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Immunizations against infectious diseases and childhood cancers

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Summary. A study based upon an unusally large series of childhood cancers and matched controls found a significant deficit of case/control pairs in which the cancer case had fewer immunizations against infectious diseases than the matched control. All types of immunizations and cancers were affected but the case/control differences were more pronounced for older cases with late immunizations than for younger cases with early immunizations, and more pronounced for solid tumours than leukaemia. Therefore there may be immune system responses to immunizations (or simulated infections) which make it difficult for small clones of cancer cells to enlarge and are more successful in preventing localised tumours in adolescents than childhood leukaemias.

Introduction

Immunizations against infectious diseases might, at least in theory, have effects on incipient cancers. This possiblity exists because resistance to infections is the result of certain immune system cells first recognising attacks by foreign organisms and then stimulating further production of relevant antibodies and leucococytes. The antibodies produced in response to actual emergencies (i.e. infections) or simulated emergencies (i.e. immunizations) are highly specific but the cell stimulation might be sufficiently non-specific to be felt by macrophages or cells which are suspected of selectively killing cancer cells [9].

The following tests of cancer latency effects of immunization are based on 12,281 case/control pairs from the Oxford Survey of Childhood Cancers (OSCC data) [2]. Each pair included a child who died from a malignant disease before 16 years of age during the period 1953–77 (cancer case) and a live child (matched control) and the two children were concordant for sex, date of birth and Local Authority Region. In addition, the same survey doctor or nurse first interviewed the mother of the dead child and then interveiwed the mother of the live child after inserting on this interview schedule the date when the dead child first showed signs of the fatal illness. This "cancer onset date" was supposed to mark the end of the "pre-onset period" for both children and, in the following analysis only dated immunizations belonging to pre-onset periods were included.

Most of the immunizations were the result of programmes organised by Local Authority Health Departments. Therefore, provided the mothers of cases and controls were equally reliable witnesses, and provided there was correct use of the dating conventions by survey doctors, straightforward comparisons between matched cases and controls should be sufficient to detect any cancer effects of the immunizations. For example, a significant excess of case/control pairs in which only the dead child was immunized would indicate a harmful (e.g. cancer promotor) effect; the opposite finding would indicate a beneficial (e.g. cancer inhibitor) effect, and the ratio of "case only" to "control only" pairs would provide a rough measure of whichever effect was observed.

Preliminary tests

For all types of immunization there was a deficit of "case only" pairs, and for all immunizations represented by more than 60 children – which only excluded one of the seven groups in Table 1 – the deficit was statistically significant and compatible with each type of immunization having the same, beneficial effect. Thus, for smallpox there were 1837 "case only" and 2033 "control only" pairs (ratio 0.90). For diphtheria and tetanus, the corresponding figures were 1269 and 1582 (ratio 0.80), and for BCG vaccinations they were 416 and 507 (ratio 0.82).

These preliminary findings ruled out any harmful effects of the immunizations and made it unnecessary to consider better reporting on behalf of dead than live children. But this still left two alternatives: either non-specific effects of the immunizations had reduced the risk of a cancer death, or faulty application of the "pre-onset period" to the live childrens records had caused a spurious excess of "control only" pairs. Therefore, before including all the pre-onset immunizations in further tests of anti-tumour effects, it was necessary to observe the effects of advancing the cut-off dates for the immunizations and comparing the truncated series of immunizations with the original series.

Truncated series of pre-onset immunizations

The effects of (1) excluding all immunizations less than 2 years before the cancer onset date, and (2) allowing overall numbers of immunizations to determine concordance or

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Table 1. Numbers of case control pairs concordant and non-concordant for several immunizations against infections

Immunizations[1] against:-	Concordant pairs (A)	(B)	Non-concordant pairs (C)	(D)	Non-concordance ratio (C:D)
Smallbox	5829	2582	1837	2033	0.90
Diphtheria and tetanus	2902	6528	1269	1582	0.80
Pertussis	3815	5179	1444	1843	0.78
Measles	11346	363	259	313	0.83
Rubella	12231	6	16	28	0.57
Poliomyelitis	5157	3820	1475	1829	0.81
Tuberculosis (BCG)	10982	376	416	507	0.82

[1] Restricted to immunization whose recorded dates were earlier than the cancer onset dates or corresponding dates for matched controls
Immunizations: *A* Neither child, *B* Both children, *C* Case only, *D* Control only
All non-concordance ratios except the one for rubella are significantly different from unity ($P < 0.05$)

Table 3. Comparison between the truncated and the original series of immunizations according to the relative frequency of case and matched control immunizations

Immunizations Paired case/control frequency		Truncated series	Original series
Case deficit	−5+	28	54
	−4	259	363
	−3	441	616
	−2	627	857
	−1	1,393	1,826
No difference		7,088	5,491
Case Excess	+1	1,301	1,597
	+2	547	691
	+3	355	476
	+4	218	267
	+5+	24	43
Test statistic[1]		−0.059	−0.089
SE		0.013	0.011

[1] $2\ m/S^2$ See text

non-concordance of case/control pairs, are shown in Tables 2 and 3.

In Table 2 all pairs showing a higher frequency of case than control immunizations (case$^+$) are shown alongside all pairs showing the same difference in the opposite direction (control$^+$). For five groups with a difference of only one between the two frequencies, the non-concordance ratios (case$^+$/control$^+$) ranged from 0.82 to 1.08 and averaged 0.93. For four groups with a difference of two the ratios ranged from 0.73 to 0.93 and averaged 0.87, and for six groups with bigger differences they ranged from 0.62 to 1.13 and averaged 0.82.

Table 2. Truncated series of immunizations. Comparisons between pairs with a case or control excess of immunizations more than 2 years before the cancer onset dates

Truncated series of immunizations				
Pairs with more cases than controls		Pairs with more controls than cases		
Case/control Frequency	Pairs (A)	Case/control Frequency	Pairs (B)	Ratio A:B
1/0	188	0/1	174	1.08
2/1	148	1/2	180	0.82
3/2	378	2/3	422	0.90
4/3	506	3/4	526	0.96
5+/4	81	4/5+	91	0.89
2/0	221	0/2	254	0.87
3/1	153	1/3	172	0.89
4/2	137	2/4	152	0.90
5+/3	36	3/5+	49	0.73
3/0	282	0/3	341	0.83
4/1	64	1/4	92	0.70
5+/2	9	2/5+	8	1.13
4/0	210	0/4	246	0.85
5+/1	8	1/5+	13	0.62
5+/0	24	0/5+	28	0.86
Total	2,445	Total	2,748	0.89

In Table 3 both the truncated and the original series of immunizations are included in a test of cancer effects which makes use of the following Miettenin/Breslow arguments:- [3]

(1) In a series of case/control pairs, if m is the mean deficit of case immunizations and S^2 is the mean square of this difference, then $2\ m/S^2$ will be approximately equal to the logarithm of the effect of one immunization (test statistic).

(2) Provided the value of 2 m is small, e.g. less than half the value of S^2, the percentage decrease in risk caused by one immunization should be approximately equal to $100 \times 2\ m/S^2$ (risk estimate).

For the truncated series of immunizations there were 2445 "case only" and 2748 "control only" pairs (ratio 0.89) and for the original series the corresponding figures were 3074 and 3716 (ratio 0.83). For the smaller series the Miettenin/Breslow test statistic was −0.059 (SE 0.013) and for the original series it was −0.089 (SE 0.011).

According to these results the preliminary findings were unlikely to be caused by misuse of the dating conventions. Therefore further tests of cancer latency effects were based on the original series of pre-onset immunizations. In these tests each case/control pair was classified, as in Table 3, according to the relative frequency of the paired immunizations. Table 4 shows the effects of varying cancer ages and immunization ages and Table 5 shows the effects of recognising several types of cancer. For the youngest of four cancer onset age groups (under 2 years) there was only 1 choice of immunization age but, for older cases there were 2, 3 or 4 choices. Therefore, there are 10 test statistics in Table 4 to compare with 7 in Table 5.

Table 4. Case deficit or excess of immunizations within sub-groups defined by cancer onset ages and immunization ages

All immunizations Case deficit (−) or excess (+)	Cancer onset ages									
	0–1 yrs 2609 pairs	2–4 yrs 4089 pairs		5–9 yrs 3493 pairs			10–15 yrs 2090 pairs			
	Immunization ages									
	0–1	0–1	2–4	0–1	2–4	5–9	0–1	2–4	5–9	10–15
−5	6	17	0	13	0	0	5	0	0	0
−4	67	136	2	88	2	4	39	0	3	0
−3	109	209	18	158	19	23	117	8	20	4
−2	166	215	43	243	43	47	206	34	58	37
−1	318	581	292	515	259	314	355	155	296	252
0	1344	1925	3445	1555	2813	2743	748	1702	1418	1579
+1	241	593	240	460	285	296	327	152	256	198
+2	133	189	36	224	52	54	161	32	52	12
+3	115	167	9	145	18	9	83	6	14	7
+4	44	105	4	84	2	3	46	0	0	1
+5	6	6	0	8	0	0	3	1	0	0
Test factor[2]	−0.126	−0.076	−0.144	−0.040	+0.062	−0.070	−0.074	−0.022	−0.084	−0.240
SE	0.024	0.020	0.058	0.022	0.056	0.054	0.026	0.074	0.056	0.072

[2] 2 m/S² see text

Table 5. Case deficit or excess of immunizations for seven diagnostic groups[1]

All immunizations Case deficit (−) or excess (+)[(2)]	Leukaemia	Lymphoma	Wilms	Cerebral tumour	Neuroblastoma	Osteosarcoma	Other solid
−5	25	6	0	10	7	1	5
−4	162	36	28	44	29	23	41
−3	261	43	44	101	54	23	90
−2	395	95	54	124	51	32	106
−1	844	155	117	272	131	64	243
0	2481	444	370	811	514	141	730
+1	781	145	71	252	100	73	175
+2	316	71	42	81	58	25	98
+3	226	36	30	77	36	10	61
+4	132	20	15	36	14	7	43
+5	13	8	2	7	3	2	8
Test factor[2]	−0.070	−0.091	−0.156	−0.097	−0.125	−0.169	−0.069
SE	0.017	0.037	0.045	0.029	0.041	0.057	0.015

[1] Without control for immunization ages (see Table 4)
[2] 2 m/S² see text

In Table 4 all but 1 of the 10 test statistics carried a negative sign, and in 5 instances the numerical value of the test statistic was over twice its standard error. In Table 5 all of the test statistics had values which were indicative of a significant deficit of immunized cases. According to these statistics there was an anti-tumour effect which was strongest for the latest immunizations (over 10 years) of the oldest cases (10–15 years), and weakest for three groups of children with cancer onset ages between 5 and 10 years. In addition, there was evidence of a stronger anti-tumour effect for solid tumours than for leukaemia.

None of the test statistics had a value of more than 0.240, which meant that 2 m always had a much lower value than of S^2. Therefore, in Table 6, the percentage reduction in risk for each immunization is assumed to be approximately equal to $100 \times 2\ m/S^2$. [3] On this basis the average reduction in risk for each immunization was approximately equal to 9% of the normal risk of a cancer death. For immunizations after 10 years of age the estimate was much higher (24% of the normal risk) and for three groups of solid tumours the effect of a single immunization was roughly equal to 12% of the normal risk.

Table 6. Risk estimates or cancer inhibitor effects of a single immunization

Age groups				Diagnostic groups		
Cancer onset	Immunization	Risk estimate	SE	Cancer sites	Risk estimate	SE
years	years	%			%	
0–1	0–1	12.6	*2.4***	Leukaemia	7.0	*1.7***
2–4	0–1	7.6	*2.0***	Lymphoma	9.1	*3.7**
	2–4	14.4	*5.8***	Wilms	15.6	*4.5***
10–15	0–1	7.4	*2.6**	Cerebral tumour	9.7	*2.9***
	0–1	7.4	*2.6**	Neuroblastoma	12.5	*4.1***
	10–15	24.0	*7.2***	Osteosarcoma	16.9	*5.7**
	All ages	8.9	*1.1***	Other solid	6.9	*1.5***

* $P > 0.05$
** $P > 0.01$

Discussion

Studies of immunizations and childhood cancers began with some observations by an Australian haematologist which led to the suggestion that human lymphoreticular tissues might be "provoked to, or conditioned for neoplasia by antigenic stimulation" [7]. This impression of a harmful effect from antigenic stimulation was based on 59 cases of leukaemia and 343 controls and was not borne out by an early sample of the OSCC data. In this relatively small set of case/control pairs relating to cancer deaths before 10 years of age, there were fewer immunizations of dead than live children (4505 and 4649) [10].

The next set of epidemiological data was reported by a group of microbiologists in Quebec [5]. They compared 407,900 Canadian children who had received BCG vaccination with 341,860 controls and found that the former had fewer leukaemia cases (96) than the latter (191). Following this report there were several studies of BCG vaccinated and non-vaccinated populations, all with negative findings for leukaemia [1, 4, 6, 8]. However, in tumour-bearing mice, infection with the attenuated tuberculosis bacillus does seem to have some anti-tumour effects [9].

Therefore, although the present finding of anti-tumour effects for several immunizations stands more or less alone, it could be a sign that simulated infections have immune system effects which impede or prevent further development of a cancer in situ, and that an unrecognised effect of recent immunization programmes has been a reduced frequency of solid tumour deaths in young adolescents.

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