original article

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Risk for second malignancies in non-Hodgkin's lymphoma survivors: a meta-analysis

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Background: Late side-effects are becoming an important issue in non-Hodgkin's lymphoma (NHL) survivors. We intended to estimate pooled relative risk (RR) of secondary malignant neoplasms (SMNs), to evaluate site-associated RR and the impact of different treatments.

Design: We carried out an electronic search of Medline and EMBASE seeking articles investigating the risk of SMNs and reporting RR measures. The studies were evaluated for heterogeneity before meta-analysis and for publication bias. Pooled RRs were estimated using fixed- and random-effects models.

Results: A total of 23 studies met the inclusion criteria. Pooled RRs of SMNs overall and for solid tumors were 1.88 and 1.32, respectively. We found an excess of risk for several specific cancer sites. Radiotherapy alone did not increase the risk for SMNs, while chemotherapy and combined treatments augmented the RR. Regression analyses revealed a positive significant association for all SMNs with total body irradiation, and for solid SMNs with younger age. No publication bias was observed.

Conclusions: Our results indicate that NHL patients experience a higher risk for SMNs than the general population and that various treatments have different impact on RR. More information will be necessary to evaluate possible interactions with genetic susceptibility and environmental exposure.

Key words: meta-analysis, NHL, relative risk, secondary malignancies

introduction

Chemotherapy with or without radiation therapy has been the mainstay of non-Hodgkin's lymphoma (NHL) treatment. In the past few years, evolving therapies have led to improved long-term survival for some histological subtypes, and the introduction of monoclonal antibody treatments has further improved the prognosis of indolent [1–3] and aggressive [4–8] B-cell NHL. High-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) and allogeneic bone marrow transplantation has emerged as another promising approach for the treatment of relapsed lymphoma or as part of planned treatment of neoplasm with a poor prognosis [9–12]. As a result of these advances, the prevalence of NHL survivors is expected to increase and late side-effects of treatment such as secondary malignant neoplasms (SMNs) are becoming an important issue.

Carcinogenesis linked to specific tumor sites was highlighted as a late effect associated with exposure to chemotherapeutic drugs [13–18] or radiotherapy [15, 19–21] as single-modality therapy, or combined-modality approaches including conventional-dose chemotherapy with radiotherapy [22] or with total body irradiation (TBI) [23], ASTC following high-dose chemotherapy [24–26], and TBI used in the preparative regimen for ASTC [27]. Nevertheless, several studies have failed to detect a significant relationship between therapy exposure and SMNs, probably because the estimation was often based on a small number of patients. Although several previous descriptive literature reviews [28–35] have discussed the risk for a second cancer, overall risk for therapy-related SMNs is less certain and the comparison of SMNs risk for NHL survivors with a general population yielded conflicting results among the studies.

Therefore, we carried out this meta-analysis to provide a quantitative assessment on the risk for SMNs. The purposes were to estimate the pooled relative risk (RR) of SMNs overall and for solid tumors, to evaluate the site-associated RR, and to examine the risk linked to treatment modality.

methods

This meta-analysis was carried out according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group [36]. We did not carry out methodological quality assessment of the studies because quality scoring in meta-analysis is controversial [37], *ad hoc* scores can fail validation, and results may not be associated with quality [36, 38]. In place of a subjective quality score, we carried out subgroup and sensitivity analyses [36].

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Studies were reviewed and data extracted and cross-checked independently by two reviewers (RM and MP); disagreements were resolved by consensus with another author (LM).

search strategy

We identified studies of interest by first conducting an electronic literature search of the databases Medline and EMBASE. We used exploded Medical Subject Heading terms 'lymphoma, non-Hodgkin', 'lymphoma, t-cell', and 'lymphoma, b-cell'. The terms were combined with 'neoplasm, second primary' using the Boolean operator 'and'. In the second step, these keywords were combined using the Boolean operator 'and' with the terms 'standardized incidence ratio', 'observed to expected', and 'standardized morbidity ratio'. In addition, we reviewed the reference lists of relevant studies to identify additional relevant published articles.

selection criteria

We included studies that met each of following criteria: (i) published in English language between January 1985 and December 2008; (ii) included naive patients with any stage of NHL; (iii) investigated the risk for SMNs in NHL survivors; (iv) reported RR, specified as standardized incidence ratios or data allowing such outcomes to be derived; and (v) published as original papers (no reviews, comments, letters, or editorials).

Of the studies on specific NHL histologies, we excluded hairy cell leukemia and chronic lymphocytic leukemia because in population-based studies, these diseases are normally classified as leukemia. When two or more articles reported duplicate data, we included the most recently updated data or most informative study.

data extraction

A standardized form was used for each study included in the meta-analysis. Extracted data included paper characteristics (first author's last name, publication year, country in which the study was carried out, and data source), study design, number of NHL patients, histological subtype, mean/median age of patients, duration of follow-up, therapy, number of cases observed with SMNs and expected number of cases, and/or RR with corresponding 95% confidence interval (CI). Where not reported, we computed the CI for the RR assuming a Poisson distribution for the observed number of cases. Standard error (SE) for the natural logarithm of RR [ln(RR)] was derived from CI, applying the following equation: $SE = \ln(\text{upper 95\% CI}/\text{lower 95\% CI})/(2 \times z_{1-\alpha/2})$.

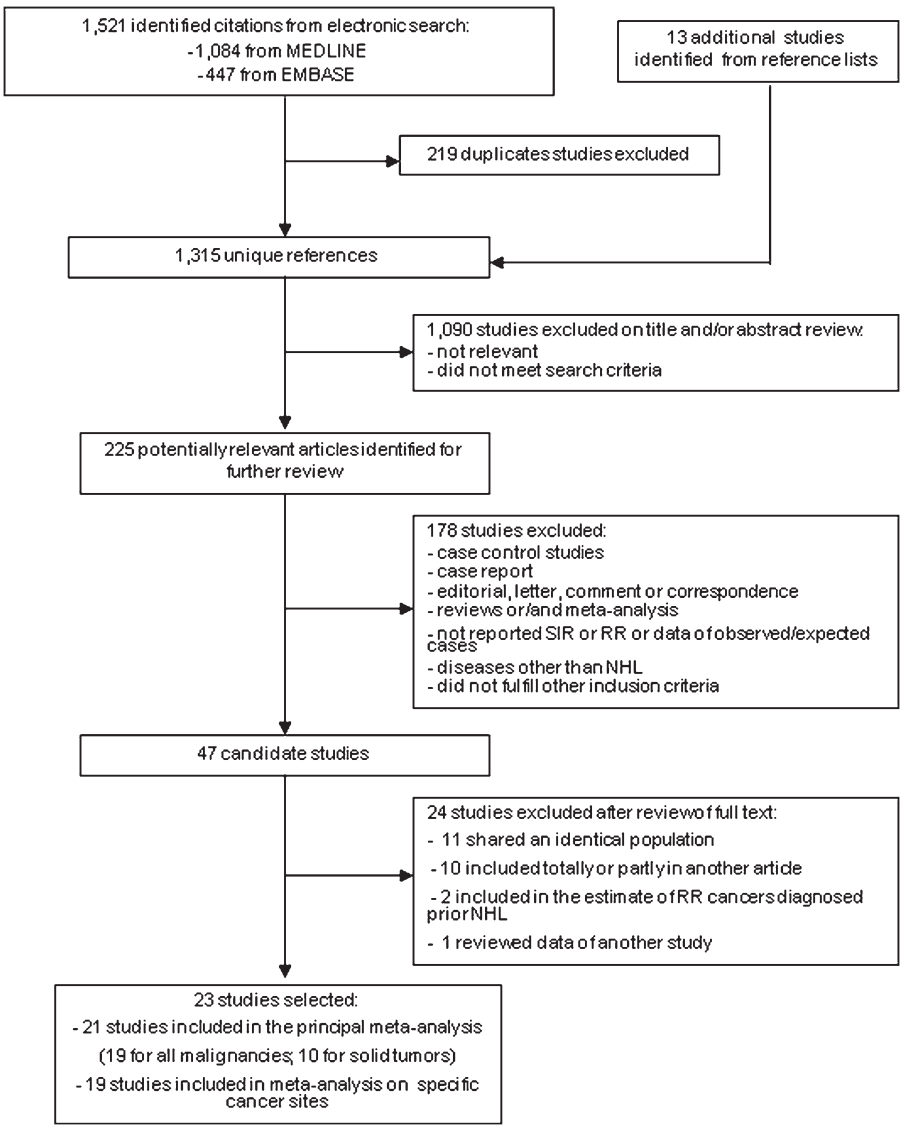

Figure 1. Flow chart of literature search. SIR, standardized incidence ratio; RR, relative risk; NHL, non-Hodgkin's lymphoma.

Table 1. Characteristics of studies included in the meta-analysis

Study (reference)	Country	Source of data, study period	No. of cases of primary NHL, histology	Treatment	Median age at diagnosis, years	Median follow-up	No. of secondary malignancies	All malignancies RR (95% CI)	No. of solid tumors	Solid tumors RR (95% CI)
Data from clinical trials										
Barista et al. 2002 [71]	United States	Two M.D. Anderson trials, 1994–2000	156, mantle cell	Hyper-CVAD/ M-A ± TBI ± SCT	59.5	26 months	7	100.0 (49.3–186.6)	–	–
André et al. 2004 [17]	France	Three GELA trials, 1984–1998	947 F and 1320 M, aggressive NHL	CHOP-like ± RT	54	74 months	22 F[a], 44 M[a]	0.94 (0.59–1.42), 0.92 (0.67–1.24)	14 F[a], 35 M[a]	0.63 (0.35–1.06), 0.77 (0.54–1.07)
Moser et al. 2006 [72]	Four European Countries	Four EORTC trials, 1980–1999	748, aggressive NHL	CHOP-like ± RT ± SCT	49[b]	8.9 years	–	–	37[b]	1.0 (0.7–1.3)
Mudie et al. 2006 [18]	UK	BNLI, 1973–2000	2456, B-cell histologies	Alk, CHOP ± RT, RT alone	46.5[b]	7.7 years[b]	123[a]	1.3 (1.1–1.6)	103[a]	1.1 (0.9–1.4)
Sacchi et al. 2008 [73]	Italy	GISL trials, 1988–2003	563, indolent NHL	Alk ± anthracycline ± fludarabine ± RT	60	62 months	39	1.9 (1.4–2.7)	–	–
Sacchi et al. 2008 [74]	Italy	GISL trials, 1988–2003	1280, diffuse large B cell	PBC, CHOP, CHOP-like ± RT	58	51 months	48	1.1 (0.8–1.5)	–	–
Data from hospital- or specialist center-based studies										
Takenaka et al. 1985 [75]	Japan	National Cancer Center Hospital, 1962–1983	407, various histologies	Combined CHT ± RT, RT alone, surgery ± combined CHT ± RT	50	–	11	1.0 (0.50–1.81[c])	–	–
Lavey et al. 1990 [76]	United States	Duke University Medical Center, 1970–1981	686, various histologies	CHOP-like ± RT, RT alone[d]	54.6	5.5 years	48	0.8 (0.5–1.1)	39	0.6 (0.4–0.9)
Lishner et al. 1991 [77]	Canada	Princess Margaret Hospital, 1970–1985	3021, various histologies	WW, Alk, combined CHT± RT	59	4 years	119	1.0 (0.8–1.2)	–	–
Travis et al. 1996 [23]	United States	Harvard Joint Center, 1965–1980	61, various histologies	Low-dose TBI ± Alk ± RT	50	8.6 years	12	2.8 (1.5–4.9)	8	2.0 (0.9–4.0)

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Table 1. (*Continued*)

Study (reference)	Country	Source of data, study period	No. of cases of primary NHL, histology	Treatment	Median age at diagnosis, years	Median follow-up	No. of secondary malignancies	All malignancies RR (95% CI)	No. of solid tumors	Solid tumors RR (95% CI)
Tanaka et al. 1997 [78]	Japan	Osaka Medical Center, 1978–1994	592, various histologies	Combined CHT ± RT, RT alone	56.3[b]	3.7 years[b]	27	1.53 (1.01–2.23)	24	1.42 (0.91–2.11[c])
Leung et al. 2001 [79]	United States	St Jude Hospital, 1970–1997	497, various histologies	Poorly described	10.7	13.6 years	16	10.8 (6.1–16.9)	9	6.7 (3.0–11.9)
Brown et al. 2005 [27]	United States	DFCI, 1982–1997	605, B-cell histologies	Combined CHT + Alk + TBI + ASTC	44	9.5 years	116[b]	6.43 (5.31–7.71[c])	–	–
Guadagnolo et al. 2006 [80]	United States	Harvard area hospitals, 1972–2000	106, follicular (stages I–II)	RT, TBI ± combined CHT	55	12 years	14	1.56 (0.85–2.61[c])	–	–
Iannitto et al. 2006 [81]	Italy	Three Italian hospitals, 1988–2003	129, splenic marginal zone B –cell	WW, surgery, Alk, purine analogs	65	32.6 months	12[b]	2.03 (1.05–3.56)	–	–
Arcaini et al. 2007 [82]	Italy	2 Italian hospitals, 1991–2004	157, nongastric MALT	WW, surgery, Alk, CHOP ± RT	64	3 years	9[b]	1.32 (0.69–2.55)	–	–
Bluhm et al. 2008 [21]	United States	CCSS, 1970–1986	1082, various histologies	Combined CHT (included CHOP-like) ± RT ± SCT ± surgery, RT alone	10	17 years[b]	31	3.5 (2.4–5.0)	27	3.9 (2.6–5.7)
Data from population-based studies										
Greene and Wilson 1985 [83]	United States	Connecticut CR, 1935–1982	6734, various histologies	Poorly described	58[b]	4 years[b]	319	1.24 (1.11–1.39)	–	–
Brennan et al. 2005 [84]	11 countries	13 CRs, 1943–2000	109 451, various histologies	Poorly described	Data in class	Data in class	6673	1.47 (1.43–1.51)	–	–
Tward et al. 2006 [19]	United States	CRs of SEER Program, 1973–2001	77 823, various histologies	Poorly described	61	60 months	6188	1.14 (1.11–1.17)	5363	1.11 (1.08–1.14)
Hemminki et al. 2008 [85]	Sweden	Swedish Family-Cancer Database linked to Swedish CR, 1961–2004	29 134, various histologies	CHOP ± RT ± ASCT, RT alone	Data in class	Data in class	–	–	2290	1.65 (1.59–1.72)

Table 1. (*Continued*)

Study (reference)	Country	Source of data, study period	No. of cases of primary NHL, histology	Treatment	Median age at diagnosis, years	Median follow-up	No. of secondary malignancies	All malignancies RR (95% CI)	No. of solid tumors	Solid tumors RR (95% CI)
Study included for specific cancer sites										
Levi et al. 1996 [86]	Switzerland	CR of Swiss Canton, 1974–1993	1767, various histologies	Poorly described	43.5[b]	4.2 years[b]	–	–	–	–
Dores et al. 2006 [87]	United States	CRs of SEER Program, 1973–2000	73 958, various histologies	Poorly described	Data in class	Data in class	–	–	–	–

[a]Except nonmelanoma skin cancer (Mudie et al. [18] excluded also NHL as secondary malignancy).
[b]Mean.
[c]The 95% CI was computed assuming a Poisson distribution of observed number of cases.
[d]The study by Lavey et al. [76] included a part of patients that did not receive anthracycline.
NHL, non-Hodgkin's lymphoma; RR, relative risk; CI, confidence interval; Hyper-CVAD/M-A, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternated with methotrexate and cytosine arabinoside; TBI, total body irradiation; SCT, stem-cell transplantation; GELA, Groupe d'Etudes des Lymphomes de l'Adulte; F, female; M, male; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiotherapy treatment; EORTC, European Organisation for Research and Treatment of Cancer; BNLI, British National Lymphoma Investigation; Alk, alkylating (including chlorambucil, cyclophosphamide, carmustine, and melphalan); GISL, Gruppo Italiano Studio Linfomi; PBC, ProMECE-CytaBOM (methylprednisolone, cyclophosphamide, epidoxorubicin or doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate); CHT, chemotherapy; WW, watch and wait; DFCI, Dana-Farber Cancer Institute; ASTC, autologous stem-cell transplantation; MALT, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue; CCSS, Childhood Cancer Survivor Study; CR, Cancer Registry; SEER, Surveillance, Epidemiology, and End Results.

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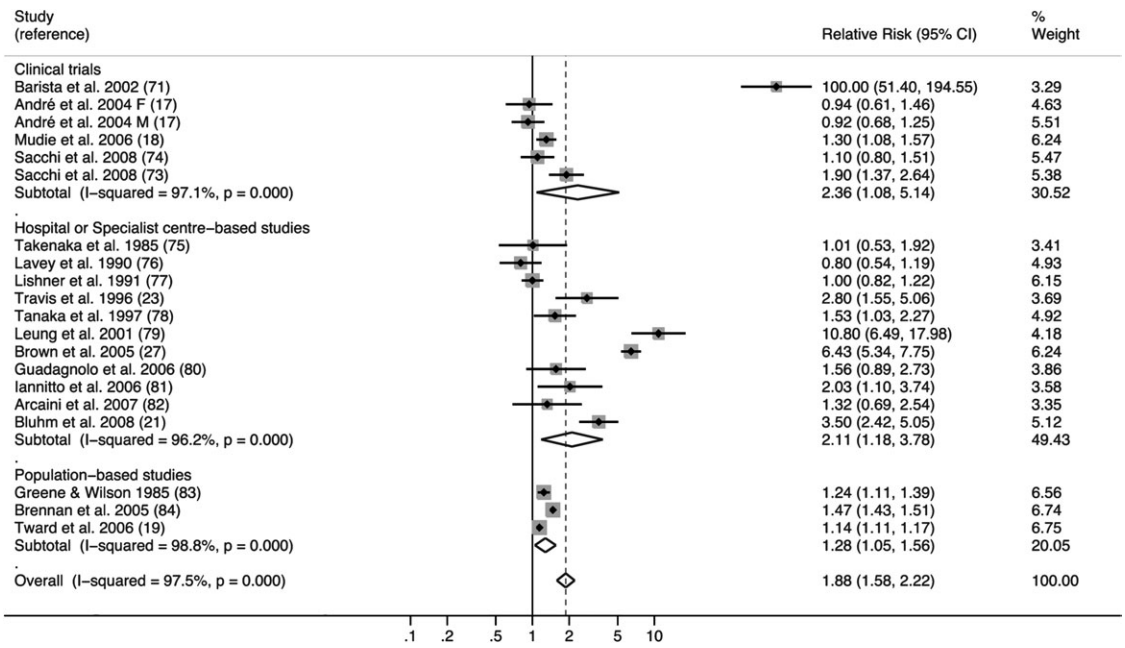

Figure 2. Forest plot of the meta-analysis relating risk for secondary malignancy in non-Hodgkin's lymphoma survivors. Squares represent the relative risk of each single study (size of the square reflects the study-specific statistical weight); horizontal lines represent 95% confidence intervals (CIs); diamonds represent the pooled estimates, based on the random-effects meta-analysis of the studies, with corresponding 95% CIs. F, female; M, male.

Table 2. Meta-analysis of risk for overall secondary malignancy and overall solid tumors in non-Hodgkin's lymphoma survivors

Type of study	Model used	No. of studies (reference)	*Q* test (*P* value)	I^2, %	RR	95% CI
Secondary malignancy						
Clinical trial	Fixed effects	6 [17F, 17M, 18, 71, 73, 74]	<0.001	97.1	1.43	1.26–1.62
	Random effects	6 [17F, 17M, 18, 71, 73, 74]	<0.001	97.1	2.36	1.08–5.14
Hospital- or specialist center-based study	Fixed effects	11 [21, 23, 27, 75–82]	<0.001	96.2	2.42	2.19–2.69
	Random effects	11 [21, 23, 27, 75–82]	<0.001	96.2	2.11	1.18–3.77
Population-based study	Fixed effects	3 [19, 83, 84]	<0.001	98.8	1.29	1.26–1.31
	Random effects	3 [19, 83, 84]	<0.001	98.8	1.27	1.04–1.56
Overall study	Fixed effects	20 [17F, 17M–19, 21, 23, 27, 75–84]	<0.001	97.5	1.31	1.29–1.34
	Random effect	20 [17F, 17M–19, 21, 23, 27, 75–84]	<0.001	97.5	1.88	1.58–2.22
Solid tumors						
Overall study	Fixed effects	10 [17F, 17M, 18, 19, 21, 23, 76, 78, 79, 85]	<0.001	97.2	1.25	1.23–1.29
	Random effect	10 [17F, 17M, 18, 19, 21, 23, 76, 78, 79, 85]	<0.001	97.2	1.32	1.07–1.63

Pooled relative risks (RRs) and relative 95% confidence intervals (CIs) were from fixed or random models. F, female; M, male.

Cancer sites with at least three RR estimates meeting our meta-analysis criteria are reported separately. When studies showed that the observed number of cases was zero, we simply added 1 to both the observed and the expected number of cases to enable computation of an estimate of the ln(RR) and its associated SE [39]. Some authors were contacted for clarification and additional and unreported information for the meta-analysis.

statistical analysis

Statistical heterogeneity of RR across the studies was explored with the Cochran's *Q* test [40] and I^2 statistic [41, 42]. A *P* value >0.10 for the *Q* statistic and an I^2 value <50% was interpreted as signifying a low level of heterogeneity. The pooled estimates of RR, together with associated 95% CIs, were obtained using the DerSimonian and Laird random-effects model [43] and the Mantel–Haenszel fixed-effects model [44], according to heterogeneity statistics.

For the principal meta-analysis, we calculated pooled RR, associated with 95% CIs with fixed and random effects to evaluate the effects of any small studies [45].

Publication bias was sought using the funnel plots and quantified using the rank correlation test as proposed by Begg and Mazumdar [46] and the regression asymmetry test by Egger et al. [47]. All statistical tests were

two-sided. One-way sensitivity analysis was used to investigate the influence of each study on the overall estimate by calculating a pooled RR omitting each estimate one at a time [48]. Additionally, subgroup sensitivity analysis was carried out to evaluate the robustness of results. Meta-regressions were fitted by restricted maximum likelihood algorithm. The ln(RR) was the dependent variable, and the characteristics analyzed included type of data source (clinical trials, hospital- or specialist center-based studies, and population-based studies), average age of NHL patients (median or mean), average period of calendar recruitment of patients, and follow-up duration (<5 years, ≥5 years); for the meta-regression on all malignancies, we took into account the exposure of patients to TBI (as a dummy variable). We first conducted a univariate regression analysis for each factor, followed by a multivariate regression (including only the studies for which the factors of interest were available). A permutation test was applied to fitted models to establish the true statistical significance of a positive finding, incorporating 20 000 Monte Carlo simulations [49].

Statistical analyses were carried out using the Stata software package, version 10.1 (StataCorp, College Station, TX).

results

search results

We initially identified 1521 potentially eligible studies (Figure 1). After exclusion of duplicate references, nonrelevant literature, and papers that did not satisfy inclusion criteria, 47 candidate articles remained for further review. The full text of these articles was carefully read, and 24 candidate papers were excluded due to overlapping publications or nonsatisfaction of inclusion criteria [14, 15, 20, 50–70].

We used a total of 23 studies for the meta-analyses. Of these, 21 studies contributed to principal meta-analysis on the risk for SMNs and/or solid SMNs: 6 were studies from clinical trials [17, 18, 71–74], 11 were studies carried out in hospitals or specialist centers [21, 23, 27, 75–82], and 4 were population-based studies, i.e. based on data from cancer registries [19, 83–85]. Nineteen studies were identified that provided risks for specific cancer types [17–19, 21, 23, 27, 72, 74–79, 81, 83–87]. Two studies were included in the meta-analysis, although they partially overlapped other papers. The study by Hemminki et al. [85] was included because it covered a recent time period (1999–2004) not present in the previous large study by Brennan et al. [84]. The paper of Dores et al. [87], a chapter in a multiauthored book, was included in our meta-analysis for the specific cancer sites not reported in a subsequent article [19]. The main features of the studies included in the meta-analysis and the estimated RR with 95% CIs are showed in Table 1.

meta-analysis results

overall secondary malignancy risk. The analyzed dataset encompassed 19 articles (Table 1). Studies included a total of 208 643 NHL survivors who developed 13 878 SMNs recruited during the period 1935–2004. Twelve studies [18, 19, 21, 23, 27, 71, 73, 78, 79, 81, 83, 84] reported positive association between risk for SMNs and previous NHL, whereas 7 [17, 74–77, 80, 82] showed no association. The statistical heterogeneity tests yielded highly significant results (Cochran's Q test, $P < 0.001$; $I^2 = 97.5\%$) giving evidence of statistical heterogeneity. Figure 2 presents the results of the random-effects model meta-analysis. The pooled RR of SMNs was 1.88 (95% CI 1.58–2.22), an increased, statistically significant value in comparison with the risk of the general population. The pooled RRs calculated from each subgroup (for clinical trials, hospital-based studies, and population-based studies, RRs were 2.36, 2.11, and 1.28, respectively) were significant. The pooled RR of SMN using the fixed-effect model was 1.31 (95% CI 1.29–1.34) (Table 2) and showed that any small-study effects had little impact on the intervention effect estimate.

The funnel plot was symmetric (data not shown), and the Begg–Mazumdar and Egger test results provided no evidence of publication bias.

Sensitivity analyses demonstrated the substantial stability of our results (Figure 3A). However, excluding the study by Barista et al. [71] that reported a very high RR, we found a lower pooled RR for all malignancies (RR = 1.63; 95% CI 1.40–1.91), and the subanalysis on studies carried out on patients from clinical trials showed no excess of risk (RR = 1.20; 95% CI 0.95–1.52).

A meta-regression analysis showed a significant positive association between ln(RR) and the follow-up ≥5 years ($P = 0.038$) and exposure to TBI ($P = 0.002$). After correction for multiple testing, only exposure to TBI was found significant ($P = 0.014$).

overall solid tumors risk. We did not carry out a meta-analysis for solid SMNs according to the type of studies because the

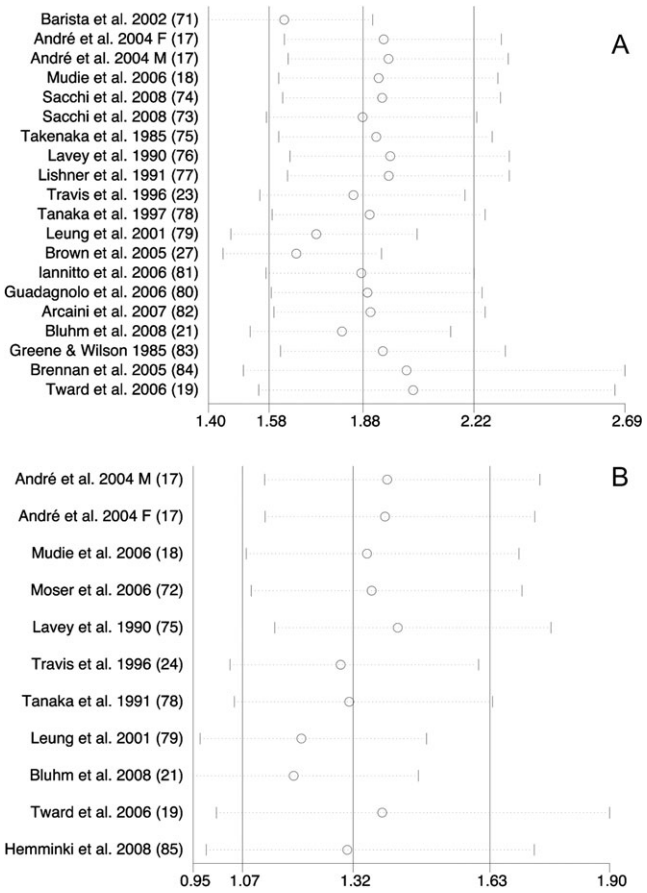

Figure 3. Sensitivity analysis conducted for meta-analysis on risk for overall (A) and solid (B) secondary malignancy. Pooled relative risks and 95% confidence intervals were calculated by omitting each study in turn. F, female; M, male.

number of available articles was limited. A total of 10 studies encompassing 115 916 NHL patients, recruited from 1961 to 2004, were included in the analysis (Table 1), and 7949 patients developed solid SMNs. Two population-based studies [19, 85] and two institutional studies [21, 79] reported a significant positive association for the risk for solid SMNs and previous NHL. The statistical tests indicated substantial heterogeneity across the studies (Cochran's Q test, $P < 0.001$; $I^2 = 97.2\%$). Meta-analysis carried out on all studies showed a significant association between previous NHL and the risk for solid SMNs (Figure 4); the random-effects combined estimate resulted in an RR of 1.32 (95% CI 1.07–1.63). The pooled RR of SMN using the fixed-effect model was 1.25 (95% CI 1.23–1.29) (Table 2) and showed that any small-study effects had little impact on the intervention effect estimate. Neither Egger's nor Begg–Mazumdar's test supported publication bias.

Sensitivity analysis (Figure 3B) showed that the omission in turn of each study did not appreciably change the pooled RR, and the estimates in each case were within the CI of the pooled estimate.

By regression analysis, we identified a significant association between young age at diagnosis ($P = 0.011$). Following a permutation test in multivariate analysis, age was revealed as having a significant influence on the ln(RR) of SMNs ($P = 0.024$).

site-specific incidence. Table 2 summarizes the meta-analysis results by cancer site. The 19 papers available for analysis were published between 1985 and 2008; of these, 4 present data from clinical trials [17, 18, 72, 74], 9 were hospital-based studies [21, 23, 27, 75–79, 81] and 5 were population-based studies [19, 83–86]. The majority of investigated sites manifested a statistically significant RR increase for solid tumors in comparison with the reference population (Table 3). For corpus uteri, we found a significant negative association with primary NHL. Among lymphohematopoietic tumors, we did not discover significant differences with respect to the general population for second primary NHL, while an excess of risk was observed for multiple myeloma, Hodgkin's lymphoma, leukemia, and nonlymphocytic leukemia. Publication bias was not evident when the Begg and the Egger tests were used.

impact of different treatments. Table 4 presents the pooled RRs according to treatment modality. The use of any type of chemotherapy alone was associated with higher risk for SMNs. A similar result was observed in the subanalysis on patients treated only with alkylating agents, while the pooled RR of SMNs for patients who underwent treatment with cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) or CHOP-like or radiotherapy alone was raised but not statistically significant. A combined modality of treatment was significantly associated with the risk for overall SMNs but not for solid tumors.

In addition, we evaluated the effect of TBI exposure limiting the analysis to the studies that explicitly described the therapies. We examined the association between TBI exposure and overall

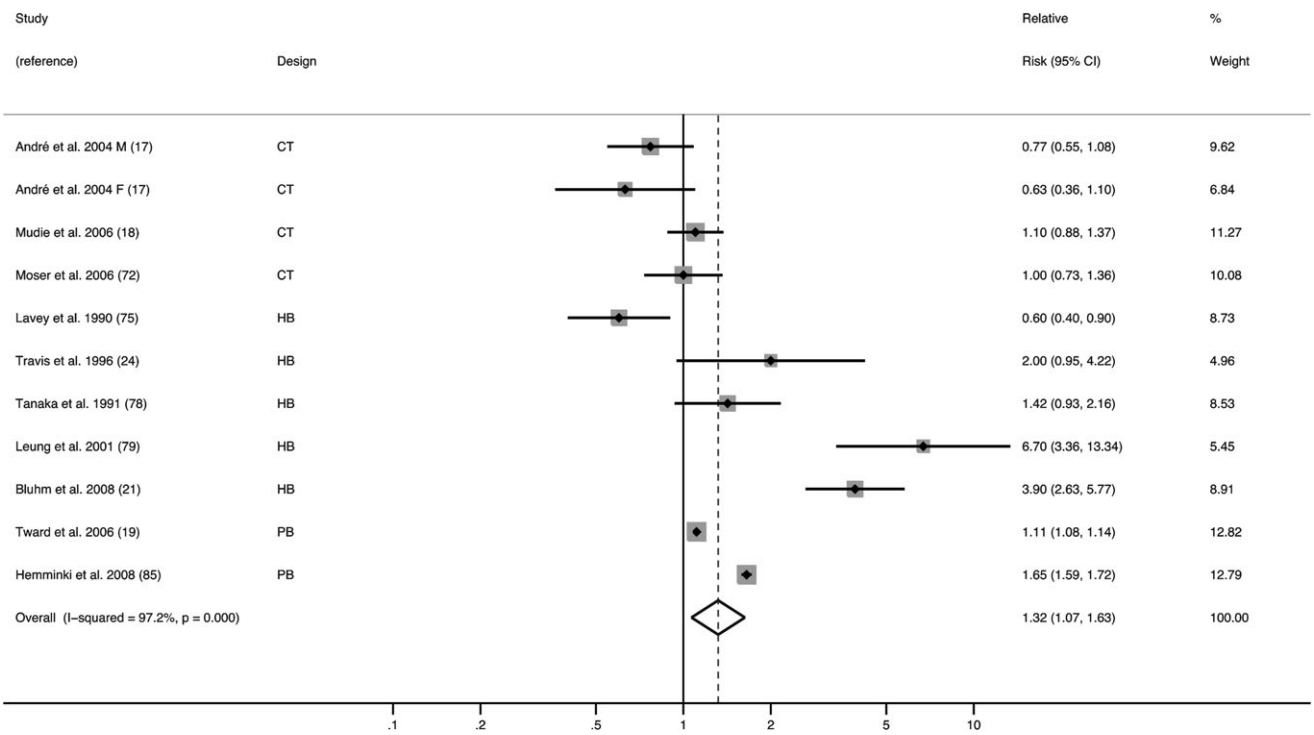

Figure 4. Forest plot of the meta-analysis relating risk for secondary solid tumors in non-Hodgkin's lymphoma survivors. Squares represent the relative risk of each single study (size of the square reflects the study-specific statistical weight); horizontal lines represent 95% confidence intervals (CIs); diamonds represent the pooled estimates, based on the random-effects meta-analysis of the studies, with corresponding 95% CIs. F, female; M, male; CT, data from clinical trials; HB, data from hospital- or specialist center-based studies; PB, data from population-based studies.

Table 3. Meta-analysis of risk for selected cancer sites in NHL survivors

Second primary malignancy	No. of studies (reference)	No. of primary NHL	Heterogeneity statistics		Model used	Pooled effect	
			Q test (*P* value)	I^2, %		RR	95% CI
Solid tumors							
Tongue	4 [77, 83, 84, 87]	193 164	0.148	43.9	Fixed effects	**1.67**	**1.24–2.25**
Salivary gland	5 [77, 83–85, 87]	222 298	0.473	0.0	Fixed effects	**2.02**	**1.50–2.71**
Oropharynx	3 [77, 84, 87]	186 430	0.317	12.9	Fixed effects	**2.11**	**1.41–3.16**
Esophagus	6 [18, 19, 77, 83–85]	228 619	0.161	36.8	Fixed effects	1.16	0.99–1.37
Stomach	9 [18, 19, 23, 75, 77, 78, 83–85]	229 679	0.510	0.0	Fixed effects	**1.33**	**1.22–1.44**
Colon	5 [18, 19, 77, 83, 84]	199 485	0.030	62.7	Random effects	**1.16**	**1.00–1.33**
Rectum	6 [18, 19, 23, 77, 83, 84]	199 546	0.504	0.0	Fixed effects	1.03	0.93–1.13
Liver	5 [19, 78, 83–85]	223 734	0.001	79.6	Random effects	**1.47**	**1.05–2.07**
Pancreas	8 [18, 19, 72, 77, 78, 83–85]	229 959	0.036	53.2	Random effects	1.16	0.92–1.45
Nose and nasal cavity	3 [84, 85, 87]	212 543	0.012	77.6	Random effects	**2.78**	**1.36–5.65**
Larynx	5 [77, 83–85, 87]	222 298	0.888	0.0	Fixed effects	**1.20**	**1.00–1.43**
Lung	12 [17[a]–19, 27, 72, 74 ,77, 78, 81, 83–85]	233 293	0.001	64.5	Random effects	**1.53**	**1.36–1.73**
Soft tissue	6 [18, 19, 27, 77, 83, 84]	200 090	0.108	44.6	Fixed effects	**2.14**	**1.76–2.59**
Melanoma	7 [18, 19, 27, 77, 83–85]	230 991	0.032	54.4	Random effects	**1.85**	**1.54–2.23**
Bone	5 [18, 21, 83, 84, 87]	193 681	0.338	11.9	Fixed effects	**3.49**	**2.43–4.99**
Eye	3 [83, 84, 87]	190 143	0.359	2.3	Fixed effects	1.45	0.95–2.22
Brain	6 [19, 21, 77, 83–85]	227 245	<0.001	83.9	Random effects	**1.84**	**1.18–2.87**
Thyroid	7 [19, 21, 27, 72, 83–85]	225 577	<0.001	84.5	Random effects	**3.55**	**1.92–6.55**
Breast (female)	12 [17[a]–18, 19, 21, 23, 27, 72, 74, 77, 83–85]	235 232	<0.001	81.7	Random effects	1.10	0.88–1.37
Uterine cervix	6 [18, 77, 83–85, 87]	224 754	0.289	19.1	Fixed effects	1.06	0.85–1.32
Uterine corpus	6 [18, 77, 83–85, 87]	224 754	0.134	40.7	Fixed effects	**0.85**	**0.75–0.97**
Ovary	7 [18, 27, 78, 83–85, 87]	222 930	0.309	15.8	Fixed effects	1.03	0.89–1.19
Prostate	11 [18, 19, 23, 27, 72, 74, 77, 78, 83–85]	231 905	0.001	66.8	Random effects	1.05	0.91–1.20
Testis	4 [19, 77, 83, 84]	197 029	0.175	39.5	Fixed effects	**1.78**	**1.18–2.69**
Bladder	11 [18, 19, 21, 27, 72, 77, 78, 81, 83–85]	231 775	0.038	47.9	Fixed effects	**1.42**	**1.33–1.52**
Lymphohematopoietic tumors							
Myeloma multiple	6 [18, 19, 77, 83–85]	228 619	0.006	69.4	Random effects	**1.74**	**1.60–1.89**
Hodgkin's lymphoma	7 [18, 19, 72, 77, 83–85]	229 367	<0.001	87.7	Random effects	**7.00**	**3.84–12.73**
NHL	3 [83, 85, 87]	109 826	<0.001	98.7	Random effects	1.63	0.50–5.32
Leukemia	6 [18, 19, 72, 78, 83, 85]	117 487	<0.001	97.0	Random effects	**3.21**	**1.51–6.83**
Nonlymphocytic leukemia	9 [18, 23, 76–79, 83, 84, 87]	197 456	<0.001	96.1	Random effects	**11.1**	**4.67–26.25**

Pooled RRs and relative 95% CIs were from fixed- or random-effects models according to the results of Cochran's *Q* test and the I^2 value. The pooled-RR in bold were statistically significant.

[a]The study by André et al. [17] reported a lung cancer RR for men only.

NHL, non-Hodgkin's lymphoma; RR, relative risk; CI, confidence intervals.

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Table 4. Stratified analysis of pooled relative risks (RR) of second malignancy according to treatment

Treatment	No. of studies (reference)	Heterogeneity statistics		Model used	Pooled effect	
		Q test (*P* value)	I^2, %		RR	95% CI
Chemotherapy, any type of drugs[a,b]						
All malignancies	7 [18, 19, 73–76, 78]	<0.001	80.5	Random effect	**1.49**	**1.11–2.10**
Solid tumors	3 [18, 19, 76]	0.317	13.1	Fixed effect	**1.10**	**1.07–1.13**
Alkylating[b]						
All malignancies	2 [18, 73]	0.802	0.0	Fixed effect	**1.43**	**1.07–1.90**
Solid tumors	0					
CHOP or CHOP-like[b]						
All malignancies	4 [17, 18, 74, 76[c]]	<0.001	84.0	Random effect	1.28	0.79–2.05
Solid tumors	3 [17, 21, 76[c]]	<0.001	91.1	Random effect	1.16	0.58–2.30
Radiotherapy, only therapy						
All malignancies	4 [18, 75, 76, 78]	<0.898	0.0	Fixed effect	1.18	0.84–1.64
Solid tumors	2 [18, 76]	<0.514	0.0	Fixed effect	1.23	0.88–1.70
Additional radiotherapy to any type of chemotherapy						
All malignancies	8 [18, 19, 73–76, 78, 80[d]]	<0.001	77.6	Random effect	**1.50**	**1.03–2.20**
Solid tumors	5 [18, 19, 21, 72, 80[d]]	<0.001	87.5	Random effect	1.29	0.87–1.92

[a]The analysis on any type of chemotherapy presents the results derived from studies for which we were able to trace the RR only for this type of therapy; thus, we did not include the RR calculated in the studies by André et al. 2004 [17], Bluhm et al. [21], and Moser et al. [72] because a part of patients was treated also with radiotherapy.

[b]The RR reported in the studies used to estimate the pooled RR for specific chemotherapeutic agents (alkylating and CHOP or CHOP-like) can include a proportion of patients undergoing radiotherapy.

[c]The study by Lavey et al. [76] included a part of patients that did not receive Anthracycline.

[d]The study by Guadagnolo et al. [80] was included among studies analyzed in the group of patients treated with local radiotherapy after chemotherapy because only six patients (6%) received extended-field radiotherapy or low-dose total body irradiation.

RR, relative risk; CI, confidence interval; CHOP, cyclophosphamide, adriamycin, vincristine, and prednisolone. The pooled-RR in bold were statistically significant.

risk for SMNs using the RR reported in each study, discriminating on the basis of the proportion of patients undergoing TBI (Figure 5). We found a significantly increased risk for SMNs for exposed and unexposed patients; however, the risk estimated among the studies including patients undergoing TBI was higher.

discussion

This meta-analysis was designed to estimate the risk for SMNs in patients with a history of NHL. Our goals were to evaluate the RR for overall and solid SMNs, to assess site-associated RR, and to estimate the risk related to treatment modality. We showed that NHL survivors face a 1.88-fold increased risk for SMNs in comparison with the general population. When the analysis was restricted to solid tumors, we also observed an increased risk that resulted associated with younger age of patients. A statistically significant increase in risk was also found for several specific cancer types. Finally, we assessed association between treatment exposure and risk for SMNs, although we could not explore this aspect in detail because treatment information was ill described for some studies as also chemotherapy dose schedule. We found evidence of effects to exposure to chemotherapeutic agents, especially alkylating agents, alone or in combination with radiotherapy. Furthermore, a stronger association with risk for SMNs was observed for patients undergoing TBI.

Our meta-analysis faces specific limitations. First, we did not search for unpublished studies, and we imposed limits on the computerized literature search, such as publication in the English language. However, the likelihood of publication bias in our results is small and not statistically significant. Secondly, we observed a very large heterogeneity among the studies. We can suggest various explanations for this variability, such as study design, NHL histology, period of recruitment, duration of follow-up, geographical and genetic variations, and therapies utilized, but we were unable to account for all these variables. Moreover, studies included in our analysis recruited patients over an extended time period (1935–2004), and great changes occurred in therapeutic regimes during this time. Furthermore, when we carried out the analysis for risks for specific cancer types, we found that tumors were coded according to different revisions of the International Classification of Diseases and grouped in categories that were not always homogeneous.

The strengths of our study include the use of rigorous systematic review and meta-analysis techniques to retrieve and pool data. We incorporated diverse data sources, including data from observational studies, which may obviate the risk that

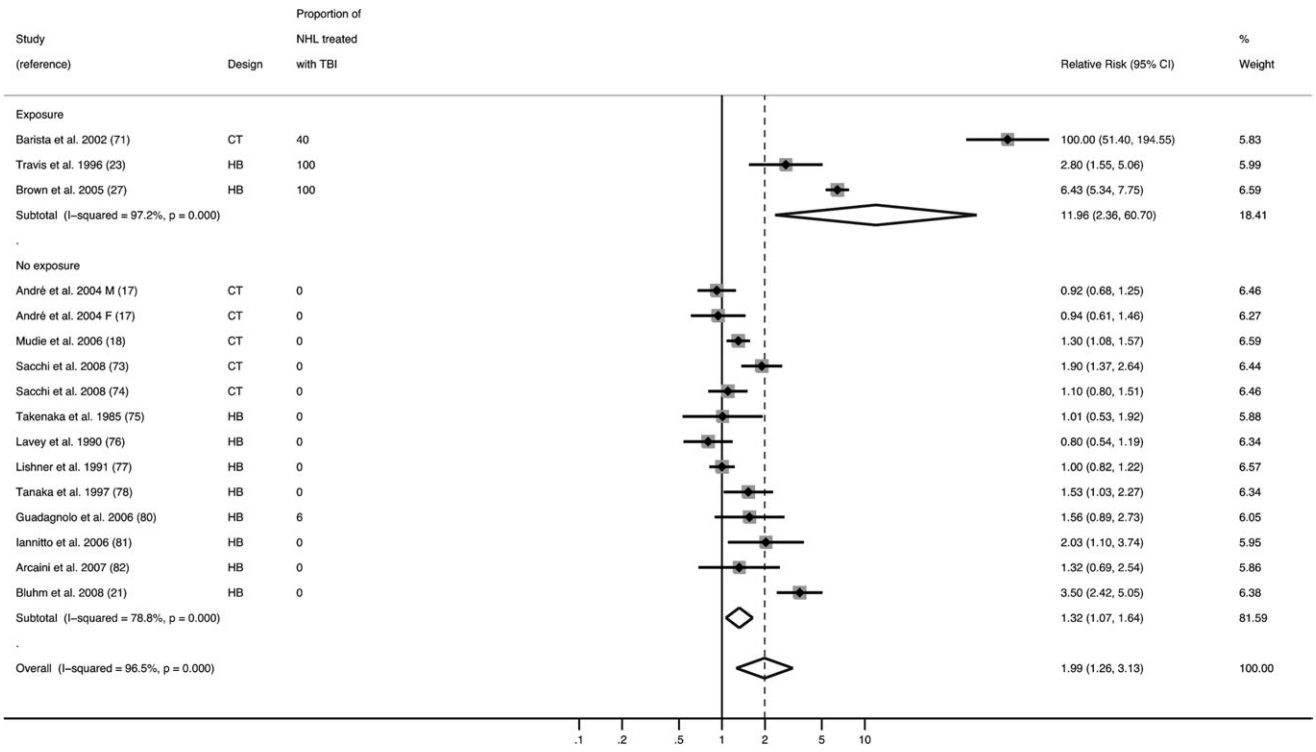

Figure 5. Forest plot of relative risk of secondary malignancy in non-Hodgkin's lymphoma survivors according to exposure to total body irradiation (TBI). Squares represent the relative risk of each single study (size of the square reflects the study-specific statistical weight); horizontal lines represent 95% confidence intervals (CIs); diamonds represent the pooled estimates, based on the random-effects meta-analysis of the studies, with corresponding 95% CIs. [†]The study by Guadagnolo et al. [80] was included among studies that provided an estimate of relative risk for patients without exposure to TBI because only six patients (6%) received extended-field radiotherapy or low-dose TBI. F, female; M, male; CT, data from clinical trials; HB, data from hospital- or specialist center-based studies; PB, data from population-based studies.

clinical trial results may not be generalized to wider groups of patients [88]. Finally, our estimates of pooled RR for all and solid SMNs were substantially robust across sensitivity analyses.

Several explanations may account for our demonstration of a higher overall risk of developing SMNs in NHL survivors in comparison with the general population. First, risk of therapy-associated effects in NHL survivors may contribute to increased RR. It is well known that an excess risk for bladder cancer and acute nonlymphocytic leukemia in NHL survivors is associated with alkylating agent therapy [13, 14, 16]. This chemotherapeutic agent produces DNA damage, and several DNA lesions are mutagenic, contributing to cellular transformation [89]. In our meta-analysis, we found a significant association between risk for SMNs and alkylating treatment.

The relationship between radiation therapy and SMNs is not completely clarified. Radiation therapy could trigger a multistage mechanism of carcinogenesis, significantly increasing the risk for specific types of tumors [34]. We did not find a positive significant association with SMNs, but our analysis did not consider dose, field size, treatment site, and patient age. Previous studies suggest that low-dose TBI followed by salvage chemotherapy including alkylating agents may have synergistic leukemogenic effects [23, 32]. In our analysis of all malignancies, including the data on TBI treatment resulted in a positive association with the increase of pooled RR for SMNs.

In addition to late effects of cancer therapy, other factors such as genetic instability may play simultaneous and causal roles [32, 89]. Friedman et al. [90] studied the increased risk for cancer among siblings of long-term childhood cancer survivors and discovered a statistically significant risk of 1.8 for siblings of NHL probands. In contrast, Landgren et al. [91] did not observe an excess of risk for SMNs among NHL patients with positive family histories of cancer with respect to patients lacking the family history. The contribution of shared environmental influences may be a third explanation for the high RR observed. For example, smoking is an important environmental risk factor for lung cancer, and several studies have found that patients treated for lymphoma with history of smoking had a greater risk for the development of lung cancer [92, 93]. Furthermore, Moser et al. [72] in a multivariate analysis of occurrence of SMNs have highlighted the role of tobacco use as an additional risk factor for developing SMNs, as well as of CHOP-like chemotherapy and age.

Some studies argued that the risk for SMNs after NHL appeared to be age related [18, 72, 77, 85]. We found that a younger age at NHL diagnosis was significantly associated with the risk for SMNs for solid tumors, while the RR for all malignancy increased but was not statistically significant. In contrast, a longer follow-up could allow the emergence of neoplasms with long latencies. We also consider other age-related explanations for our observation, such as the higher susceptibility of children to the mutagenic effects of therapy and the prevalence of cell proliferation during the early stages of development [94].

In conclusion, to the best of our knowledge, this is the first meta-analysis of SMNs in NHL survivors. Our results demonstrate that these patients experience a higher risk for SMNs than the general population and stressed the possible carcinogenic effect of chemotherapy and combined-modality therapy. To clarify the underlying mechanisms involved, it would be necessary to obtain more information on the treatments and dose schedule used. Additionally, it is important to consider the complexity of a study addressing possible interactions with genetic susceptibility and environmental exposures.

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disclosure

The authors declare no conflict of interest.

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