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The Immune System and Cancers of Foetal Origin

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Summary. *Evidence of early loss of immunological competence in cases of neoplasms occurring in juveniles was found in an analysis of OSCC data (Oxford Survey of Childhood Cancers). The effects observed included heightened sensitivity to infection from birth onwards for all types of childhood cancer, higher levels of sensitivity for leukaemia than for lymphomas, and higher levels for lymphomas than for other solid tumours. The findings as a whole are consistent with in utero loss of immunological competence, which is an essential promoter of cancers of foetal origin and thus allows the outcome of an in utero cancer induction to be influenced both by maternal levels of immunological competence and postnatal infection.*

Introduction

Foetal origins for neoplasms occurring in juveniles have been established in several epidemiological studies [7, 9, 10, 13–14]. Therefore, long before these diseases are clinically recognisable there could be changed reactions to other causes of death, which depend partly upon the nature of the affected tissues and partly on how these tissues are related to the immune system. The following tests of this hypothesis are based on records from the Oxford Survey of Childhood Cancer (OSCC) [10]. The original sources of these OSCC data include interviews with the mothers of children who have recently died of leukaemia or other neoplasms and the mothers of living controls. The tracing of cases and controls began in 1955 and is still being carried out. Therefore, there is now a long series of case/control pairs (with matching for sex, date of birth, region and interviewer) and several cohorts have been followed up for more than 10 years. For example, children who were born in England, Scotland, and Wales between 1953 and 1962 and died of cancer before the age of 13 years are now represented by 6,002 case/control pairs.

First Measure of Infection Sensitivity Based on Cancer Cases

Included in the OSCC data are the claims of mothers with respect to illnesses and injuries from which the children had

Table 1 Onset ages of nine groups of cancer cases (OSCC data)[a]

Onset age in years	Leukaemias			Lymphoma	Brain tumour	Neuro-blastoma	Wilms'	Other malignant	Borderline malignancy
	Lymphatic	Myeloid	Acute						
0	251	163	175	100	338	320	165	400	395
1	475	160	190	86	320	294	198	286	93
2	736	160	241	127	279	258	195	246	65
3	694	147	191	139	298	194	175	154	53
4	506	115	182	141	280	146	159	146	50
5	381	114	134	129	266	99	77	117	46
6	276	109	94	132	275	68	50	130	36
7	248	112	86	107	253	58	29	123	41
8	203	103	94	137	200	40	27	154	48
9	155	93	78	100	162	42	14	108	47
10	162	84	64	87	114	32	9	120	44
11	122	96	72	101	115	26	6	166	35
12	150	108	78	105	84	19	4	156	29
13	129	89	58	110	90	18	4	193	29
14	105	98	54	84	65	13	1	154	22
15	52	36	34	37	30	4	2	46	16
Total	4,645	1,787	1,825	1,722	3,169	1,631	1,115	2,699	1,049

[a] *Cancer onset age.* The age when the mother first noticed signs of the fatal illness or corresponding age for matched controls

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Table 2. Pre-onset illnesses of 19,642 cancer cases[a]

Pre-onset illnesses 0–9 years		
Specifications	No.	%
Measles	6,002	25.4
Chickenpox	3,810	16.2
Mumps	2,061	8.7
Whooping cough	1,926	8.2
Rubella	1,815	7.7
Other infections	5,178	21.9
Injuries	1,837	7.8
Allergies and miscellaneous	976	4.1
Total	23,605	100.0

[a] *Pre-onset illness.* The illness from which the children had fully recovered before the cancer onset date or corresponding date for matched control (see footnote to Table 1)

recovered fully before the date of the first sign of the fatal disease, or corresponding dates for living controls (so-called pre-onset illnesses). Earlier, a Mantel-Haenszel analysis of these data had been performed to look for evidence of reporting bias by the mothers of living and dead children. Definite evidence of this was found with regard to minor injuries and infections towards the end of the pre-onset periods [12]. Therefore, our first measure of cancer-induced sensitivity to infection was based only on case records, i.e., 19,642 children who had died of leukaemia or solid tumours before the age of 15 years (Table 1). For these children the number of pre-onset illnesses before 10 years of age was 23,605 and 88% of these illnesses were infections (Table 2). From these data, 115 sets of age-specific incidence rates were computed for the express purpose of obtaining standards for different types of cancer (Table 3). Some of the results achieved by comparing

Table 3. Expected rates for age-specific illnesses of age-specific cancers basis of the first measure of infection sensitivity[a]

Cancer onset, age in years	No. of cases	Rates (per 10^3) for age-specific illness[a]. Illness age in years									
		0	1	2	3	4	5	6	7	8	9
0	2,307	152	–	–	–	–	–	–	–	–	–
1	2,102	383	136	–	–	–	–	–	–	–	–
2	2,307	371	272	101	–	–	–	–	–	–	–
3	2,045	375	278	205	95	–	–	–	–	–	–
4	1,725	322	281	282	184	78	–	–	–	–	–
5	1,363	431	280	324	215	187	93	–	–	–	–
6	1,170	421	356	309	299	220	137	96	–	–	–
7	1,057	306	301	354	283	241	212	170	75	–	–
8	1,006	269	258	322	355	261	244	190	178	73	–
9	799	222	181	258	280	323	262	220	215	118	65
10	716	156	122	130	205	250	260	187	201	122	148
11	739	152	78	111	143	189	329	245	198	204	217
12	733	164	85	120	116	154	190	289	284	214	188
13	720	160	97	93	103	86	165	211	265	290	229
14	596	149	74	70	86	81	119	164	195	221	273
15	257	66	82	70	78	78	93	109	113	187	222

[a] The figures in this table are incidence rates for pre-onset illnesses. Therefore, mean rates specific for each *illness age* can be obtained by averaging the figures in each colum; likewise for each *cancer onset age* by averaging the figures in each row, and likewise for each *pre-onset interval* by averaging along each diagonal. For definitions see footnote to Tables 2 and 4

Table 4. Average rate ratios (ARR) of pre-onset illnesses for 11 cancer groups[a]

Diagnostic groups	Illness age[b] (years)			Pre-onset interval[c] (years)			Cancer onset age[d] (years)			All illnesses[e]
	0	1–4	5–9	0	1–4	5–9	0	1–4	5–9	
Lymphatic leukaemia	109	103	108	96	101	113	131	99	103	106
Myeloid leukaemia	118	117	104	121	101	109	165	120	110	112
Acute leukaemia	121	126	133	131	134	143	143	112	139	128
Lymphoma	96	105	104	115	102	107	105	112	101	103
Brain tumour	83	86	87	94	88	83	97	94	89	86
Neuroblastoma	102	92	77	79	91	94	101	97	87	90
Wilms' tumour	101	108	100	110	78	111	104	101	106	102
Other malignant	117	92	96	90	90	95	69	94	93	97
Borderline malignancy	72	85	81	105	77	75	80	90	79	82
RES neoplasma	109	109	111	110	107	113	138	105	109	109
Other cancers	91	89	87	92	91	84	84	95	89	88

[a] See Table 3 for expected rates for all age-specific illnesses of all cancer cases
[b] The age in years of each pre-onset illness
[c] Interval in years between each pre-onset illness and the cancer onset age
[d] See Table 1
[e] Obtained by averaging age-specific ARRs across 115 strata (see Table 3)

Table 5. Consistency of ARR ranking positions of pre-onset illnesses for ten cancer groups

Diagnostic groups	Ranking positions for ten sets of pre-onset illnesses[a]					
	1st	2nd	3rd	4th	5th–8th	9th
Acute leukaemia	8	2	–	–	–	–
Myeloid leukaemia	2	5	2	1	–	–
Lymphatic leukaemia	–	2	3	2	3	–
Lymphosarcoma	–	2	2	3	3	–
Wilms' tumour	–	–	3	2	5	–
Other malignant	–	–	1	–	8	1
Neuroblastoma	–	–	–	–	8	2
Brain tumour	–	–	–	–	10	–
Residue	–	–	–	–	3	7

[a] See ARRs in Table 4

these standards with the nine diagnostic groups in Table 1 are shown in Table 4.

The figures in Table 4 are average-rate ratios (ARR) obtained by averaging ratios of observed to expected illnesses in a vertical direction (thus holding constant the illness age), diagonally (likewise for pre-onset interval), horizontally (likewise for cancer-onset ages) and across all 115 strata (to obtain a single ARR for each diagnostic group). They show that compared with the standard for all cancers, the group formed by leukaemias and lymphomas (RES neoplasms or cancers of the immune system) had 9% too many pre-onset illnesses, and the remaining cases (solid tumours) had 12% too few illnesses. The ratios were higher for leukaemias than for lymphomas, and were also higher for malignant than for doubtfully malignant tumours. For two extreme groups, namely illnesses within a year of birth and illnesses within a year of cancer onset, there were minor differences in the

Table 6. First serious infections of 6,002 case/control pairs from the 1958–1962 birth cohorts

First serious infection of each child	RES neoplasms		Other cancers		All cases		Living controls	
Pneumonia	101	*22*	74	*15*	175	*37*	133	*17*
Bronchitis	306	*55*	266	*43*	532	*98*	291	*58*
Upper respiratory	225	*30*	170	*29*	395	*59*	396	*44*
Intestinal	81	*13*	59	*10*	140	*23*	96	*8*
Other[a]	198	*37*	145	*28*	343	*65*	191	*19*
All illnesses	911	*157*	674	*125*	1,585	*282*	1,207	*146*
No. of children at risk	3,199	*517*	2,803	*438*	6,002	*955*	6,002	*692*

Figures in italics show the number of children who also had records of pregnancy X-rays
[a] For detailed specifications see Kneale and Stewart [12]

Table 7. Age distributions of the illnesses in Table 6

Group	Death[a] age in years	At risk	Illness ages in years						All illnesses	
			0–	2–	4–	6–	8–	10+	Dated	Undated
RES neoplasma	0–	446 *59*	54 *11*	–	–	–	–	–	54 *11*	5 *1*
	2–	767 *118*	160 *21*	28 5	–	–	–	–	188 *26*	13 *4*
	4–	795 *137*	113 *21*	47 *10*	18 *2*	–	–	–	178 *33*	34 *4*
	6–	530 *92*	77 *13*	51 *7*	30 *9*	4 *1*	–	–	162 *30*	20 *1*
	8–	394 *61*	50 *4*	28 *1*	27 *9*	18 *2*	5	–	128 *16*	19 *4*
	10–	267 *50*	27 *7*	13 *4*	17 *3*	13 *6*	10 *3*	1	81 *23*	29 *4*
	0–11	3,199 *517*	481 *77*	167 *27*	92 *23*	35 *9*	15 *3*	1	791 *139*	120 *18*
Other cancers	0–	613 *104*	64 *12*	–	–	–	–	–	64 *12*	5
	2–	740 *123*	134 *31*	27 *5*	–	–	–	–	161 *36*	12 *1*
	4–	501 *53*	63 *7*	35 *6*	5	–	–	–	103 *13*	15 *2*
	6–	363 *69*	28 *6*	34 *5*	26 *5*	6 *4*	–	–	94 *20*	14 *2*
	8–	334 *51*	40 *11*	19 *3*	20 *2*	20 *2*	5	–	104 *18*	13 *3*
	10–	252 *38*	15 *2*	17 *5*	14 *2*	12 *3*	7 *2*	1	66 *14*	23 *4*
	0–11	2,803 *438*	344 *69*	132 *24*	65 *9*	38 *9*	12 *2*	1	592 *113*	82 *12*
Living controls	0–	1,059 *117*	69 *8*	–	–	–	–	–	69 *8*	13 *1*
	2–	1,507 *174*	206 *20*	35 *2*	–	–	–	–	241 *22*	41 *9*
	4–	1,296 *132*	151 *18*	83 *7*	14 *1*	–	–	–	248 *26*	50 *6*
	6–	893 *116*	81 *11*	49 *8*	49 *6*	6	–	–	185 *25*	38 *7*
	8–	728 *94*	52 *6*	32 *6*	32 *4*	33 *6*	6 *2*	–	155 *24*	34 *5*
	10–	519 *59*	31 *4*	22 *2*	21 *1*	22 *3*	12 *2*	1	109 *12*	24 *1*
	0–11	6,002 *692*	590 *67*	221 *25*	116 *12*	61 *9*	18 *4*	1	1,007 *117*	200 *29*

Figures in italics are X-rayed children
[a] Or equivalent for living controls

Table 8. Expected rates for age-specific illnesses of age-specific cancers. Basis of the second measure of infection sensitivity[a]

Death or termination age in years	No. of children[b]	No. of serious infections. Age in years					
		0, 1	2, 3	4, 5	6, 7	8, 9	10, 11
0–1	2,118	187	–	–	–	–	–
2–3	3,014	500	90	–	–	–	–
4–5	2,592	327	165	37	–	–	–
6–7	1,786	186	134	105	16	–	–
8–9	1,456	142	79	79	71	16	–
10–11	1,038	73	52	52	47	29	3
Total	12,004	1,415	520	273	134	45	3
		Expected infection rates/10^3					
0–1	2,118	88	–	–	–	–	–
2–3	3,014	166	30	–	–	–	–
4–5	2,592	126	64	14	–	–	–
6–7	1,786	104	75	59	9	–	–
8–9	1,456	98	54	54	49	11	–
10–11	1,038	70	50	50	45	28	3

[a] See dated illnesses in Table 7
[b] See numbers at risk in Table 7

Table 9. Serious infections: average rate ratios[a]

Groups	Death age in years	Average rate ratios (ARR)		
		RES neoplasms	Other cancers	Living controls
Illness ages	0–1	132	102	82
	2–3	114	119	83
	4–5	127	103	83
	6–11	117	131	77
Cancer onset ages	0–1	137	118	74
	2–3	124	116	80
	4–5	121	90	89
	6–11	118	120	82
Pre-onset periods	0–1	125	128	74
	2–3	109	113	90
	4–5	119	115	85
	6–11	130	105	82
All illnesses[b]		122	115	82

[a] See Table 8 for expected rates for all age-specific illnesses
[b] Obtained by averaging age-specific ARRs across 21 strata (see Table 8)

ranking positions of the nine diagnostic groups, but acute leukaemias headed the list eight times and tumours of doubtful malignancy appeared at the bottom seven times (Table 5). Therefore, the findings are suggestive of: (i) long-standing differences between cancers of the immune system and other neoplasms; (ii) higher levels of infection sensitivity for leukaemias than for lymphomas; (iii) higher levels for malignant than for benign tumours.

Second Measure of Infection Sensitivity Based on Cases and Controls

The living controls were now needed to discover how the cancer cases compared with normal children. Therefore, since the reporting bias had not affected serious illnesses and injuries [12], the first *serious* infections of 6,002 case/control pairs from the 1953–1962 birth cohorts were used to set the standards for a second measure of infection sensitivity (Table 6). From these data and those in Table 7 (which show the age distribution of the illnesses for three diagnostic groups), 21 age-specific illness rates were computed (lower half of Table 8) prior to obtaining a series of ARRs comparable to the series in Table 4 (Table 9).

According to the ARRs in Table 9, the children who eventually developed RES neoplasms or solid tumours had 22% and 15% more pre-onset illnesses than expected, while the occurrence of comparable illnesses in matched controls was 18% below average. For illnesses in the first year of life the corresponding percentages were +32%, +2% and −18%; for illnesses occurring more than 6 years before the onset of cancer they were +30%, +5% and −18%.

Idiopathic and Radiogenic Cancers

The findings for pre-onset illnesses in the first year of life were suggestive of in utero damage to the immune system by cancers with embryonic origins. If this were the case, the cancers caused by obstetric radiography (or third-trimester exposures) might be less affected than non-X-rayed cases. According to earlier estimates, only 5% of the cases in the OSCC data were a direct result of pregnancy X-rays [9, 10]. However, these radiogenic cases probably accounted for 40% of the X-rayed cases. Therefore, comparisons between X-rayed and non-X-rayed cases might provide a test of this hypothesis.

Only a very small difference was expected between the X-rayed and non-X-rayed cases. Therefore, evidence was sought in a life table analysis of the dated illnesses of the 6,002 case/control pairs in Table 7. Children who had lived to a given age without having a serious infection were labelled "survivors" in a life table terminology and the subgroup of X-rayed cases was distinguished from the group of all cases. Also, living controls were included in order to be quite certain that there had been no under-reporting of X-rays in older age groups (Table 10).

The figures in Table 10 show: (i) how the number of children ("survivors") who avoided a serious infection and/or

Table 10. Life table formation of the illness and X-ray data for 6,002 case/control pairs

Group	Death age in years	All children				X-rayed children			
		A	B	C	D	A	B	C	D
RES neoplasma	0–1	3,199	54	427	392	517	11	66	48
	2–3	2,623	28	139	579	392	5	22	92
	4–5	1,580	18	74	617	273	2	21	104
	6–7	871	4	31	368	146	1	8	62
	8–9	468	5	10	266	75	–	3	45
	10–11	187	1	–	186	27	–	–	27
	$\sum$		110	681	2,408		19	120	378
Other cancers	0–1	2,803	64	280	549	438	12	57	92
	2–3	1,910	27	105	579	277	5	19	87
	4–5	1,199	5	60	398	166	–	9	40
	6–7	736	6	32	269	117	4	5	49
	8–9	429	5	7	230	59	–	2	33
	10–11	187	1	–	186	24	–	–	24
	$\sum$		108	484	2,211		21	92	325
Living controls	0–1	6,002	69	521	990	692	8	59	109
	2–3	4,422	35	186	1,266	516	2	33	152
	4–5	2,935	14	102	1,048	329	1	11	96
	6–7	1,771	6	55	708	221	–	9	91
	8–9	1,002	6	12	573	121	2	2	70
	10–11	411	1	–	410	47	–	–	47
	$\sum$		131	876	4,995		13	114	565

A, Children still at risk of death or serious infection
B, Serious infections followed by death (or "termination date")
C, Serious infection only
D, Death (or "termination date") only

Table 11. Observed and expected numbers of children with X-rays and serious infections

Group	Period at risk of serious infection in life years	All children			Children with serious infections				t Value
		Total at risk No.	X-rayed children		Total at risk No.[a]	X-rayed children			
			No.	%		Observed[a]	Expected[b]	Variance[c]	
RES neoplasms	0–12	3,199	517	16.2	481	77	77.7	55.39	−0.09
	2–12	2,326	392	16.8	167	27	28.1	21.73	−0.24
	4–12	1,580	273	17.3	92	23	15.9	12.39	+2.02*
	6–12	871	146	16.7	35	9	5.9	4.69	+1.43
	8–12	468	75	16.0	15	3	2.4	1.96	+0.43
	10–12	187	27	14.4	1	–	0.1	0.12	−0.29
Other cancers	0–12	2,803	483	15.6	344	69	53.7	34.80	+2.59**
	2–12	1,910	277	14.5	132	24	19.1	15.24	+1.26
	4–12	1,199	166	13.8	65	9	9.0	7.34	0.00
	6–12	736	117	15.9	38	9	6.0	4.82	+1.36
	8–12	429	59	13.8	12	2	1.7	1.39	+0.25
	10–12	187	24	12.8	1	–	0.1	0.11	−0.30
Live controls	0–12	6,002	692	11.5	590	67	68.0	54.27	−0.14
	2–12	4,422	516	11.7	221	25	25.8	21.65	−0.17
	4–12	2,935	329	11.2	116	12	13.0	11.39	−0.30
	6–12	1,771	221	12.5	61	9	7.6	6.44	+0.55
	8–12	1,002	121	12.1	18	4	2.2	1.87	+1.31
	10–12	411	47	11.4	1	–	0.1	0.10	−0.31
		Totals	Cancer cases			252	219.7	159.96	+2.55**
			Living controls			117	116.7	95.72	+0.03

[a] See 6th and 7th column of Table 10
[b] Based on all X-rayed children (see 3rd column)
[c] Calculated from Mantel-Haenszel procedures
Significance tests * $P < 0.05$; ** $P < 0.01$

cancer death (or "termination date" in the life table terminology) gradually dwindled from 12,004 to zero; (ii) how the subgroup of children with records of pregnancy X-rays differed from the group of all cases; (iii) how the living controls compared with the groups with RES neoplasms and other cancers. They also provide the basis for Table 11, where six periods (measured in life years) are compared in various ways. Thus, the first and second columns of Table 11 correspond to the first and fifth columns of Table 10 and show how many X-rayed and non-X-rayed children were still at risk of death or serious infection ("termination" in the life table terminology) at the beginning of each period. Also, the fourth column of Table 11 corresponds to the second and third columns of Table 10 (numbers of serious infections during each period); the fifth column of Table 11 corresponds to the sixth and seventh columns of Table 10 (likewise for X-rayed children). In the final analysis, the percentage of X-rayed children for each period sets the standard for the expected numbers of children with pregnancy X-rays *and* serious infections. In addition, the variance in the difference between each pair of observed and expected numbers is calculated (and summed) as in a Mantel-Haenszel analysis.

The sum of the expected numbers for six periods was less for both RES neoplasms and solid tumours than the sum of the observed numbers of children with X-rays *and* illnesses, and for the combined group of 2,006 cancers the difference between the two totals (219.4 and 252) was significant at the 1% level. Finally, there was no question of this difference being due to under-reporting of X-rays by older children, since the observed and expected numbers for living controls corresponded almost exactly (117 and 116.7).

Discussion

Levels of immunological competence at birth are evidently lower for cancer-prone than for normal children. They are also lower for immune system cancers (RES neoplasms) than for other neoplasms, and lower for fully metastatic than for tumour-forming cancers of the immune system. These findings are unlikely to be the result of inherited diseases, since there is only a weak familial element in the aetiology of childhood cancer [6]. However, they would be understandable if, in addition to favouring metastatic spread of well-established neoplasms, immunosuppression was necessary for the survival of newly formed mutants. Evidence of mounting sensitivity to infection during the latent pahse of childhood cancers in general and leukaemia in particular has already been found in OSCC data [12]. If immunosuppression is a necessary adjunct of in utero cancer inductions, we would expect to find some evidence of this effect among the pre-pregnancy and pregnancy illnesses of mothers of cancer-prone children.

In Britain and other countries with similar infection risks, leukaemia and neural tumours account for over 80% of childhood cancer. There are also ten times as many children with leukaemia as other RES neoplasms, and metastatic lymphomas, such as lymphosarcoma or lymphadenoma, are much commoner than single tumours or Burkitt lymphoma [16]. In tropical Africa and other places where there is continuous and widespread exposure to the malarial parasite, Burkitt lymphoma accounts for 90% of childhood cancers [4]; children with leukaemia and neural tumours are conspicuous by their absence and chloromatous myeloid leukaemia is almost as common as the fully metastatic disease [5]. Therefore, it is possible that repeated attacks of malaria leave pregnant women with sufficiently high levels of immunological competence to prevent some in utero cancer inductions and exert such a restraining influence on the early stages of RES neoplasms that slow-growing (lymphatic) cases emerge as quasi-benign tumours and even fast-growing (myeloid) cases make some attempt at tumour formation.

The present study has shown that levels of immunological competence at birth are appreciably lower for myeloid than for lymphatic leukaemia. Therefore, the suggestion that myeloid leukaemia may be a cause of sudden infant deaths is not without some foundation [15]. This hypothesis was originally advanced to account for certain contrasts between seasons of birth in the incidence of subsequent sudden deaths and infant leukaemias, but it would also explain why the discovery of antibiotics was followed by an increase in childhood leukaemia affecting only lymphatic cases and deaths after 1 year of age [8].

The study has also shown that the serious infections of children whose cancers followed foetal irradiation are compatible with there being an aetiologically distinct group of radiogenic cancers, whose levels of immunological competence at birth are relatively normal, because most of these cases are the result of third-trimester inductions [10]. When Bross and Natarajan found similar differences between the X-rayed and non-X-rayed cases in TSLS data (Tri-State Leukaemia Study), they postulated the existence of genetic faults, which increase sensitivity to cancer-induction effects of radiation and certain illnesses [1–3]. However, the Mantel-Haenszel analysis of OSCC data is consistent with there being a much higher proportion of first-trimester inductions for non-X-rayed than for X-rayed cases [11]. Therefore, even if the X-rayed and non-X-rayed cases in both surveys had exactly the same levels of infection sensitivity at the same stage of the cancer process, the incidence of *non-fatal infections* (which are the only ones considered in OSCC and TSLS data) would still be higher for the former than the latter.

In short, the cancer experiences of European and African children are consistent with neoplasms of foetal origin in juveniles, and with loss of immunological competence having cancer induction as well as cancer promotion effects. Furthermore, the illnesses of children whose cancers followed involvement in obstetric radiography are consistent with there being fewer cancer inductions towards the end than the beginning of foetal life and more radiogenic cases and higher levels of immunological competence at birth among the former than the latter.

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