

**Brinton LA et al.** Childhood tumor risk after treatment with ovulation-stimulating drugs. *Fertil Steril*, 2004, 81, 1083-91

Type of study	- Record linkage study (retrospective) - Case-cohort (nested case-control)
Where	Denmark
When	Early 1960s - 1996
Characteristics of the cohort	Infertility patients and their offspring as identified through medical records (from medical files, microfilms, local computerized systems, the Danish National Patient Register since 1977). The cohort was linked to the Medical Birth Register, the Central Personal Register, the Danish Cancer Registry
Characteristics of the disease	Not indicated (admission to hospital/private fertility clinic resulted in a diagnosis of infertility)
Ascertainment of drug exposure	Hospital-outpatient records: medical interventions for infertility, including the types of infertility drugs prescribed and the number of treatment cycles. For each cycle, dates of starting and stopping were abstracted to define the windows of exposure to these drugs. Dosage information was not always available
Exposure definition	Women treated with ovulation-stimulating drugs
Size of the study	Cohort study: - infertility cohort: 51,468 women recruited; 51,063 children born to 30,364 women; 51 cases of cancer born after the mother's entrance in the cohort - reference group: the cancer occurrence (51 cases) compared with that of the general population: ? Case-cohort (nested case-control) study: - cases: 47 children diagnosed with cancer (hematopoietic malignancies 19, neural tumors 19, other tumors 9) - subcohort (control): 868 children
Exposed cohort	Infants whose mothers were treated with a group of drugs
Control	Cohort study: all infants in the general population Case-cohort (nested case-control) study: a randomly selected subcohort of children (of stratified random sample of women based on age and calendar year of entry to the infertility cohort)
Prevalence of exposure among controls	Case-cohort study (nested case-control): ever ovulation-stimulation: 38.5%
Outcome ascertainment : tumor	Danish Cancer Registry: to identify tumor cases among the children (0-20 years), the cohort was linked to the registry, which has recorded tumor incidence nationwide in Denmark since 1943
Outcome definition : tumor	Information based on the Danish Cancer Registry
Prevalence of outcome among control offspring: tumor	Cohort study: expected 44.7 (all malignant neoplasms)
Analysis	Cohort study: Standardized incidence ratio (SIR), defined as the ratio of the observed numbers of tumors to those expected and 95% CI Case-cohort (nested case-control) study: Rate ratio (RR), adjusted RR (maternal exposure to ovulation-stimulating drugs adjusted for mother's age at birth of study subject) estimation, 95% CI and regression analyses (the observations for the study children were weighted by the inverse of the sampling fraction, namely the number of eligible children in the family) (Cox's proportional hazards regression model)
Strengths	- Nation-wide population based study - Exposure data not dependent on patient recall - Information based on recorded data - Evaluation of the study's power analyses

	- The largest study to date
Weaknesses	<ul style="list-style-type: none"> <li>- Despite the size of the study, limited ability to detect alterations in risk, especially for specific tumor types</li> <li>- Limited ability to adjust for maternal age effects (small numbers of exposed cases)</li> <li>- Possibility of confounding by indication</li> <li>- No information about indications for drug usage</li> <li>- Limited follow up (for tumors that occur at older ages)</li> <li>- Information on the timing of drug usage with respect to conception was not analyzed</li> </ul>
Main results	<p>A total of 51 cancers were identified among the study children (SIR 1.14, 95% CI 0.8-1.5, comparable to that of the general population of children in Denmark). Usage of any fertility drug was associated with RR 0.82 (95% CI 0.4-1.6) and clomiphene citrate with RR 0.77 (95% CI 0.4-1.6). Non significant elevations in the risk of cancers occurring later in life, especially childhood hematopoietic malignancies (RR for use of any ovulation-stimulating drugs 2.30, 95% CI 0.8-6.6), may have been related to underlying reasons for medication usage</p>