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Childhood infectious diseases and risk of multiple myeloma: an analysis of the Italian multicentre case-control study

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Abstract

Common childhood infectious diseases have been associated with a reduced risk of following haematopoietic malignancies, but investigations on multiple myeloma (MM) are scarce. Information about 213 MM cases and 1128 healthy controls were obtained from a multicentre population-based Italian case-control study. The association between chickenpox, measles, mumps, pertussis and rubella and the MM risk was estimated by unconditional logistic regression, adjusting for age, gender and residence area. No association was found between MM risk and any considered infectious disease. The number of infections was slightly inversely associated with the risk of MM, but statistical significance was not reached (OR 0.87, 95% CI 0.55–1.4 for 1-2 diseases *vs.* none and OR 0.68, 95% CI 0.41–1.1 for 3-5 diseases, respectively, $P = 0.131$). We did not find a clear evidence that common infections during childhood are associated with the subsequent risk of developing MM.

Common infections in children have been associated with a reduced risk of developing malignancies of the haematopoietic system during adulthood. In particular, an inverse association has been reported for non-Hodgkin's lymphomas, especially in relation to measles and whooping cough (pertussis) [1–3]. Furthermore, an Italian multi-centre study also reported a protective effect of pertussis on the risk of acute myeloid leukaemia [3]. However, all evidence comes from case-control investigations where the potential impact of differential recall bias cannot be excluded, then the existence of a causal link remains uncertain [2].

Studies on multiple myeloma (MM) on this topic are very rare. A case-control study in England and Wales including 499 cases and two referent groups (namely, 499 hospital-based and 260 population-based controls) did not report any association between MM and some common childhood infections [4]. Likewise, Gramenzi *et al.* [5], in a hospital-based case-control study in Italy (117 cases and 477 controls) did not find any clear association with common childhood viral infections. More recently, a case-control study in the USA, which included 481 MM patients and 351 controls selected among cases spouses, did not find any association between chickenpox infections and MM risk, but only infections diagnosed after 20 years of age were recorded in the questionnaire [6]. The potential effect of vaccination was also analysed, but a significant difference between cases and controls was not found for measles, mumps and rubella.

This study is aimed at evaluating the association between common infectious diseases during childhood and the risk of developing MM in adults analysing data from a large Italian multi-centre population-based case-control study [7]. The study was originally conceived to assess the association between different haematolymphopoietic malignancies (namely, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemias and MM) and several putative risk factors, including medical history and previous non-neoplastic diseases. With regard to MM, 270 cases, diagnosed between 1990 and 1993 and 1163 healthy controls were recruited from seven areas (namely, provinces of Forlì, Siena, Latina, Ragusa, Imperia, Florence, plus the city of Turin). In each centre, all the subjects suspect of being affected by MM were identified through periodical surveys in the departments of haematology, general medicine, surgery and pathology in all hospitals within the areas included in the study. Furthermore, specialised hospitals outside these areas, where such patients could be admitted, were also considered. Diagnosis of MM was made, according to the ICD9 code 203 and was based on morphological, cytochemical and immunological analyses. Only newly diagnosed cases resident in the selected

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areas, aged 20–74 and occurring in the study period were included. Case ascertainment was complete, as assessed by a comparison with historical data of Cancer Registries in the same areas. The control group was formed by a random sample of the population resident in each of the areas, aged 20–74. Controls were identified through record linkage with population computerised files in all areas. The interview was face to face and lasted approximately 1 h. The personnel in charge of the interviews was trained, specifically for this study, through a residential 3-day course at the Siena University.

Table 1. Association between childhood infectious diseases and risk of multiple myeloma in 1128 controls and 213 cases, Italy 1990–1993

Disease	Cases/ controls	OR	95% CI	*P*
All age[a]				
Chickenpox	41/330	0.79	0.53–1.2	0.250
Measles	83/551	0.81	0.57–1.2	0.240
Mumps	62/415	0.95	0.66–1.4	0.792
Pertussis	55/342	0.91	0.63–1.3	0.594
Rubella	41/285	0.89	0.60–1.3	0.549
Any infection	85/555	0.78	0.52–1.2	0.245
Number of infections				0.131*
None	48/189	ref.	n.a.	
1–2	46/244	0.87	0.55–1.4	
⩾3	39/311	0.68	0.41–1.1	
<65 years[a]				
Chickenpox	22/259	0.69	0.40–1.2	0.168
Measles	48/413	0.90	0.55–1.5	0.668
Mumps	37/322	1.1	0.68–1.8	0.665
Pertussis	27/264	0.70	0.42–1.1	0.150
Rubella	22/223	0.74	0.44–1.3	0.266
Any infection	49/402	1.1	0.59–2.1	0.744
Number of infections				0.412*
None	17/108	ref.	n.a.	
1–2	28/156	1.5	0.76–3.0	
⩾3	21/246	0.78	0.38–1.6	
⩾65 years[a]				
Chickenpox	19/71	0.85	0.46–1.5	0.583
Measles	35/138	0.71	0.42–1.2	0.197
Mumps	25/93	0.82	0.47–1.4	0.491
Pertussis	28/78	1.3	0.73–2.2	0.406
Rubella	19/62	0.99	0.54–1.8	0.986
Any infection	36/153	0.56	0.31–1.0	0.051
Number of infections				0.141*
None	31/81	ref.	n.a.	
1–2	18/88	0.52	0.26–1.0	
⩾3	18/65	0.62	0.30–1.3	

OR, Odds ratio adjusted for age, gender and residence area; *P*, *P*-value obtained by likelihood ratio test; ref., reference category.
*likelihood ratio test for trend.
[a]Age at diagnosis of multiple myeloma (cases) or study recruitment (controls).

The following childhood infectious diseases were included in the questionnaire: chickenpox, measles, mumps, pertussis and rubella. For the present study, only those infections occurring within 14 years of age were included in the analyses. All subjects gave their informed consent to participate in the study. More details about the study design and the questionnaire structure have been published elsewhere [7].

The association between each considered infectious disease and the subsequent risk of developing MM was analysed by unconditional logistic regression. Estimates of association, adjusted for age (linear and quadratic term), gender and area of residence, were expressed as odds ratios (OR) and their related 95% confidence intervals (95% CI). Only cases and controls who responded directly to the interview and could remember the age at the onset of the infectious disease were analysed. All analyses were carried out by stratifying the studied subjects by age at diagnosis of MM or recruitment (<65 years *vs.* ⩾65 years) and Stata for Windows (release 13.1, Stata Corporation, College Station, TX) was the statistical package used.

After exclusion of interviews to next-of-kin, 213 MM cases (79%) and 1128 controls (97%) were selected for the analyses. About 15% of subjects were unable to remember the age at the onset of one or more infectious disease; in details: 37 cases (17%) and 163 controls (15%) for chickenpox; 45 cases (21%) and 205 controls (18%) for measles; 38 cases (18%) and 160 controls (14%) for mumps; 30 cases (14%) and 135 controls (12%) for pertussis; 29 cases (14%) and 140 controls (12%) for rubella. Measles was the most frequent childhood infection (49% of cases and 60% of controls), followed by mumps (35% and 43%), pertussis (30% and 34%), chickenpox (23% and 34%) and rubella (22% and 29%).

Table 1 shows the estimates of the association between each considered disease and the risk of MM. After adjusting by age at diagnosis, gender and residence area, no statistically significant association was observed. Subjects with at least one infection had a lower, not statistically significant risk (OR 0.78, 95% CI 0.52–1.2). The number of infections was slightly inversely associated with the risk of MM (OR 0.68 for at least 3 infections, 95% CI 0.41–1.1), but statistically significant was not reached ($P = 0.131$). Analysis stratified by age at diagnosis or recruitment did not find any clear association although a protective effect of any infection in the oldest group (OR 0.56, 95% CI 0.31–1.0) could be observed. However, statistical significance was borderline and there was no evidence of trend by a number of reported infections ($P = 0.141$).

The aetiology of MM is largely unknown. The suspected risk factors include immune-stimulating conditions and infections. However, in many cases, infections occurring few years before the MM onset may indicate reverse causality, in that they could be a consequence of the carcinogenesis process [8]. The hypothesis that some common infections during childhood might exert a protective effect on MM is suggested by evidence from other lymphatic and haematopoietic malignancies in studies carried out in the last two decades, even if a causal link remains unproven [1–3]. Protection against adult malignancies by childhood infection agents might result from a quite large set of both direct and indirect mechanisms [9]. For instance: an oncotropic and

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oncolytic effect has been demonstrated for some viruses, including the mumps and measles agents; antibodies against childhood viruses may favour the destruction of cancer and precursor cancer cells via partial cross-immunity; some antibiotic treatments against childhood bacterial infections may exert a toxic activity against cancer stem cells; exposure to childhood infections may enhance immune efficiency to eliminate cancer cells by favouring a balanced TH1/TH2 immunity; multiple common infections may hamper the proliferation of potentially oncogenic viruses by induction of the release of IFN [9].

In this study has no clear association emerged between the five considered childhood diseases and the risk of MM, even if a non-statistically significant trend by a number of infections was observed. Our results are in agreement with those of two previous case-control studies [4, 5]. In the Italian study, the proportion of self-reported infections by measles and mumps viruses was very similar to that observed in our investigation. However, the frequency of chickenpox among controls was near twice, whereas rubella infection was slightly less prevalent [5]. In the UK study the proportion of all infections was higher, except for pertussis and rubella, but data were not wholly comparable because the group of youngest subjects also included young adults and adolescents [4].

MM is a malignancy that involves mature memory B cells. The age at the onset is, on average, about 70 years and aging is a recognised risk factor for this disease [8]. The potential protective effect (if any) of infections during childhood on the risk of B cell malignancies might be reduced in MM as a consequence of the senescence of the immunitary system and the associated reduction of cancer immune-surveillance. Our results did not show clearly different OR estimates by age at diagnosis/recruitment, but sample size in many subgroups of cases was very small, especially in the analysis by a number of infections.

Results of the present investigation are prone to some unavoidable biases and limits, which include: the potential impact of recall bias, the relatively small number of MM cases, the self-reported information about exposure and the lack of information about vaccinations. This latter, however, should have been a negligible impact on the OR estimates, in that in Italy, during the period of the subjects recruitment, the proportion of vaccinated subjects was very low [10].

In conclusion, results from this analysis do not support the hypothesis of a clear protective effect of common childhood infections on the risk of developing MM.

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Declaration of Interest. All authors have no conflict of interest to report.

Ethical standards. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent. Informed consent was obtained from all individual participants included in the study.

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