-quality registry data and large number of participants. Today, several recent systematic reviews and meta-analyses reporting an association between the use of fertility treatment and cancer risk in children have been published. However, although the mounting evidence points to an increased cancer risk in children born via ART, several important questions remain.

First, what childhood cancer types are associated with ART? Weng et al found an increased risk of leukemia and hepatic tumors in children born after ART, which was also observed in a recent meta-analysis. However, associations for other cancers, including neuroblastomas, central nervous system tumors, sarcomas, and retinoblastomas, have also been reported. Consistency in the findings for childhood cancer types would strengthen the evidence for an association of ART with the development of cancer in children, because different cancer types likely have different etiologies. However, investigating different childhood cancer types is made difficult by their rarity, calling for large or collaborative studies.

Second, given that the association is real, what part of ART conveys the risk? Although specific fertility drugs and procedures related to ART have been associated with the risk of cancer in children, few studies have included information on the drugs or procedures used (eg, frozen or fresh embryo transfer, in vitro fertilization or intracytoplasmic sperm injection, culture media, etc). These factors may have different effects on cancer risk in children. Further examining these factors raises the
possibility of advancing the understanding of the underlying mechanisms for childhood cancer development and an opportunity for childhood cancer prevention (eg, by avoiding certain procedures or drugs).

Third, is the association confounded by factors related to the underlying subfertility of the parents? In the study by Weng et al, there was still a statistically significant increased risk of cancer in children born after ART compared with the group of children born to subfertile parents without the use of ART, indicating that it is the treatment itself rather than the underlying infertility that conveys the risk. Likewise, in a large population-based Danish cohort study, also based on nation-wide registry data, an increased cancer risk in children born after frozen embryo transfer (a type of treatment used in ART) was still observed when comparing with children born of subfertile parents without the use of fertility treatment. However, few studies have been able to take into account the underlying subfertility of the parents, and more studies are needed to further investigate the possibility of confounding by indication.

The report by Weng et al is the latest in a long line of reports demonstrating an association between the use of fertility treatment and the risk of childhood cancer, strengthening the mounting evidence of the role of fertility treatment in childhood cancer development. However, whether the increased risk is associated with specific ART procedures, certain fertility drugs, or the underlying infertility of the parents remains to be investigated and will be important for furthering the understanding and possible prevention of cancer in children.