764

Cancer incidence in children who are HIV-exposed and uninfected in England: data linkage study

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BACKGROUND

- Children who are HIV-exposed and uninfected develop in an *in utero* environment that usually includes exposure to maternal antiretroviral therapy (ART) as well as HIV
- The long-term health implications of *in utero* exposure to ART are largely unknown; and data have shown that long-term follow-up in clinical settings is not feasible.
- Linking existing data sources can be a desirable alternative for monitoring long-term outcomes
- Our aim was to estimate cancer incidence and identify associations with birth and maternal HIV/ART-related characteristics in children who were HIV-exposed and uninfected using linked surveillance and national cancer registration data from England.

METHODS

- The Integrated Screening Outcomes Surveillance Service (ISOSS) routinely collects data on pregnant people living with HIV and their infants until their infection status is determined for those who are confirmed uninfected.
- ISOSS data were linked to cancer registration data with follow up until November 2022. Analyses were restricted to children born 2002-2019 in England.
- The unit of analysis was child, and the first cancer registration was used if >1 cancer was registered during follow-up.
- Child characteristics of interest included child year of birth, sex, twin status. congenital anomalies and birth outcomes including preterm birth (PTB; <37 weeks' gestation), small-for-gestational age (SGA;<10th centile for INTEGROWTH-21), PTB-SGA (<37 weeks & <10th centile), large-for-gestational age (LGA;>90th centile). The comparison group for birth outcomes were children born with appropriate weight for gestational age (AGA; ≥10th & ≤90th centile) at term (≥37 weeks' gestation).
- Exposure related variables were ART exposure, timing of maternal ART initiation, and specific ART.
- Indirect standardisation was used to generate age-and sex-standardised incidence rates (SIR) based on the general population.
- Time-to-event analyses involved Cox's proportional hazards models to estimate hazard ratios (*p*-values from Wald test) for child characteristics and ART exposure characteristics.

Cancer incidence among children who are HIV-exposed and uninfected is similar to that reported for the general child population in England

RESULTS

- There were 14047 children who were HIV-exposed and uninfected, and 159,241 person-years follow-up; all children and young adults were aged 0-20 years inclusive.
- 19 cancer registrations (6 among males, 13 among females) were reported, all occurring in children <17 years old (Table 1)
- Overall population-level **cancer incidence was 1.07 (95% CI: 0.62-1.71) per 10,000 PY**
- Cancer events observed for males aged 0-4 years were lower than expected based on the general population (SIR: 0.14, 0.02-0.99 per 10,000 person-years) with no statistically significant differences at all other ages or among females.
- Children born SGA had a greater relative risk of cancer than children born AGA (Table 2)

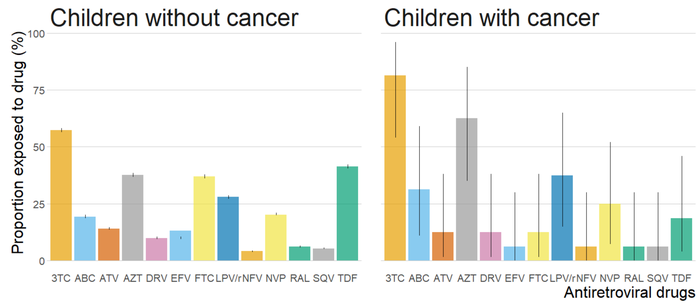
Table 2: Unadjusted Cox's proportional hazards models for child characteristics

	Person-years	*n*	HR	95% CI	*p*-value
Sex					
Male	79555	6	1		
Female	79645	11	1.83	0.68-4.95	0.234
Twin					
No	152719	15	1		
Yes	6650	2	3.10	0.71-13.6	0.133
Birth outcome					
Term and AGA	105120	8	1		
PTB	17345	2	1.51	0.32-7.11	0.602
SGA	12528	3	3.19	0.85-12.0	0.090
LGA	13484	2	1.95	0.41-9.19	0.400
Congenital anomalies					
None	119448	10	1		
One anomaly	5292	2	4.47	0.98-20.4	0.054

Table 1: Cancer site for each cancer registration reported (n=19)

Cancer site	*n*=19
Central nervous system	6
Lymphoid, haematopoietic and related tissues	4
Eye, kidney, thorax, bones, bronchus & lungs	≤3 for each site

Figure 1: Proportion of children exposed to ARVs (n=13797)



There were no statistically significant differences in ARV exposure among children with and without cancer (Figure 1)

- Data on ARV exposure was available for 98.2% (13797/14047) of children including all children with cancer
- Timing of ARV exposure was not associated with relative risk of cancer, with 70.6% (12/17) of children with cancer exposed from conception compared to 50.4% (6953/13797) in children without cancer (Fisher's exact test p=0.143)

CONCLUSIONS

- Cancer incidence did not differ from general population estimates and there were no differences in ART exposure by cancer status, although the number of cancer events was small.
- Universal risk factors for cancer were mirrored in our population of children who were HIV-exposed and uninfected, with congenital anomalies and SGA identified as risk factors based on univariable time-to-event analyses.

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