

Febrile infectious childhood diseases in the history of cancer patients and matched controls

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Abstract — The present study was designed to investigate the hypothesis that febrile infectious childhood diseases (FICDs) are associated with a lower cancer risk in adulthood, since biographical considerations are of great importance in anthroposophic medicine. Cancer patients and control patients of 35 anthroposophic general practitioners in Switzerland were matched with respect to gender, age and physician. All patients completed a questionnaire on their FICD. We collected 424 cases; of these we could analyze 379 matched pairs. The study consistently revealed a lower cancer risk for patients with a history of FICD. The strongest associations were found between patients with non-breast cancers and rubella respectively chickenpox. A strong association was also found with the overall number of FICD both 'classical' (measles, mumps, rubella, pertussis, scarlet-fever and chickenpox) and 'other'. None of these associations was apparent for patients with breast cancer. Unexpectedly, we found that cancer was diagnosed significantly earlier in life in cancer patients with a history of FICD compared to those without FICD. Our retrospective study showed a significant association between FICD and the risk of developing cancer. The number of FICD decreased the cancer risk, in particular for non-breast cancers. The relationship with tumor site seems to be important also, but can only be addressed in a larger study.

Introduction

The association of febrile infectious diseases and cancer was postulated a long time ago. As early as 1910 Schmidt (1) found, of 241 cancer patients, only 109 with a history of FICD. Schmidt distinguished between a 'diathesis inflammatoria' and an 'afebrile diathesis'. The latter was associated with a higher cancer risk. Schmidt's findings were confirmed later by some studies based on anamnestic inquiries of cancer patients only (c.f. Braunstein (2), Ungar (3), Kofler and Hussarek (4) and Schulz (5)). Other publications are based on case-control studies. Engel (6,7)

found that, of 300 cancer patients, 113 had no FICD, compared to 300 controls with only 16 without FICD. This association holds true also when corrected for age. Sinek (8) found similar results in a study based on 232 cancer patients and 2444 controls. Witzel (9) and Remy et al (10) focused on the occurrence of febrile diseases within 5–10 years prior to the first cancer diagnosis and confirmed the same association. Three case-control studies by West (11), Wynder et al (12) and Newhouse et al (13) report a decreased cancer risk for women with a FICD history.

In contrast, in a critical review of previously published data, Abel et al (14) concluded that, 'The

early studies, which gave impressive relative risks or established associations between childhood infections and cancer in adults, had severe deficiencies in design and analysis'. Abel therefore initiated an extensive case-control study of 255 patients with cancer of stomach, colon, rectum, breast or ovary and 485 controls, using a lengthy standard questionnaire containing 76 questions. A negative association was shown between a history of common cold or gastroenteritis within 5–10 years prior to the interview and the risk of developing cancer. In regard to FICD, Abel found slightly reduced odds ratios relative to the population controls. The *P*-value was 5 to 10% for chickenpox and pertussis.

The aim of our case-control study was to re-evaluate the hypothesis by focusing on FICD and considering the respective age of FICD and the time of cancer diagnosis. To analyse a particular, presumably more homogeneous population we considered patients of anthroposophic general practitioners.

Method

The study was designed as a matched case-control study based on the patients of anthroposophic general practitioners of Switzerland. Of the 50 anthroposophic general practitioners in Switzerland, 15 declined to participate because of lack of time. We included all of the remaining 35 practitioners in order to reduce observer bias, to have a large number of practitioners, and to obtain a sufficiently large number of cases.

Cases

All patients with a diagnosis of carcinoma (malignant solid epithelial tumor) who for any reason were seen in the office of a participating practitioner between 1 June 1993 and 31 January 1994 were accepted as cases. A limit of 20 patients per office was chosen in order to avoid any preponderance of a particular office and to limit the amount of work for one doctor. We collected 424 cases; 410 were accepted; 14 cases whose diagnosis did not meet the criteria (4 lymphomas, 2 myelomas, 4 sarcomas, 1 leukemia, 1 glioblastoma, 2 men with a breast cancer) had to be eliminated. A short questionnaire regarding the history of FICD was filled out by the patients without the doctor's help.

Controls

For each case, a control person of the same gender, the same age group (± 3 years) and of the same practitioner, but without a diagnosis of malignancy,

was drawn randomly from the alphabetical patient register in the practitioner's office. As cases and controls were drawn from the same register, it seemed to be acceptable to assume that their respective places of residence were close to each other. Control patients were contacted either in a subsequent consultation, by phone or by mail and were asked to fill out the same questionnaire. Nine controls (2.2%) had to be eliminated because of unsuitable matching. Eighteen controls (4.4%) did not return the questionnaire, and 4 questionnaires contained insufficient data, leaving a final total of 379 matched pairs (93%). For the analysis of the cases, we used the information of all relevant patients.

Questionnaire

Cases and controls received the questionnaire knowing neither the aim of the study nor their group affiliation. Information was collected about gender, age at interrogation, number of brothers and sisters, a possible history of 'classical' FICD (measles, mumps, rubella, chickenpox, pertussis, scarlet fever) including the corresponding age, the frequency of 'other' FICDs (fever $> 39^{\circ}\text{C}$) up to the age of 21, and some other questions of minor importance. It is obvious that it may be difficult to remember the FICD, in particular for older patients. However, we believe that cases and controls remember their FICD in the same way. Because of matching and random selection this should not influence our analysis negatively.

To answer the questions about FICD, the patients chose among 'yes', 'uncertain yes', 'uncertain no' and 'no'. (By giving 4 options, we wanted to avoid a tendency to pick the middle choice in a 3-option system). This allowed us also to analyze to a certain degree the memory effect.

The doctors added medical information including the tumor's localization and the year of diagnosis (for the cases) as well as any possible diagnosis of hypertension, arthrosis or depression. In order to obtain optimal compliance, the questionnaire was kept very simple.

Statistical method

The main question of this study concerned the risk relation between the diagnosis of cancer and the prior history of FICD, the corresponding age and the treatment of FICD. The data were analyzed using standard methods for case-control studies (15,16) using odds ratios.

Part A: Cancer patients and controls

Odds ratios (ORs) were chosen for description and

tests performed with the usual level of 5%. In order to confine the great amount of data, the confidence intervals are stated for the most important findings only.

The data were further analyzed using an explorative statistical approach. Because in almost 50% of the cases the diagnosis was breast cancer and age might influence the variables of FICD, we analyzed the following subgroups:

- breast cancers vs non-breast cancers
- Age ≤ 60 vs > 60 years

We used two different methods for the analysis of the FICD answers: in version 1 we opposed the two positive to the two negative options; in version 2 we weighted 'yes' as 1, 'uncertain yes' as $\frac{2}{3}$, 'uncertain no' as $\frac{1}{3}$ and 'no' as 0 (which is an arbitrary choice). Furthermore, LW considered a rather strict version 3 using the weights 1 for 'yes' and 'no' and 0 for the other two. This version is not discussed here; however, the results are similar to those achieved with version 2.

Part B: Age of initial cancer diagnosis

We also analyzed the cases separately to explore different relationships. For instance, we considered whether there was a relationship between the age when a cancer was first diagnosed and the patient's FICD history, by means of the Kruskal–Wallis test (17). We limit our presentation to the more important part of the whole statistical analysis.

Results

The mean age was 62.7 years in the case group and 62.5 in the control group, with a range of 27–93 years. There are many more women than men because of the cases of breast cancer (Table 1). The mean number of brothers and sisters, possibly relevant for FICD, is about the same (2.7 in the case group and 2.8 in the control group).

Table 1 gives an overview of the frequency of tumor sites and the age at diagnosis for the 388 cases. We observe different percentages of tumor sites as compared to the overall Swiss population. For instance, we have a high percentage of breast cancer patients due to the large number of female patients. However, the group of non-breast cancer consists of 89 men and 110 women, being more balanced.

Note that the mean age of patients with a breast cancer (53.1 years) is 7 years lower than that of non-breast-cancer patients (60.3 years). Therefore it is reasonable to analyze these different groups individually.

Table 1 Frequency of tumor sites and mean age at initial diagnosis

Localization	Men	Women	Total	Percentage	Mean age
Breast	0	189	189	48.7	53.1
Gastrointestinal	18	28	46	11.9	62.8
Genital	0	42	42	10.8	55.5
Prostate	29	0	29	7.5	71.7
Skin	9	17	26	6.7	54.6
Lungs	7	6	13	3.4	63.5
Ear-Nose-Throat	6	6	12	3.1	60.6
Testicles	7	0	7	1.8	38.0
Others	13	11	24	6.2	60.9
Total	89	299	388	100.0	

Generally, we found that patients with frequent 'classical' FICD also reported to have experienced 'other' FICDs frequently. Older patients tended to report fewer FICDs than younger patients (which could be a memory effect), where the association was stronger for the controls than for the cases.

Part A: Cancer patients and controls

Table 2 shows the ORs for all matched pairs as well as for the subgroups (under age 60, over age 60, breast cancers and non-breast cancers).

The results of this study consistently show a lower cancer risk in patients with a history of FICD, since all significant ORs point in the same direction.

The number of FICDs both 'classical' and 'other' was associated with a decreased cancer risk, especially in the group of non-breast cancer, where for the 'classical' FICD the reduction was 20% per disease ($P = 0.007$) in version 1, 23% ($P = 0.004$) in version 2. The corresponding 95% confidence intervals were [6%; 32%] and [8%; 35%], respectively (Fig. 1).

Considering each 'classical' FICD separately, statistical association with cancer risk was most evident in the group of non-breast cancers, where the strongest cancer risk reduction was found for rubella: the ORs were 0.439 ($P = 0.0006$) in version 1 and 0.377 ($P = 0.003$) in version 2, with corresponding 95% confidence intervals [0.274; 0.702] and [0.221; 0.641], respectively (Fig. 2). A less strong but still significant association was found for chickenpox in two groups, namely the non-breast cancers and those less than 60 years old. In the younger patients we also found a significant risk reduction for measles. A history of pertussis, mumps and scarlet fever did not show a significant effect on the cancer risk.

The age at which the FICD occurred had, in this case-control analysis, no consistent influence on the cancer risk.

Table 2 Odds ratios for the association between a diagnosis of a carcinoma and the anamnestic information

(A) All pairs					(C) Age > 60				
FICD	Version ¹	n ²	OR	P	FICD	Version ¹	n ²	OR	P
Measles	1	375	0.980	.921	Measles	1	230	1.222	.439
	2	375	0.873	.548		2	230	1.253	.425
Mumps	1	372	1.000	1.000	Mumps	1	228	1.122	.557
	2	372	1.009	.957		2	228	1.147	.522
Rubella	1	362	0.742	.055	Rubella	1	221	0.609	.015
	2	362	0.647	.014		2	221	0.535	.007
Pertussis	1	368	0.924	.599	Pertussis	1	224	0.961	.842
	2	368	0.917	.592		2	224	0.992	.971
Scarlet fever	1	366	0.902	.612	Scarlet fever	1	224	1.154	.593
	2	366	0.822	.350		2	224	1.037	.893
Chickenpox	1	372	0.800	.158	Chickenpox	1	227	0.930	.703
	2	372	0.752	.099		2	227	0.893	.594
Number of FICD					Number of FICD				
≥ 1 FICD (vs none)	1	346	0.538	.187	≥ 1 FICD (vs none)	1	209	0.600	.323
Trend 1	1	346	0.912	.108	Trend 1	1	209	0.917	.377
≥ 1 FICD (vs none)	2	346	0.400	.058	≥ 1 FICD (vs none)	2	209	0.417	.100
Trend 1	2	346	0.882	.041	Trend 1	2	209	0.904	.189
Other FICD		314			Other FICD		186		
1-2 times			0.655	.028	1-2 times			0.664	.090
3-4 times			0.573	.046	3-4 times			0.552	.142
More than 4 times			0.440	.001	More than 4 times			0.264	.0004
Reference: never had another FICD					Reference: never had another FICD				
(B) Age ≤ 60					(D) Breast cancers				
FICD	Version ¹	n ²	OR	P	FICD	Version ¹	n ²	OR	P
Measles	1	145	0.708	.277	Measles	1	184	1.037	.893
	2	145	0.446	.043		2	184	0.854	.609
Mumps	1	144	0.850	0.486	Mumps	1	183	1.091	.677
	2	144	0.842	.499		2	183	1.174	.477
Rubella	1	141	1.000	1.000	Rubella	1	177	1.175	.454
	2	141	0.866	.609		2	177	1.040	.872
Pertussis	2	144	0.878	.569	Pertussis	1	181	1.023	.916
	2	144	0.832	.446		2	181	0.959	.852
Scarlet fever	1	142	0.640	.163	Scarlet fever	1	179	0.828	.493
	2	142	0.576	.105		2	179	0.743	.300
Chickenpox	1	145	0.576	.055	Chickenpox	1	180	0.946	.814
	2	145	0.542	.042		2	180	0.939	.802
Number of FICD					Number of FICD				
≥ 1 FICD (vs none)	1	137	0.333	.341	> 1 FICD (vs none)	1	170	0.800	.739
Trend 1	1	137	0.904	.284	Trend 1	1	170	1.054	.532
≥ 1 FICD (vs none)	2	137	0.333	.341	≥ 1 FICD (vs none)	2	170	0.750	.706
Trend 1	2	137	0.844	.101	Trend 1	2	170	1.010	.907
Other FICD		128			Other FICD		158		
1-2 times			0.668	.208	1-2 times			0.692	.166
3-4 times		0.631	.251		3-4 times			0.756	.473
More than 4 times		0.687	.301		More than 4 times			0.829	.598
Reference: never had another FICD					Reference: never had another FICD				

Table 2 (cont'd)

(E) Non-breast cancers				
FICD	Version ¹	n ²	OR	P
Measles	1	191	0.917	.768
	2	191	0.895	.740
Mumps	1	189	0.911	.666
	2	189	0.852	.501
Rubella	1	185	0.439	.0006
	2	185	0.377	.0003
Pertussis	1	187	0.833	.394
	2	187	0.875	.565
Scarlet fever	1	187	1.000	1.000
	2	187	0.925	.798
Chickenpox	1	192	0.698	.093
	2	192	0.617	.044
Number of FICD				
≥ 1 FICD (vs none)	1	176	0.375	.147
Trend 1	1	176	0.801	.007
≥ 1 FICD (vs none)	2	176	0.273	.046
Trend 1	2	176	0.771	.004
Other FICD		156		
1-2 times			0.601	.071
3-4 times			0.398	.026
More than 4 times			0.240	.0001
Reference: never had another FICD				

¹Weights: Version 1: 1 = yes or uncertain yes
 0 = no or uncertain no
 Version 2: 1 = yes, ½ = uncertain yes,
 ½ = uncertain no, 0 = no

²Number of pairs

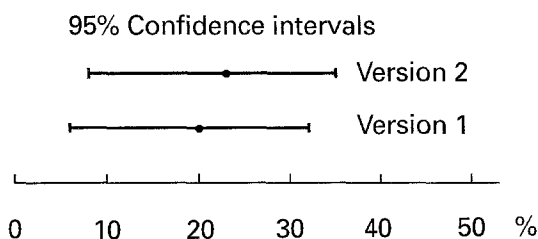


Fig. 1 Confidence intervals for the decrease of OR per FICD.

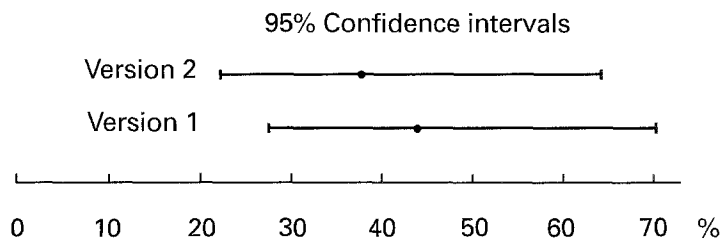


Fig. 2 Confidence intervals for the OR for rubella in the group of non-breast cancers.

Also, the non-classical FICDs reveal a significant association with the cancer risk, in particular in the group of non-breast cancers.

The study also showed significant relationships between the treatment of FICD and the cancer risk. We noted that a history of external applications (frictions and compresses) was associated with a lower cancer risk in the group of non-breast cancers (OR = 0.159, *P* = 0.002, 95% CI = [0.051; 0.498]) as well as in the group of those over the age 60 (OR = 0.282, *P* = 0.003, 95% CI = [0.123; 0.644]).

Part B: Age at initial cancer diagnosis

Although having a FICD history seems to lower the cancer risk (part A), those cancer patients who did have such a history had their cancer diagnosis significantly earlier in life than those who did not. The age cancer was first diagnosed was decreased by 1.3 years per childhood disease (*P* = 0.021, 95% CI = [0.2; 2.4]). The strongest age reductions were found for chickenpox (5–6 years, *P* = 0.0001, 95% CI = [2.9; 8.4]), for rubella (4–5 years, *P* = 0.001, 95% CI = [1.3; 8.1]), for pertussis (2–3 years, *P* = 0.044, 95% CI = [0.1; 5.4]) and for measles within the group of the over-60-year-olds (4–5 years, *P* = 0.012, 95% CI = [1.0; 8.4]). No association was found for mumps or scarlet fever.

Discussion

Great attention was paid to the reduction of observer bias because of the comments by Abel et al (14). Therefore the questionnaire was filled out by the patients without help of the physicians, who had to complete the questionnaire only after collection with same anamnestic information.

The possibility of anamnestic bias could not be eliminated completely. It is possible that carcinoma patients differ systematically from controls in regard to their ability and willingness to give reliable anamnestic information on their childhood diseases.

This problem was extensively discussed by Abel et al (14), who came to the conclusion that an anamnestic bias in their own study was unlikely. We could not observe in our study that this bias influenced our results strongly, because the different versions of weighting the given answers were revealing similar conclusions. We did not ask the patients to report on the severity of their FICDs. This would be even more dependent on the memory of the patients. But we cannot exclude the possibility that this factor may have influenced our results. Another factor might be the use of antibiotics, which was asked for in our questionnaire. For obvious reasons, there are few cases in our study where antibiotics were used in the treatment of FICD. We do not believe that these few cases had an influence on our results.

The present study reveals fairly consistently a lower cancer risk for patients with a history of FICD. Our data confirm our basic hypothesis and are also consistent with those from previous case-control studies. However, the associations are not as evident as expected. While there are significant associations within the group of non-breast cancers, no significant relationships were found within the group of breast cancers. In regard to the tumor site, all previous investigations differ widely from each other. Abel (14) states without further specification: 'There were distinct differences between the cancer sites in odds ratios for various childhood infections'. This suggests that, in subsequent studies, the different cancer sites should be analyzed in more details. This is not possible with our study because of the small sample sizes of the subgroups.

The finding that a FICD history is associated with an earlier cancer diagnosis is contrary to our hypothesis and needs further investigations for its biological interpretation. The population of our cases, selected in offices of anthroposophic general practitioners, is representative for the general population of Switzerland and allows us no generalization of our results.

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