

Maternal smoking during pregnancy, birth outcomes and the risk of childhood cancer

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The NSW Government agency dedicated to the control and cure of cancer through prevention, detection, innovation, research and information.



Background:

- Effect of parental smoking on children is well established
- Maternal smoking during pregnancy is associated with
 - Low birth-weight
 - Pre-term delivery
 - Higher risk of childhood asthma
- Adverse outcomes may result in adult co-morbidity
- Effect of gestational smoking on childhood cancer remains disputed
 - Weak, inconsistent and even negative trends have been shown

Aims:

- To
 - (i) determine whether an association exists between childhood cancer in NSW and
 - (a) maternal factors, (including smoking during pregnancy)
 - (b) birth factors
 - Impact of tumour type and stage stratification also considered
 - (ii) investigate secondary outcomes of interest including impact of maternal smoking status on
 - Birth-weight
 - Gestational age
 - Admission to Neonatal Intensive Care Unit
 - Baby length of stay

Methods:

All data from the Midwives Data Collection (MDC) relating to births from 1 Jul 1994 to 31 Dec 2005 were linked with the NSW Central Cancer registry (NSW CCR) for cases of any cancer in children occurring between 1994-2005

Data sources

- The NSW CCR receives notifications of cancer in NSW. It is managed by the Cancer Institute NSW for the NSW Health Department, and operates under the authority of the Public Health Act 1991. The Registry maintains a record of all cases of cancer diagnosed in NSW residents since 1972. The registry is run according to the International Association of Cancer Registries' guidelines.
- The MDC is a state wide surveillance system that monitors patterns of pregnancy care, services and pregnancy outcomes. It covers all births in New South Wales, that is, live born babies regardless of gestational age and stillbirths of at least 20 weeks gestation or 400 grams birth weight.

Methods:

Master Linkage Key

- Identifying information (eg name, address, date of birth, gender) from the CCR and the MDC are included in the Master Linkage Key (MLK) maintained by the Centre for Health Record Linkage (CHeReL) for record linkage. Records were matched using probabilistic record linkage methods and 'ChoiceMaker' software.
- A total of 1,045,966 MDC baby records for the specified time period were matched to 948 cancer cases in the CCR. The parameters for the extract from the MLK were such that the false positive and false negative rate were each <0.1%.

CCR (CI NSW)

CCR ID (encrypted)
Identifying information (e.g. name, sex, DOB, ...)

MDC

Patient ID (encrypted)
Identifying information (e.g. baby name, sex, DOB, ...)

LINKAGE UNIT (CheReL)

Matching CCR Identifying information with MDC identifying information

Allocate a person identifier for each person in the research project (Project Person ID)

Send person ID and source ID to relevant data custodians

CCR (CI NSW)

Receives file from linkage unit

CCR ID (encrypted)
Project Person ID

Adds CCR data and removes CCR ID

Project Person ID
CCR data (e.g. type of cancer, date of diagnosis)

MDC

Receives file from linkage unit

Patient ID (encrypted)
Project Person ID

Adds MDC data & removes MDC ID

Project Person ID
Patient data (e.g. birth-weight, gestational age, maternal smoking etc)

ANALYSIS GROUP

Merge the CCR and MDC de-identified files to create the analysis dataset

Project Person ID
CCR data (e.g. type of cancer, date of diagnosis)
MDC data (e.g. Birth-weight, maternal smoking status)

Methods:

Other variables

- Cases were allocated to the 2001 local government areas (LGA) based on residential address at the time of diagnosis.
 - Accessibility/ Remoteness Index for Australia (ARIA+) values were applied to cases via the LGA based on the 2001 census information from the Australian Bureau of Statistics
 - Socioeconomic status was estimated using the Index of Relative Socioeconomic Disadvantage (IRSD), one of four Socio Economic Indexes for Areas (SEIFA) created by the ABS.
- Analyses were performed with respect to maternal smoking during pregnancy by all cancers and on the International Classification of Childhood Cancer (ICCC-3):
 - leukaemias, myeloproliferative diseases and myelodysplastic diseases
 - lymphomas and reticuloendothelial neoplasms
 - central nervous system, miscellaneous intracranial and intraspinal neoplasms, neuroblastoma and other peripheral nervous cell tumours
 - Retinoblastoma
 - Renal tumours
 - Hepatic tumours

Methods:

Statistical Analyses

- Examination of the factors associated with a diagnosis of childhood cancer occurring or not was performed using logistic regression and reported as crude (univariate) and adjusted odds ratios .
 - Statistical significance was taken at the $p < 0.05$ (two-tail) level.
 - Potential dose-response relationship between smoking during the second half of pregnancy and childhood cancer were examined with smoking categories of:
 - Did not smoke during pregnancy;
 - None;
 - 1-10 cigarettes per day;
 - >10 cigarettes per day.

Results:

MDC factors	No Cancer N=1,042,981 (%)	Childhood Cancer N=940 (%)	Crude OR	Adjusted OR*	p-value
Baby Sex					
Male	537,236 (51.5)	512 (54.5)	1.14 (1.00-1.29)	1.06 (0.89-1.27)	0.51
Female	506,990 (48.6)	427 (45.5)	Referent	Referent	
Age Mum					
≤34 years	812,275 (77.9)	759 (80.8)	Referent	Referent	0.66
≥35 years	166,104 (15.9)	160 (17.0)	1.02 (0.86-1.22)	1.05 (0.84-1.32)	
Birth-weight					
<2,500g	60,871 (5.8)	62 (6.6)	1.17 (0.90-1.50)	1.58 (1.10-2.25)	0.01
≥2,500g	917,999 (88.0)	858 (91.3)	Referent	Referent	
APGAR score (5min)					
1-4	15,572 (1.5)	6 (0.6)	0.33 (0.08-1.30)	0.38 (0.12-1.19)	0.10
5-7	30,131 (2.9)	35 (3.7)	1.68 (1.10-2.58)	1.54 (1.00-2.37)	0.05
8-10	999,323 (95.8)	899 (95.7)	Referent	Referent	
Baby length of stay					
≤10 days	949,638 (91.0)	882 (93.8)	Referent	Referent	0.55
≥11 days	29,232 (2.8)	38 (4.0)	1.40 (1.01-1.94)	1.16 (0.71-1.88)	
Mother smoke					
No	853,486 (81.2)	793 (84.4)	Referent	Referent	0.09
Yes	190,429 (18.2)	146 (15.5)	0.82 (0.63-1.05)	0.80 (0.62-1.04)	

* Adjusted for ARIA+, IRSD, Maternal diabetes, Maternal hypertension, Gestational diabetes, Pre-eclampsia

- Interactions between birth-weight x admission NIC/x premature birth all significant

Results:

MDC factors	No Cancer N=1,042,981 (%)	Childhood Cancer N=940 (%)	Crude OR	Adjusted OR*	p-value
Admitted Neonatal ICU*					
No	677,115 (64.9)	467 (49.7)	Referent	Referent	<0.001
Yes	18,369 (1.8)	40 (4.2)	3.28 (2.37-4.54)	3.29 (2.28-4.75)	
Mother smoke					
No	853,486 (81.2)	793 (84.4)	Referent	Referent	0.11
Yes	190,429 (18.2)	146 (15.5)	0.82 (0.63-1.05)	0.81 (0.62-1.05)	

MDC factors	No Cancer N=1,042,981 (%)	Childhood Cancer N=940 (%)	Crude OR	Adjusted OR*	p-value
Gestational age					
≤36 weeks	67,857 (6.5)	82 (8.7)	1.89 (1.45-2.47)	2.08 (1.53-2.83)	<0.001
>36 weeks	911,013 (87.3)	838 (89.1)	Referent	Referent	
Mother smoke					
No	853,486 (81.2)	793 (84.4)	Referent	Referent	0.10
Yes	190,429 (18.2)	146 (15.5)	0.82 (0.63-1.05)	0.80 (0.62-1.04)	

* Adjusted for all other factors (excluding birth-weight)

Results: Maternal smoking & association with cancer

Cancer type	Mother smoked [#] (n=180,822)	No smoking [#] (n=798,968)	Crude OR	Adjusted OR*	p-value
Any cancer	146 (80.7 per 100,000)	793 (99.3 per 100,000)	0.83 (0.70-1.00)	0.81 (0.63-1.05)	0.11
Lymphoma	11 (6.1 per 100,000)	26 (3.2 per 100,000)	1.87 (0.92-3.78)		0.08
Leukaemia	46 (25.4 per 100,000)	312 (39.1 per 100,000)	0.65 (0.48-0.89)	0.66 (0.42-1.02)	0.06
CNS/neuro etc	54 (29.9 per 100,000)	257 (32.2 per 100,000)	0.93 (0.69-1.24)	1.04 (0.69-1.56)	0.86
Retinoblastoma	14 (7.7 per 100,000)	38 (4.8 per 100,000)	1.63 (0.88-3.00)	1.08 (0.24-4.72)	0.92
Renal	14 (7.7 per 100,000)	66 (8.3 per 100,000)	0.94 (0.53-1.70)	0.95 (0.42-2.16)	0.90
Hepatic	4 (2.2 per 100,000)	26 (3.3 per 100,000)	0.68 (0.24-1.95)		0.47

**Adjusted for: Admission NIC, Baby's sex, APGAR (5min), ARIA+, IRSD, Age mum
#where smoking status is known*

No effect of degree of spread; no effect of quantity smoked

Results: Admission to NIC & association with Cancer

Cancer type	No Admission NIC (n=624,039)	Admission NIC (n=16,823)	Crude OR	Adjusted OR*	p-value
Any cancer	454 (72.7 per 100,000)	40 (237.8 per 100,000)	3.29 (2.38-4.54)	2.72 (1.81-4.08)	<0.001
Lymphoma	13 (2.1 per 100,000)	0 (0.0 per 100,000)			
Leukaemia	189 (30.3 per 100,000)	7 (41.6 per 100,000)	1.38 (0.65-2.92)	1.17 (0.54-2.58)	0.68
CNS/neuro etc	152 (24.4 per 100,000)	15 (89.2 per 100,000)	3.66 (2.15-6.22)	3.72 (2.12-6.51)	<0.001
Retinoblastoma	23 (3.7 per 100,000)	3 (17.8 per 100,000)	4.84 (1.45-16.1)	3.96 (1.07-14.6)	0.04
Renal	43 (6.9 per 100,000)	5 (29.7 per 100,000)	4.41 (1.75-11.2)	5.11 (2.00-13.3)	<0.001
Hepatic	14 (2.2 per 100,000)	4 (23.8 per 100,000)	10.6 (3.5-32.2)		<0.001

*Adjusted for: Baby's sex, APGAR (5min), ARIA+, IRSD, Age Mum, Maternal smoking
#where smoking status is known

Results: Lower birth-weight & association with Cancer

Cancer type	Higher birth-weight (n=920,577)	Lower birth-weight (n=61,141)	Crude OR	Adjusted OR*	p-value
Any cancer	858 (93.2 per 100,000)	63 (103.0 per 100,000)	1.65 (1.22-2.24)	1.63 (1.20-2.23)	0.002
Lymphoma	37 (4.0 per 100,000)	0 (0.0 per 100,000)			
Leukaemia	333 (36.2 per 100,000)	25 (40.9 per 100,000)	1.72 (1.07-2.76)	1.70 (1.04-2.77)	0.03
CNS/neuro etc	289 (31.4 per 100,000)	23 (37.6 per 100,000)	1.82 (1.10-3.00)	1.77 (1.06-2.96)	0.03
Retinoblastoma	50 (5.4 per 100,000)	2 (3.3 per 100,000)	1.34 (0.32-5.65)	0.76 (0.09-6.26)	0.80
Renal	75 (8.1 per 100,000)	5 (8.2 per 100,000)	1.49 (0.54-4.15)	1.00 (0.22-4.62)	1.00
Hepatic	25 (2.7 per 100,000)	5 (8.2 per 100,000)	4.58 (1.51-13.91)		0.007

Results: Premature birth & association with Cancer

Cancer type	Not Premature (n=913,550)	Premature (n=68,168)	Crude OR	Adjusted OR*	p-value
Any cancer	838 (91.7 per 100,000)	83 (121.8 per 100,000)	2.03 (1.56-2.65)	1.99 (1.52-2.61)	<0.001
Lymphoma	36 (3.9 per 100,000)	1 (1.5 per 100,000)			
Leukaemia	326 (35.7 per 100,000)	32 (46.9 per 100,000)	2.06 (1.35-3.13)	2.00 (1.30-3.06)	0.002
CNS/neuro etc	280 (30.6 per 100,000)	32 (46.9 per 100,000)	2.14 (1.36-3.34)	2.12 (1.34-3.35)	0.001
Retinoblastoma	49 (5.4 per 100,000)	3 (4.4 per 100,000)	1.17 (0.28-4.96)	0.96 (0.22-4.21)	0.96
Renal	75 (8.2 per 100,000)	5 (7.3 per 100,000)	1.31 (0.47-3.64)	1.39 (0.50-3.92)	0.53
Hepatic	24 (2.6 per 100,000)	6 (8.8 per 100,000)	5.41 (1.93-15.18)		0.001

Results:

Secondary objectives: Smoking and selected outcomes

Outcomes	No Smoking N= 798,968(%)	Any smoking N=180,822 (%)	Crude OR	Adjusted OR*	p-value
Birth-weight <2,500g ≥2,500g	42,803 (5.4) 756,165 (94.6)	18,130 (10.0) 162,692 (90.0)	Referent 0.48 (0.46-0.49)	Referent 0.45 (0.44-0.46)	<0.001
Gestational age ≤36 weeks >36 weeks	747,399 (93.5) 51,569 (6.5)	164,452 (90.9) 16,370 (9.1)	1.50 (1.46-1.53) Referent	1.55 (1.51-1.59) Referent	<0.001
Baby length of stay ≤10 days ≥11 days	776,647 (97.2) 22,321 (2.8)	173,873 (96.2) 6,949 (3.8)	Referent 1.52 (1.47-1.58)	Referent 1.56 (1.52-1.61)	<0.001
Admitted Neonatal ICU No Yes	519,213 (65.0) 13,290 (1.7)	104,580 (57.8) 3,520 (1.9)	Referent 1.32 (1.27-1.37)	Referent 1.48 (1.42-1.54)	<0.001

*Adjusted for: Baby's sex, APGAR (5min), ARIA+, IRSD, Maternal age, Maternal hypertension, Maternal diabetes, Gestational diabetes, Pre-eclampsia

- Interactions between smoking x birth-weight/ x admission NIC/x premature birth all significant

Discussion:

- Smoking is significantly associated with lower birth-weight; premature birth, increased baby length of stay and admission to NIC
- Lower birth-weight; Premature babies and those admitted to NIC have increased risk of any childhood cancer and some cancer subtypes

Limitations:

- Under-reporting of smoking status
- BMI, nutrition, health-status of mother
- Environmental exposure to tobacco
- Independence of observation

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