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Childhood adverse events in Hodgkin and non-Hodgkin lymphomas: a discriminant function

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SUMMARY

The aim of the present study is to evaluate the association between childhood adverse events and the diagnosis of lymphoma, while also taking into account the type of lymphoma. One hundred three patients (59 females; mean age 55.2±15.6 years) and 103 healthy control subjects matched for age, gender, and education were enrolled. Childhood adverse events were assessed through the Florence Psychiatric Interview and the Childhood Experience of Care and Abuse Questionnaire. Of the 103 patients included in the study, 53 had been diagnosed with Hodgkin lymphoma and 50 withnon-Hodgkin lymphoma. Patients with lymphoma displayed higher frequencies of childhood adverse events than controls.The discriminant function model satisfied assumption criteria and was significant (Wilks lambda (^)=.58, p<.001).The frequency of early adversities did not differ between the Hodgkin and non-Hodgkin groups.This is the first study thatinvestigatesthe possible relationship between childhood trauma and incidence of lymphoma in adulthood.

INTRODUCTION

The impact of psychosocial factors on the development of cancer has been widely studied. A comprehensive meta-analysis showed that stress-related psychosocial factorsare associated with a higher incidence of cancer, poorer survival rates, and higher cancer mortalityrates (1). However, most studies have focused exclusively on the stressful events that occur immediately prior to the onset of cancer, whereas scant attention has been given to the events that occur during development. It has been shown that childhood adverse events can interfere with the correct development of the Hypothalamic-Pituitary-Adrenal (HPA) axis (2-4), particularly the glucocorticoid receptor (5, 6), a phenomenon that is probably due to transcriptional/epigenetic mechanisms (7-9). Once hyper-activated during the developmental process, the HPA axis remains

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permanently unstable, over-reactive, or dysfunctional, and can lead to an altered hormonal response in stressful situations that emerge later in life (10). Such alterations in the HPA axis functioning could therefore affect the cellular process in the repair of damaged DNA, therebyfacilitating the establishment of oncogenic mutations (11-13) and reducing protection against oncogenic viruses (14-17).

The association between stress-related psychosocial factors, immunity dysregulation, and lymphomas has received scant attention. Maternal stress during pregnancy has been reported to increase the risk of lymphoma (as well as of hepatic and testicular cancer) in children during their first ten years of life (18). The changing rates of lymphomas observed in Singapore have been related to the social changes in the area (19-22).

However, to our knowledge, no study has specifically investigated the possible relationship between childhood traumatic events and lymphomas in adulthood, though some evidence has been produced for other kinds of cancers (23, 24). The present study aims to address this issue by evaluating the presence of childhood adverse events in patients suffering from lymphoma, compared to a matched sample of people who are representative of the general population.

DESIGN AND METHODS

Participants

The study enrolled 110 patients who were suffering from lymphomas and were admitted to the Section of Hematology and Bone Marrow Transplantation Unit, Careggi University Hospital (Florence, Italy) between March 2nd, 2012, and March 30th, 2013. Exclusion criteria were: age <18 and >75 years, intellectual disability, and not fluent in Italian. Of the 110 patients contacted, 103 agreed to participate. A control group of 103 subjects (matched for age, gender and education to the clinical group) was selected using a case-control method from a pool of 1077 subjects representative of the general population living in the same area (the region of Tuscany, central Italy).

These were randomly recruited from the regional lists of the Italian National Health System (99.7% of the citizens are included in the list of the NHS).

The study was approved by the local ethical committee and a written informed consent was obtained from all the participants prior to enrolment.

Measures

During the enrollment phase, socio-demographic information (age, gender, education, marital status, job) and a complete medical history were collected. The type of oncological diagnosis, age of onset, stage of cancer, current and past treatments (i.e. chemotherapy, radiotherapy and surgical operation), information regarding cancer support therapy, and use of psychotropic drugs use were recorded.

Childhood adverse events (CAE) were investigated by means of the Childhood Experience of Care and Abuse Questionnaire (25), and by a semi-structured interview for early trauma (26). Respondents were asked whether they had experienced the following types of adversity before the

age of 15: death of mother, death of father, death of any other cohabitating relative, separation from mother, separation from father, separation from any other cohabitating relative, severe childhood disease, physical abuse, and sexual abuse. Personal accounts were recorded extensively, including the contexts, circumstances, and timing of any specific adversity. Once patients and controls were randomly mixed, these accounts were presented to assessors who did not participate in the interview and were uninformed as to whether a given account referred to a case or a control.

The presence of childhood adverse events was evaluated according to the following criteria:

- loss of parent: whenever a death or continuous separation for one year or more from either parent was reported;
- loss of any other cohabitating relative: includes death of sibling or grandparent who had been looking after the child;
- severe childhood disease:any disease that is sufficient to interfere with the development of normal social relationships;
- sexual and physical abuse events: when the CECA-Q or the interview revealed the presence of physical and sexual abuse;
- motherneglect: based on the CECA-Q scores in the scale "Mother's Neglect" according to the cut-off ≥22 proposed by Bifulco et al. (25).
- father neglect: based on the CECA-Q scores in the scale "Father's Neglect"according to the cut-off ≥24 proposed by Bifulco et al. (25).

When available, the information retrieved about CAE was also confirmed by a close relative of the patient (usually a sibling).

Statistics

Chi-square (χ^2) and Odds ratios were used to compare categorical variables, while the student's t-test was used with continuous data. Discriminant analysis was performed to determine whether CAE could allow to distinguish between patients and controls.The Statistical Package for the Social Sciences for Windows SPSS (IBM, 2011) version 20.0 was employed for data analysis.

RESULTS

Of the 103 patients who participatedto the study, 53 had a diagnosis of Hodgkin lymphoma (HL) and 50 of non-Hodgkin lymphoma (NHL). Since patients and control subjects were matched for sex, age, and educational level, no differences between patients and controls were found for gender (42.7% *vs* 42.9% females), age (M±SD =55.2±15.6 *vs* M±SD =53.7±14.9) and education years (M±SD=10.5±4.1 *vs* M±SD=10.6±4.0).

The comparisons between patients and controls for the frequency of CAE are reported in *Table 1*. Patients with lymphoma (both taken as a whole and divided by the type of lymphoma) displayed a higher frequency of adverse events during childhood than controls, with the exception of the loss of other cohabitating relative, sexual abuse, and physical abuse. No significant difference was found between HL patients and NHL patients in the frequency of CAE (*Figure 1*).

As CAE were often associated with

each other, a discriminant function analysis was performed, using the status of patients and controls as dependent variables, and single events as independent variables. As the risk for childhood adversity may be influenced by social factors, gender, age, marital status, education, occupation, number of children and family oncological story were entered into the

TABLE 1 • Frequencies of CAE: comparisons between patients and controls.

	Lymphoma any types (N=103)		Hodgkin's lymphoma (N=53)		Non-Hodgkin's lymphoma (N=50)		Controls (N=103)
	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)
Loss of mother	25 (24.3)	2.9 (1.3-6.6) **	13 (24.5)	3.0 (1.2-7.5)* *	12 (24.0)	3 (1.2-7.4) **	10 (9.7)
Loss of father	28 (27.2)	6.0 (2.4-15.3) **	14 (26.4)	5.8 (2.1-16.2) **	14 (28.0)	6.3 (2.2-17.6) **	6 (5.8)
Loss of other cohabitating relatives	24 (23.3)	1.2 (.6-2.3)	12 (22.6)	1.14 (.51-2.55)	12 (24.0)	1.23 (.55-2.76)	21 (20.4)
Severe childhood disease	18 (17.5)	5.2 (1.7-16.1) **	9 (17.0)	5.06 (1.5-17.3)**	9 (18.0)	5.4 (1.6-18.6)**	4 (3.9)
Physical Abuse	5 (4.9)	1.05 (1.0-1.09)	2 (3.8)	1.04 (.98-1.09)	3 (6.0)	1.06 (.99-1.14)	0
Sexual Abuse	1 (1.0)	1.01 (.99-1.03)	0	0	1 (2.0)	1.02 (.98-1.06)	0
Mother Neglect	88 (85.4)	7.5 (3.8-14,8) **	45 (84.9)	7.25 (3.1-16.9) **	43 (86.0)	7.9 (3.2-19.2) **	45 (43.7)
Father Neglect	91 (88.3)	9.4 (4.6-19.2) **	47 (88.7)	9.7 (3.8-24.7) **	44 (88.0)	9.0 (3.5-23.07) **	46 (44.7)

Odds ratios (OR) refer to the comparison with controls; **p<.01.

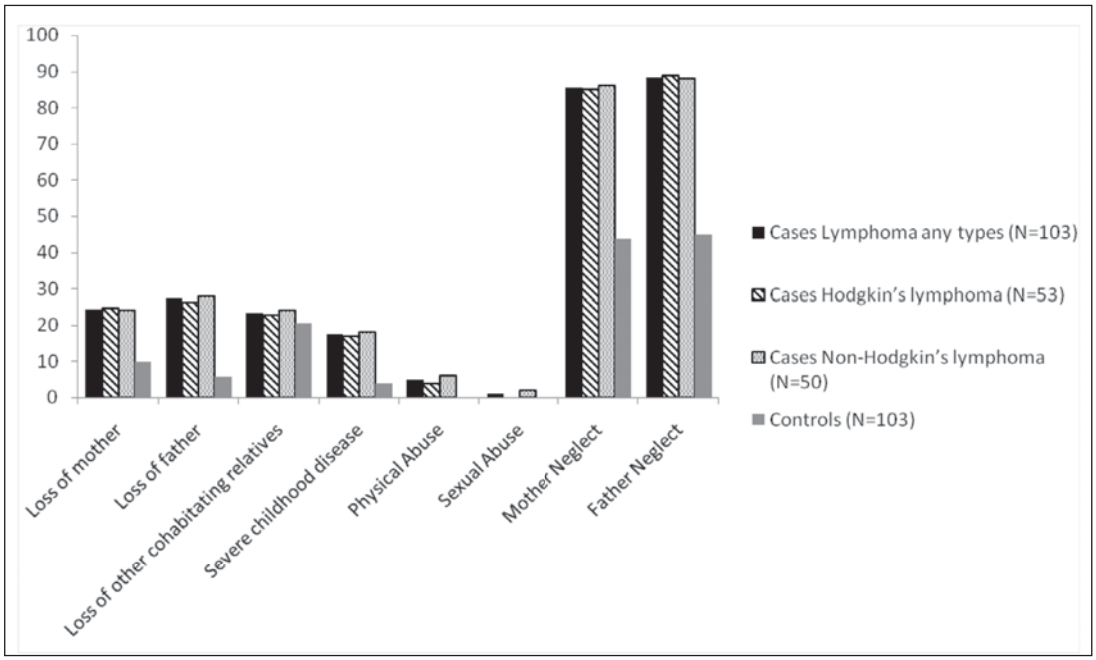

FIGURE 1 • Prevalence (%) of CAE: comparisons between clinical groups and controls.

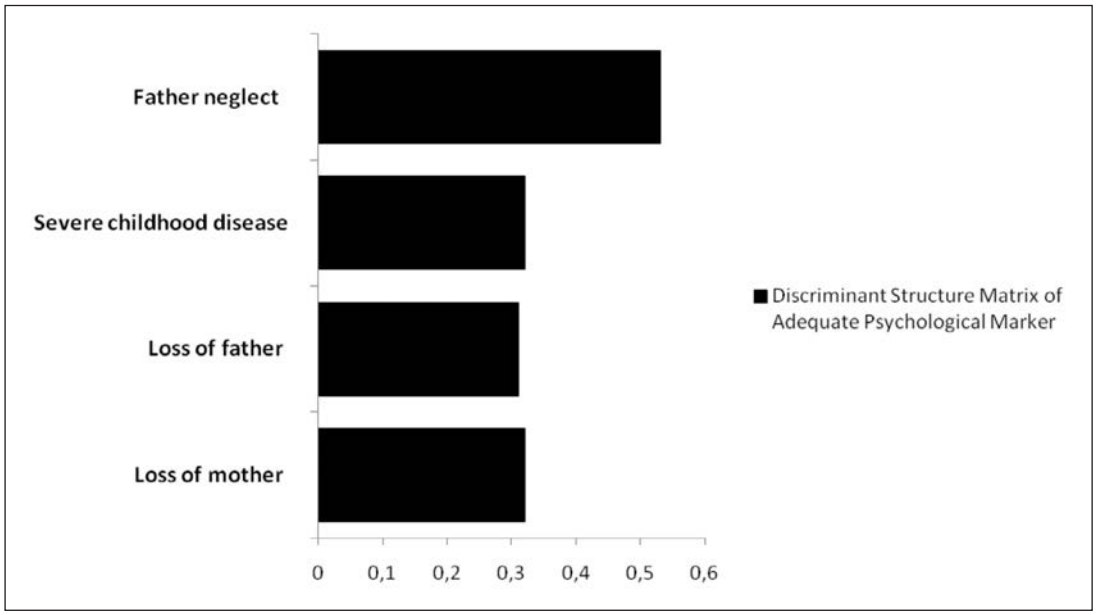

FIGURE 2 • Discriminant Structure Matrix of Adequate Psychological Marker, cut off >| .30 |.

discriminant analysis. The discriminant function model was significant *(Wilks lambda (^)*=.58, χ^2=93.05, *p*<.001), correctly classifying 80.8% of cases with loss of mother (.32), loss of father (.31), severe childhood disease (.32), mother neglect (.56) and father neglect (.53) having loadings >.30 of the discriminant function (*Figure* 2).

DISCUSSION

The main finding of the present study is that childhood adverse events seem to be associated with lymphomas (both HL and NHL). Only the loss of other cohabitating relatives and sexual and physical abuse failed to show a significantly higher prevalence among patients with lymphomas. As we are not aware of similar studies carried out in lymphomas, no comparison with other findings can be made. However, similar findings have been reported in other types of cancer (i.e. breast and gynaecological cancer) (27-29), thereby suggesting that stressful events during development could be aspecific risk factors for cancer.

It is known that sociodemographic factors such as poverty, immigration, low cultural level, urbanicity and other forms of social disadvantage may increase the risk of childhood adversity. For this reason, we matched the samples for education, that is an indirect indicator of the social status in the past, in addition to age and sex. Patients and controls resulted homogeneous also for marital status, number of children and occupation. Since fluent Italian was required, both groups were entirely made up of Caucasians, with migration and ethnicity not being a factor that could influence results. A family history for oncological disorders was equally distributed in the groups

and did not influence the risk of early adversity. We could not explore in detail the other sociodemographic variables of childhood that could affect the occurrence of early events (e.g. city and ward of residence, family composition, economical and educational status of parents): patients and controls, however, were highly comparable for all the factors related to social class, thus suggesting that also the social origin was likely to be homogeneous. Considering these aspects, it is reasonable to conclude that the differences we found in the frequency of early traumata are mainly due the patient or control status of the sample.
Several models may explain the relationship between stress, endocrine and immunological factors, and cancer (1, 14-17).
The effects of stressful life events on cancer might be mediated by several different mechanisms. It has been proposed that stress can affect the cellular process involved in the repair of damaged DNA and could thereby facilitate the establishment of oncogenic mutations (12, 13). Furthermore, stress hormones can also accelerate tumor-cell growth viaseveral pathways and can reduce protection against oncogenic viruses and impair immune-surveillance (14-17). McEwen (15) hypothesized that early stressful experiences are risk factors for allostatic load later in life, mainly through alterations in HPA axis and autonomic nervous system functioning, thus rendering individuals susceptible to the development of various diseases. Moreover, high level of stress during childhood may promote high-risk behaviors in adulthood such as smoking, poor diet, lack of exercise, obesity, excessive alcohol consumption, poor sleep, or lower treatment adherence (1). However, it is still unclear whether psychosocial factors have either a direct impact on endocrine, immune, and nervous systems or an indirect impact by affecting behaviors, such as diet, exercise, and sleep. Finally, other risk factors, be they environmental or constitutional (e.g."impact" and "stress adaptive capacity", coping skills, and social support), could potentially modulate the relationship between life events and cancer (28, 30).
It is of great interest to note that no difference in the frequency of early life events was observed between HL and NHL.
Despite the different histopathological and clinical presentations, severe stress during childhood seems to have the same predisposing role for both groups of lymphomas, which is in line with the aforementioned hypothesis regarding the aspecificity of CAE.
Some limitations of the present study must be acknowledged. The retrospective and cross-sectional design of the study obviously introduces the possibility of a recall bias caused by cancer diagnosis or memory distortion, as patients re-evaluate their lives on the basis of their health state and might selectively recall their experience before the diagnosis.
For these reasons, only objectively verifiable early events were assessed and, when possible, confirmed by a relative of the patient. Furthermore, the sample size was limited, especially when comparisons between HL and NHL were performed.
A larger sample and a more detailed investigation are therefore necessary to confirm the association between childhood traumata and adult lym-

phomas, and to evaluate other factors that may modulate the response to traumatic childhood events (e.g. temperament, attachment and parental style).
To our knowledge, this is the first study that specifically investigatesthe possible relationship between childhood adverse events and lymphomas incidence in adulthood, offering additional information regarding the predisposing effect of stress on incidences of cancer.

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Declaration of interests
All authors declare that they have no conflict of interests.

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