Risk of second breast cancer in female Hodgkin’s lymphoma survivors: a meta-analysis

Ezzeldin M Ibrahim1†, Khaled M Abouelkhair1, Ghieth A Kazkaz1, Osama A Elmasri1 and Meteb Al-Foheidi2†

Abstract

Background: Women treated for Hodgkin’s lymphoma (HL) have an elevated risk of developing second breast cancer (SBC) compared with the general population. We planned this meta-analysis to quantify the long-term risk of SBC and analyze the contributing risk factors among HL survivors.

Methods: According to predefined selection criteria, literature search identified 34 studies that were included in the analyses.

Results: After eliminating overlapping or duplicate data, 957 incidences of SBC were encountered in 24,505 females with HL over a median follow-up of 14.9 years. The medians: age at the diagnosis of HL, age at diagnosis of SBC, and latency since HL treatment to the development of SBC were 23.7, 35.0, and 17.7 years, respectively. The pooled relative risk (RR) of SBC was 8.23 (95% CI, 5.43-12.47, $I^2 = 96\%$), with a median absolute excess rate of 22.9 per 10,000 person-years. The RR was found inversely related to age at diagnosis of HL with the highest rate (68.7; [95%CI, 28.08-168.11], $I^2 = 79\%$), occurred in young patients ($\leq 15$ years old), where the RR in older women ($\geq 40$ years old) was not significant (0.55; [95% CI, 0.09-3.52]). Analysis of RR by 5-year increments since the treatment of HL showed that the risk was highest after 15–19 years of latency (13.87; [95% CI, 7.91-24.30], $I^2 = 89\%$). Analysis of the effect of treatment modalities showed that the RR rates were (4.70; [95% CI, 3.28-6.75], $I^2 = 74\%$), (5.65; [95%CI, 2.94-10.88], $I^2 = 91\%$), and (1.19; [95% CI, 0.50-2.82], $I^2 = 65\%$), for radiotherapy (RT) only, combined RT and chemotherapy (CT), and CT only, respectively. To investigate the demonstrated heterogeneity, meta-regression analysis was performed when feasible. In most such analyses, the natural logarithm of RR was inversely associated with age at HL diagnosis.

Conclusions: We conclude that, the current meta-analysis provided the most recent comprehensive estimate of the risk of SBC in a broad-range of HL survivors. Younger age at diagnosis proved to be a dominant risk factor. The obtained results would serve providing breast cancer screening recommendations for HL survivors.

Background

Hodgkin’s lymphoma (HL) became a curable disease by radiation therapy (RT) and/or combination chemotherapy (CT) since the early 70s [1-3]. Long-term disease-free survival of 70% to 90%, depending on stage at diagnosis has been achieved [4], and even more favorable outcome has been demonstrated in pediatrics, with a 5-year survival exceeding 90% [5].

However, increased risk of second cancer following effective treatment of HL has long been reported [6]. More recently, second neoplasms after HL are being encountered with increasing frequency due to the marked improvement in survival [2,7]. The particular elevated risk of second breast cancer (SBC) among this population is not surprising in view of the reported excess risks of breast cancer (BC) after incidental low doses of ionizing radiation [8,9], therapeutic RT [10,11], or as sequelae of the carcinogenic effects of CT [12,13].

Two pertinent meta-analyses have been published and they have addressed different questions. The first meta-analysis was published in 2006 and examined all second malignancy risk associated with HL treatment in 31 randomized trials and it included 65 incidence of SBC [14]. In the second meta-analysis [15], SBC risk and BC surveillance were investigated in young females ($\leq 30$ years at the primary tumor diagnosis) receiving moderate to high doses of RT targeted to mantle and modified

---

* Correspondence: ezziabrahim@imc.med.sa
† Equal contributors
1 Oncology Center of Excellence, International Medical Center, PO Box 2172, Jeddah 21451, Saudi Arabia
Full list of author information is available at the end of the article

© 2012 Ibrahim et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
mantle fields, mediastinum, lung, and thorax [15]. The latter meta-analysis comprised 11 studies that were not restricted to patients with HL but included all primary neoplasms in that age group.

Research on the late consequences of HL has often been limited by the size and composition of the study populations and by the duration and completeness of patient follow-up. To the best of our knowledge, there is no recently published meta-analysis intended to examine the risk of SBC in a broad range of ages at HL diagnosis, various follow-up periods, and subsequent to different therapeutic modalities. Also not precisely known, is the effect of other contributing risk factors. The lack of such data has prompted the current meta-analysis.

Methods
Search strategy
Between January 1966 and October 2011, we identified studies of interest by first conducting an electronic literature search of the databases MEDLINE, EMBASE, and the Cochrane Library. We also searched for relevant abstracts in the annual conference proceedings between January 1984 to October 2011 for the American Society of Clinical Oncology, European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium. All ages of HL patients were eligible for inclusion.

We used exploded Medical Subject Heading terms or key words terms 'lymphoma,' 'Hodgkin,' 'Hodgkin’s disease' and 'Hodgkin’s lymphoma'. The terms were combined with 'neoplasm, second neoplasm, second primary' using the Boolean operator ‘and’. Search results were also filtered against the terms 'breast, breast cancer, breast neoplasm). In the second step, these keywords were combined using the Boolean operator ‘and’ with 'standardized incidence ratio,' 'relative risk,' and 'observed to expected'. In addition, we manually reviewed the reference lists of relevant studies to identify additional pertinent published articles.

Selection criteria
We included studies that met each of following criteria: (i) published in English language between January 1985 and October 2011; (ii) included naive patients at any age and with any stage of HL; (iii) investigated the risk for second malignant neoplasms (SMNs) in HL survivors; (iv) reported relative risk (RR) and/or specified as standardized incidence ratios (SIR) or data allowing such outcomes to be derived; and (v) published as original articles (no case reports, case series, reviews, comments, letters, or editorials).

When two or more references reported duplicate data, we only included in the analysis the most recent data, studies with the longer follow-up, or the most relevant studies. We excluded studies that mainly addressed the clinical characteristics of SBC. We also excluded studies that mainly intended to evaluate the potential benefits and harms associated with breast cancer surveillance among women with HL. Case–control designs, i.e. HL patients who developed BC compared with patients who did not were excluded.

Data extraction
Two authors (KMA, and GAK) independently inspected each reference title identified by the search and applied the inclusion criteria. For possibly relevant articles and in cases of disagreement between reviewers, the full article was obtained and inspected independently by the five authors. The data intended for extraction were discussed, and decisions were documented. We used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting criteria to assess the quality of studies included in the meta-analysis [16]. Any significant lack of concordance in the scores assigned by authors was discussed to reach a consensus.

Standardized Excel sheet was used for each study that fulfilled the inclusion criteria. 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 HL patients, mean/median age of patients, mean/median duration of follow-up, therapy details, number of observed and expected SBC cases, and RR or standardized-incidence rate (SIR) with corresponding 95% confidence interval (CI). The ratio of observed to expected numbers of cancers, SIR (referred to in the text as RR) was then used or calculated with likelihood-based 95% CI from Poisson models [17]. Where not reported, we computed the CI for the risk assuming a Poisson distribution for the observed number of cases. Standard error (SE) for the natural logarithm of RR (lnRR) was derived from CI, applying the following equation: \( SE = \ln(upper\ 95\%\ CI/\ lower\ 95\%\ CI)/(2 \times z_{1 - \alpha/2}) \). When appropriate, we also used the built-in calculator of the Review Manager Software (version 5.1.4 for Windows; The Cochrane Collaboration, Oxford, UK) to compute missing data. 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 allow computation of an estimate of the lnRR and its associated SE [18].

Outcome measures
The primary outcome was the overall pooled RR of incidence of SBC among women survivors of HD. The secondary end points were RR vs. various variables: source of data, age at diagnosis of HD, length of follow-up, treatment modalities, and any additional relevant risk factors. RT in this meta-analysis is referred to supra-diaphragmatic irradiation with or without other radiation fields.
Statistical analyses
We assessed heterogeneity of the studies’ results by inspecting graphical presentations and by calculating an
χ² test of heterogeneity and the I² statistic of inconsist-
ence [19,20]. Statistically significant heterogeneity was
defined as a χ² P value less than .1 or an I² statistic
greater than 50%. The estimates of RR, together with
associated 95% CI, were obtained using the DerSimonian
and Laird random-effects model [21]. Meta-regression
analysis was performed to determine to what extent the
heterogeneity is explained by various covariates using
IBM SPSS statistical package v.19. The dependent vari-
able was the lnRR weighted for the inverse of variance
to perform weighted least square linear regression. We
first conducted a univariate regression analysis for each
variable followed by a multivariate regression including
variables found significant in the univariate analysis.

Subgroup analyses were performed to assess potential
contributions of various clinical variables to outcomes.
A funnel plot estimating the precision of trials (plots of
logarithm of the RR against the sample size) was exam-
ined for asymmetry to estimate publication bias [22].
Publication bias was also quantified by the regression
asymmetry test by Egger [22].

All statistical tests were two-sided. RR was estimated
according to the inverse of variance method with the
use of Review Manager Software v5.1.4.

Results
Search results
We identified 1,647 potentially relevant articles (Figure 1).
After exclusion of duplicate references, none-relevant lit-
erature, and those that did not satisfy inclusion criteria,
41 candidate articles were considered for the meta-an-
alysis [23-62]. After careful review of the full text of these
articles, 7 studies were excluded. In 5 studies the RR was
reported based on case–control design, i.e. HL patients
who developed SBC against patients who did not
[33,43,47,63,64]. The RR in the sixth excluded study
was computed instead and it showed that patients with
HL have an almost 9-fold increase in the risk of SBC
(RR = 8.23; [95% CI, 5.43-12.47], I² = 96%). We performed
meta-regression analysis to determine to what extent the
heterogeneity is explained by the effects of study size, age
at HL diagnosis, and the latency since the completion of
HL treatment. The univariate analysis showed significant
inverse association between lnRR and age at diagnosis and
a positive relation to latency since HL treatment. With
multivariate analysis (Table 3), only younger age at diag-
nosis remained significant (<0.0001).
In Figure 3, the random-effects analysis illustrates a higher risk in institutional studies (RR = 8.86; [95% CI, 5.26-14.94]) compared with population-based analyses (6.70; [95% CI, 4.07-11.03]). The demonstrated heterogeneity ($I^2 = 96\%$) was explored by meta-regression analysis, however, none of the variables tested was found associated with lnRR in the univariate analysis (data not shown).

**RR and age at diagnosis of HL**

The excess risk of SBC as a function of age at diagnosis of HL was also explored. Figure 4 (random-effects model) shows that the RR of developing SBC decreased significantly with increasing age at diagnosis from 68.7 (95% CI, 28.8-168.11, ≤ 15 years old) to 22.32 (95% CI, 13.4-37.16, 15–19 years old), 14.43 (95% CI, 11.65-17.88, 20–24 years old), and 6.6 (95% CI, 4.24-10.29, 25–29 years old). As a significant heterogeneity was shown ($I^2 = 79\%$), we performed a meta-regression analysis, however, none of the explanatory variables was found significant (data not shown).

Several studies reported the RR at certain cut points of age at diagnosis and it also showed an inverse relation between risk and age (Figure 5, fixed-effects model). In the latter analysis and contrary to analysis of RR against more age intervals, no significant heterogeneity was noted ($I^2 = 41\%$). Of note, the RR of SBC for women who developed HL above the age of 40 years was not significant (RR = 0.55; [95% CI, 0.09-3.52]).

**RR and follow-up latency**

We performed analysis of RR by 5-year increments since the treatment of HL (Figure 6, random-effects model, $I^2 = 73\%$). By and large, the analysis demonstrated an
| Author & Year | Country       | Year       | Design                                      | Source of data                           | STROBE criteria (met/applicable) | RT only No. (%) | CTX only No. (%) | RT-CTX No. (%) | Comments                                                                 |
|---------------|---------------|------------|---------------------------------------------|------------------------------------------|---------------------------------|----------------|-----------------|----------------|---------------------------------------------------------------------------|
| Coleman 1987  | UK            | 1961-1980  | PBCS.                                       | Cancer registry                          | 25/32                          | (35–36)        | (20–28)         | (27–34)        | Therapy data for M+F HL patients. Number NR.                               |
| Hancock 1993  | USA           | 1961–1989  | Single institution cohort study             | Computerized database and patient records | 24/31                          | 383 (43)       | 30 (3)          | 341 (39)       | Therapy data for M+F HL patients. 15% did not receive any treatment.       |
| Walden 1998   | USA           | 1960-1995  | Single institution cohort study (HL Dx. ≤21y) | Computerized database and patient records | 22/31                          | 144 (47)       | 9 (3)           | 154 (50)       | Therapy data for female patients                                          |
| Walden 2000   | USA           | 1960-1997  | Single institution retrospective review      | Computerized database and patient records | 24/32                          | 37 (57)        | 1 (2)           | 27 (41)        | Therapy data for SBC patients. 27 patients received alkylating CTX.       |
| O'Brien 2010  | USA           | 1970-1990  | Single institution study of children        | Retrospective chart review and patient questionnaires | 23/31                          | 0 (0)          | 0 (0)           | 35 (100)       | Therapy data for M+F pediatric HL patients. All received low-dose RT and alkylating CTX. |
| van Leeuwen   | Netherlands   | 1966-1986  | 2 institutions cohort study                | Institutional registries and patient records | 22/30                          | 552 (29)       | 178 (9)         | 1209 (62)      | Therapy data for M+F HL patients. All SBC received RT.                    |
| De Bruin 2009 | Netherlands   | 1965-1995  | 6 institutions cohort study (5y survivors)  | Medical records, and physician questionnaires | 25/32                          | 357 (31.8)     | 80 (7.1)        | 685 (61.1)     | Therapy data for all HL female patients                                   |
| Mauch 1996    | USA           | 1969-1988  | 5 institutions cohort study                | Institutional records                     | 25/31                          | 489 (62)       | 0 (0)           | 305 (38)       | Therapy data for M+F HL patients                                          |
| Ng 2002       | USA           | 1969–1997  | 4 institutions cohort study                | Institutional records                     | 26/32                          | 665 (69)       | 0 (0)           | 296 (31)       | Therapy data for M+F HL patients                                          |
| Sankila 1996  | Nordic countries | 1940-1987 | 5 Nordic PBCS (HL Dx. ≤20y)                | National cancer registries               | 21/31                          | NR             | NR              | NR             | All SBC patients received RT                                              |
| Metayer 2000  | USA and Europe| 1935–1994 | 16 PBCS (HL Dx. ≤21y, 1-year survivors)     | National cancer registries               | 22/32                          | NR             | NR              | NR             | First raw: therapy data for M+F HL patients. (27% with unknown treatment). Second raw: therapy data for SBC patients (28% with unknown treatment) |
| Hodgson 2007  | USA and Europe| 1970-2001 | 13 PBCS (5-year survivors)                 | National cancer registries               | 22/32                          | 6461 (34)      | 4398 (23)       | 2847 (15)      | First raw: therapy data for M+F HL patients. All patients had RT          |
| Dores 2010    | USA           | 1973-2000  | 9 PBCS (5-year survivors, Dx. ≥35y)         | 9 cancer registry areas of SEER          | 22/32                          | NR             | NR              | NR             | All patients had RT                                                       |
| Aisenberg 1997| USA           | 1964-1984  | Single institution cohort study             | Review of patient records                | 21/31                          | 10 (71)        | 0 (0)           | 4 (29)         | Therapy data for SBC patients (4 patients had alkylating CTX)             |
| Alm El-Din 2009| USA          | 1964-2001  | Single institution cohort study             | Review of patient records                | 21/31                          | 130 (52)       | 0 (0)           | 118 (48)       | First raw: therapy data for all patients (26% had alkylating CTX) Second raw: therapy data for SBC (22% had alkylating CTX) |
| Hudson 1998   | USA           | 1968-1990  | Single institution                        | Review of patient records                | 21/30                          | 116 (30)       | 15 (4)          | 256 (66)       | Therapy data of M+F HL patients                                           |
| Gervais-Fagnou | Canada       | 1965-1990  | Single institution cohort study (HL Dx. at ≤30y) | Review of patient records                | 22/30                          | 225 (55)       | 0 (0)           | 186 (45)       | Therapy data of M+F HL patients                                           |
| Year       | Country | Study Period | Design                                      | Source of Data                                                                 | Study Quality | Hodgkin’s lymphoma therapy details of the 34 studies included in the meta-analysis (Continued) |
|------------|---------|--------------|---------------------------------------------|-------------------------------------------------------------------------------|---------------|-------------------------------------------------------------------------------------------------|
| 1999       | Germany | 1974-1994    | 6 institutions cohort study                 | Munich tumor registry, patient records, and patient & family contact           | 24/31         | Therapy data of M+F HL patients (8/9 SBC patients received RT)                                  |
| 2000       | USA     | 1960-1989    | Single institution cohort study (HL ≤20y at Dx.) | Patient records and mail contact                                              | 24/30         | Therapy data for SBC patients                                                                   |
| 2000       | United Kingdom | 1963-1993 | BNLI (cohort study)                         | BNLI + 2 cancer databases                                                    | 24/31         | Therapy data of M+F HL patients (all SBC had RT)                                               |
| 2001       | Italy   | 1960-1991    | Single institution cohort study             | Institutional patient records                                                | 22/30         | Therapy data of M+F HL patients (SBC patients: 6% CTX only, 94% CTX + RT)                       |
| 2001       | USA and Canada | 1970-1986 | 25 institutions (CCSS) cohort study (≤21y at HL Dx., 5-year survivors) | Institutional patient records                                            | 26/32         | Therapy data were reported for all children malignancies combined                                |
| 2004       | USA and Canada | 1970-1986 | Same as Neglia et al. [40] | Institutional patient records                                                | 26/32         | Therapy data were reported for all children malignancies combined                                |
| 2011       | USA and Canada | 1970-1986 | Same as Neglia et al. [40] and Kenny et al. [46] | Institutional patient records                                                | 26/32         | Therapy data for all HL female patients                                                         |
| 2002       | Norway  | 1968-1985    | Single institution cohort study (HD ≥1 y survivors) | National cancer registry                                                      | 21/30         | Therapy data of M+F HL patients                                                                |
| 2003       | USA and Europe | 1955-1986 | 15 institutions cohort study               | Institutional patient records                                                | 26/33         | First raw: therapy data of M+F HL patients; Second raw: therapy data of SBC patients            |
| 2003       | USA     | 1950-1993    | Single institution cohort study             | Institutional patient records                                                | 23/31         | First raw: therapy data of M+F HL patients; Second raw: therapy data of SBC patients            |
| 2004       | Germany | 1981-1989    | Multi-Institutional cohort study            | German HL database                                                          | 23/31         | Therapy data of M+F HL patients                                                                |
| 2005       | UK and France | 1954-1985 | 8 institutions cohort study                | Institutional patient records                                                | 28/32         | Therapy data of M+F HL patients                                                                |
| 2007       | UK      | 1940-1991    | PBCS                                        | National Registry of Childhood Tumors                                        | 22/31         | Therapy data of female HL patients; First raw: therapy data of female HL patients               |
| 2008       | USA     | 1960-1990    | 5 institutions cohort study (<19y at HL Dx.) | Institutional patient records                                                | 22/31         | First raw: therapy data of M+F HL patients; Second raw: therapy data of SBC patients            |
| 2009       | UK      | 1965-2008    | Cohort from a registry and single institution | Institutional patient records and a registry data                             | 27/31         | Therapy data of SBC patients                                                                   |
| 2007       | USA     | 1973-2002    | PBCS (<18y at Dx.)                          | SEER database                                                                | 29/31         | Therapy data of SBC patients                                                                   |

BNLI: British National Lymphoma Investigation, CCSS: Childhood Cancer Survivors Study, Dx.: diagnosis, HL: Hodgkin’s lymphoma, M+F: males and females, NR: not reported or data could not be calculated, PBCS: population-based cohort study, RT: radiotherapy that included supra-diaphragmatic irradiation, SBC: second breast cancer, SEER: Surveillance Epidemiology and End Results, STROBE: Strengthening the Reporting of Observational Studies in Epidemiology, y: year. (studies shaded together represent overlapping data).
| Author & Year | Country     | Year        | Design                      | Source of data                  | STROBE criteria (met/applicable) | RT only No. (%) | CTX only No. (%) | RT-CTX No. (%) | Comments |
|---------------|-------------|-------------|-----------------------------|---------------------------------|---------------------------------|----------------|-----------------|----------------|----------|
| Coleman 1987  | UK          | 1961–1980   | PBCS. Cancer registry       |                                 | 25/32                          | (35–36)        | (20–28)         | (27–34)        | Therapy data for M + F HL patients. Number NR. |
| Hancock 1993  | USA         | 1961–1989   | Single institution          | Computerized database           | 24/31                          | 383 (43)       | 30 (3)          | 341 (39)       | Therapy data for M + F HL patients. 15% did not receive any treatment. |
| Wolden 1998   | USA         | 1960–1995   | Single institution          | Computerized database           | 22/31                          | 144 (47)       | 9 (3)           | 154 (50)       | Therapy data for female patients |
| Wolden 2000   | USA         | 1960–1997   | Single institution          | Computerized database           | 24/32                          | 37 (57)        | 1 (2)           | 27 (41)        | Therapy data for SBC patients. 27 patients received alkylating CTX. |
| O’Brien 2010  | USA         | 1970–1990   | Single institution          | Retrospective chart review      | 23/31                          | 0 (0)          | 0 (0)           | 35 (100)       | Therapy data for M + F pediatric HL patients. All received low-dose RT and alkylating CTX. |
| van Leeuwen 1994 | Netherlands | 1966–1986   | 2 institutions cohort study | Institutional registries and    | 22/30                          | 552 (29)       | 178 (9)         | 1209 (62)      | Therapy data for M + F HL patients. All SBC received RT. |
| De Bruin 2009 | Netherlands | 1965–1995   | 6 institutions cohort study | Medical records, and physician  | 25/32                          | 357 (31.8)     | 80 (7.1)        | 685 (61.1)     | Therapy data for all HL female patients |
| Mauch 1996    | USA         | 1969–1988   | 5 institutions cohort study | Institutional records           | 25/31                          | 489 (62)       | 0 (0)           | 305 (38)       | Therapy data for M + F HL patients |
| Ng 2002       | USA         | 1969–1997   | 4 institutions cohort study | Institutional records           | 26/32                          | 665 (69)       | 0 (0)           | 296 (31)       | Therapy data for M + F HL patients |
| Sankila 1996  | Nordic countries | 1940–1987   | 5 Nordic PBCS               | National cancer registries      | 21/31                          | NR             | NR              | NR             | All SBC patients received RT |
| Metayer 2000  | USA and Europe | 1935–1994   | 16 PBCS (HL Dx. ≤21y, 1-year survivors) | National cancer registries | 22/32                          | NR             | NR              | NR             | First raw therapy data for M + F HL patients. (27% with unknown treatment). Second raw therapy data for SBC patients (28% with unknown treatment) |
| Hodgson 2007  | USA and Europe | 1970–2001   | 13 PBCS (5-year survivors)  | National cancer registries      | 22/32                          | 6461 (34)      | 4398 (23)       | 2847 (15)      | All patients had RT |
| Dores 2010    | USA         | 1973–2000   | 9 PBCS (5-year survivors, Dx. ≤35y) | 9 cancer registry areas of SEER | 22/32                          | NR             | NR              | NR             | Therapy data for SBC patients (4 patients had alkylating CTX) |
| Aisenberg 1997 | USA         | 1964–1984   | Single institution cohort study | Review of patient records | 21/31                          | 10 (71)        | 0 (0)           | 4 (29)          | Therapy data for SBC patients (4 patients had alkylating CTX) |
| Study                        | Country          | Year     | Study Design/Details                                      | Data Collection Methods | Patients | First raw: therapy data for all patients (26% had alkylating CTX) | Second raw: therapy data for SBC (22% had alkylating CTX) |
|-----------------------------|------------------|----------|-----------------------------------------------------------|-------------------------|----------|-----------------------------------------------------------------|----------------------------------------------------------|
| Alm El-Din 2009 [54]        | USA              | 1964-2001| Single institution cohort study                           | Review of patient records | 21/31    | 130 (52)                                                        | 118 (48)                                                 |
| Hudson 1998 [29]            | USA              | 1968-1990| Single institution                                       | Review of patient records | 21/30    | 116 (30)                                                        | 256 (66)                                                 |
| Gervais-Fagnou 1999 [31]    | Canada           | 1965-1990| Single institution cohort study                           | Review of patient records | 22/30    | 225 (55)                                                        | 186 (45)                                                 |
| Munker 1999 [32]            | Germany          | 1974-1994| 6 institutions cohort study                              | Munich tumor registry, patient records, and patient & family contact | 24/31    | 484 (43.1)                                                      | 464 (41.4)                                               |
| Green 2000 [34]             | USA              | 1960-1989| Single institution cohort study                           | Patient records and mail contact | 24/30    | 1 (25)                                                          | 3 (75)                                                   |
| Swerdlow 2000 [36]          | United Kingdom   | 1963-1993| BNLI (cohort study)                                       | BNLI + 2 cancer databases | 24/31    | 1449 (27)                                                      | 2327 (42)                                                |
| Swerdlow 2011 [62]          | United Kingdom   | 1963-2001| BNLI (cohort study)                                       | BNLI database (70 institutions) | 25/31    | 0 (0)                                                           | 3432 (59)                                                |
| Cellai 2001 [38]            | Italy            | 1960-1991| Single institution cohort study                           | Institutional patient records | 22/30    | 546 (36)                                                        | 653 (43)                                                 |
| Neglia 2001 [39]            | USA and Canada   | 1970-1986| 25 institutions (CCSS) cohort study (≤21y at HL Dx., 5-y survivors) | Institutional patient records | 26/32    | NR                                                              | NR                                                       |
| Kenney 2004 [45]            | USA and Canada   | 1970-1986| Same as Neglia et al. [40]                                | Institutional patient records | 26/32    | NR                                                              | NR                                                       |
| Castellino 2011 [59]        | USA and Canada   | 1970-1986| Same as Neglia et al. [40] and Kenny et al. [46]          | Institutional patient records | 26/32    | 263 (33)                                                        | 472 (60)                                                 |
| Foss Abrahamsen 2002 [40]   | Norway           | 1968-1985| Single institution cohort study                           | National cancer registry | 21/30    | 447 (44)                                                        | 363 (36)                                                 |
| Bhatia 2003 [42]            | USA and Europe   | 1955-1986| 15 institutions cohort study                              | Institutional patient records | 26/33    | 314 (23)                                                        | 960 (69)                                                 |

**Note:** Therapy data for M + F HL patients.

**Table 2 Clinical characteristics of the 34 studies included in the meta-analysis (Continued)**
Table 2 Clinical characteristics of the 34 studies included in the meta-analysis (Continued)

| Study                          | Country     | Period     | Study Design                      | Data Source                          | First raw: therapy data of M + F HL patients | Second raw: therapy data of SBC patients |
|-------------------------------|-------------|------------|-----------------------------------|--------------------------------------|---------------------------------------------|------------------------------------------|
| Wahner-Roedler 2003 [44]      | USA         | 1950-1993  | Single institution cohort study   | Institutional patient records         | 23/31                                       | 23/31                                    |
|                              |             |            |                                   |                                      | 32 (77)                                    | 7 (23)                                   |
| Behringer 2004 [60]           | Germany     | 1981-1989  | Multi-Institutional cohort study  | German HL database                    | 23/31                                       | 28/32                                    |
|                              |             |            |                                   |                                      | 675 (12.9)                                 | 28 (23)                                  |
| Guibout 2005 [46]             | UK and France| 1954-1985  | 8 institutions cohort study       | Institutional patient records         | 28/32                                       | 9 (7)                                    |
|                              |             |            |                                   |                                      | 28 (23)                                    | 86 (70)                                  |
| Taylor 2007 [51]              | UK          | 1940-1991  | PBCS                              | National Registry of Childhood Tumors | 22/31                                       | 121 (37)                                 |
|                              |             |            |                                   |                                      | 121 (37)                                   | 138 (43)                                 |
| Basu 2008 [52]                | USA         | 1960-1990  | 5 institutions cohort study       | Institutional patient records         | 22/31                                       | 174 (44)                                 |
| Constine 2008 [53]            |             |            | (<19y at HL Dx.)                  |                                      | 37 (9)                                     | 187 (47)                                 |
| Howell 2009 [56]              | UK          | 1965-2008  | Cohort from a registry and single | Institutional patient records and a    | 27/31                                       | 6 (26)                                   |
|                              |             |            | institution                        | registry data                        |                                            | 17 (74)                                  |
| Inskip 2007 [61]              | USA         | 1973-2002  | PBCS (< 18y at Dx)                | SEER database                        | 29/31                                       | NR                                       |

*Absolute excess rate of SBC incidence cases per 10,000 person-years of follow-up. CI confidence interval, Cum. Cumulative, DCIS ductal carcinoma in-situ, HL Hodgkin’s lymphoma, MF males and females, NR not reported or data could not be calculated, O/E observed/expected, RR relative risk, SBC second breast cancer (unless indicated, all are invasive breast cancer), y year. (Studies shaded together represent overlapping data).
increasing RR by increased duration of follow-up latency reaching the highest after 15–19 years (RR = 13.87; [95% CI, 7.91-24.30]). While there was a decrease in RR noted after 20–24 years of follow-up, further rise occurred after 25–29 years. The latter rise may be attributed to the RR reported by De Bruin et al. [55], while all the other studies demonstrated a decreased RR after 25–29 years compared with that after 20–24 years of follow-up. Due to unreported data, meta-regression analysis of the heterogeneity could only include age at diagnosis of HL as the sole explanatory variable and it showed an inverse association with lnRR (Table 3).

After ≥20 years of latency since diagnosis, 9 studies [37,40,41,44,45,48,51,54,55] reported RR of 6.95 (95% CI, 4.8-10.1). That RR was not significantly different from the rate encountered after ≥30 years of follow-up (RR = 7.03; [95% CI, 5.2-9.5]) as reported from 5 studies [42,44,51,54,55].

**RR vs. Age at HL diagnosis and follow-up latency**

To examine the interaction of both age at HL diagnosis and length of follow-up versus risk, few studies have reported adequate data. De Bruin et al. [55] reported that after 5–14 years of follow-up, those who were ≤20 years at HL diagnosis had significantly higher risk (RR = 20.0; [95% CI, 7.3-43.4]) as compared with those who were older (21–30 years old) (RR = 5.3; [95% CI, 1.9-16.6]). Similarly, after ≥25 years of follow-up,

**Figure 2** Summary statistics and corresponding forest plot for the overall relative risk (RR) of second breast cancer as reported from 23 studies. RRs were calculated using a random-effects model.

| Study or Subgroup | log[Risk Ratio] | SE | Weight | Risk Ratio | Risk Ratio |
|-------------------|----------------|----|--------|------------|------------|
| Coleman 1987      | -0.69          | 0.69 | 3.1%   | 0.50       | [0.13, 1.94] |
| Sankila 1996      | 2.83           | 0.26 | 4.3%   | 16.95      | [10.08, 28.49] |
| Wilden 1998       | 3.27           | 0.26 | 4.3%   | 26.31      | [15.59, 44.40] |
| Hudson 1998       | 3.55           | 0.45 | 3.8%   | 33.12      | [13.55, 80.94] |
| Monk 1999         | 0.88           | 0.29 | 4.2%   | 2.41       | [1.34, 4.33] |
| Gervais-Fagnou 1999 | 2.36    | 0.27 | 4.3%   | 10.59      | [6.19, 18.12] |
| Wilden 2000       | 1.55           | 0.15 | 4.5%   | 4.71       | [3.55, 6.26] |
| Green 2000        | 2.05           | 0.57 | 3.5%   | 7.77       | [2.54, 23.79] |
| Swerdlov 2000     | 0.34           | 0.21 | 4.4%   | 1.40       | [0.82, 2.15] |
| Cellai 2001       | 0.72           | 0.26 | 4.3%   | 2.05       | [1.22, 3.46] |
| Foss Abrahamsen 2002 | 1.34    | 0.22 | 4.4%   | 3.82       | [2.46, 5.94] |
| Ng 2002           | 1.9            | 0.17 | 4.5%   | 6.69       | [4.79, 9.93] |
| Wahnner-Roedler 2003 | 1.06   | 0.18 | 4.5%   | 2.89       | [1.99, 4.18] |
| Bhatia 2003       | 4.02           | 0.16 | 4.5%   | 55.70      | [40.15, 77.27] |
| Behringer 2004    | 0.64           | 0.48 | 3.7%   | 1.90       | [0.73, 4.92] |
| Guibout 2005      | 4.26           | 0.51 | 4.3%   | 70.81      | [25.96, 193.16] |
| Hodgson 2007      | 1.81           | 0.12 | 4.6%   | 6.11       | [4.80, 7.78] |
| Taylor 2007       | 2.44           | 0.26 | 4.3%   | 11.47      | [6.84, 19.25] |
| Basu 2008         | 3.62           | 0.19 | 4.5%   | 37.34      | [25.48, 54.72] |
| De Bruin 2009     | 1.72           | 0.1  | 4.6%   | 5.46       | [4.59, 6.79] |
| Alm El-Din 2009   | 2.28           | 0.34 | 4.1%   | 9.78       | [4.95, 19.30] |
| Howell 2009       | 1.06           | 0.62 | 3.3%   | 2.89       | [0.84, 9.86] |
| O’Brien 2010      | 4.28           | 0.45 | 3.8%   | 72.24      | [29.67, 175.88] |
| Castellino 2011   | 2.83           | 0.11 | 4.6%   | 16.95      | [13.61, 21.11] |

**Table 3** The results of meta-regression analyses

| Model | Covariates | Meta-regression β coefficient (SE) | 95% CI of β coefficient | p value |
|-------|------------|-----------------------------------|-------------------------|---------|
| Pooled RR for included studies (Figure 2) | Age at HL diagnosis | -0.015 (0.015) | -0.137 to -0.072 | <0.0001 0.747 |
| Latency since HL treatment | -0.010 (0.031) | -0.075 to 0.055 | 0.001 |
| RR versus follow-up intervals (Figure 6) | Age at HL diagnosis | -0.036 (0.010) | -0.057 to -0.015 | 0.003 0.212 |
| Latency since HL treatment | -0.099 (0.027) | -0.157 to -0.041 | 0.061 |
| RR versus therapy modality (Figure 7): RT vs. RT + C vs. C | Age at HL diagnosis | -0.095 (0.073) | -0.251 to 0.061 | 0.003 0.212 |
| Chemotherapy, CI confidence interval, HL Hodgkin’s lymphoma, RR relative risk, RT radiotherapy, SE standard error. |
the corresponding RRs for younger and older patients were 14.2 (95% CI, 7.9-25.4), and 9.0 (95% CI, 4.9-16.5), respectively.

**RR and treatment modalities**

Figure 7 shows the random-effects model for the RR according to HL treatment modalities. Significant heterogeneity was demonstrated ($I^2 = 87\%$). RT used as the sole therapeutic modality was associated with an almost 5-fold increase in risk (RR = 4.70; [95% CI, 3.28-6.75]), $I^2 = 74\%$ and even higher rate (RR = 14.08; [95% CI, 9.93-19.98]) when RT was used for patients $\leq 30$ years of age [32,36,41]. Two studies [24,54], reported on the mantle field RT dose where there was a small difference in RR between dose $< 40$ Gy and $\geq 40$ Gy (5.99, and 6.13, respectively). In the first study [24], 1 patient per 567 person-years risk versus 23 patients per 7876 person-years developed SBC in the lower versus higher RT dose, respectively. In the second study, 17 of 135 versus 18 of 109 patients developed SBC in the lower versus higher RT dose, respectively [54]. When reported, almost all SBC arose within or at the margin of RT field.

Figure 7 also shows that adding any CT to RT numerically increased the risk as compared with the risk associated with RT only (RR = 5.65; [95% CI, 2.94-10.88], $I^2 = 91\%$). Nevertheless, adding alkylating CT to RT did not abate SBC risk (RR = 6.59; [95% CI, 1.72-25.20), while the combination of RT and non-alkylating CT caused a non-significant effect (RR = 4.40; [95% CI, 0.83-23.38]) (data not shown). Noteworthy, only a few studies

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio  | Risk Ratio  |
|-------------------|----------------|----|--------|-------------|-------------|
|                    |                |    |        | IV, Random, 95% CI Year | IV, Random, 95% CI |
| Hudson 1998        | 3.5            | 0.456 | 3.8%  | 33.12 [13.55, 80.94] 1998 |     |
| Munker 1999        | 0.88           | 0.299 | 4.2%  | 2.41 [1.34, 4.33] 1999 |     |
| Gervais-Fagnou 1999 | 2.36          | 0.274 | 4.3%  | 10.59 [6.19, 18.12] 1999 |     |
| Wolden 2000        | 1.55           | 0.145 | 4.5%  | 4.71 [3.55, 6.26] 2000 |     |
| Green 2000         | 2.05           | 0.571 | 3.4%  | 7.77 [2.54, 23.79] 2000 |     |
| Swardlow 2000      | 0.34           | 0.216 | 4.4%  | 1.40 [0.92, 2.15] 2000 |     |
| Cellai 2001        | 0.72           | 0.266 | 4.3%  | 2.05 [1.22, 3.46] 2001 |     |
| Foss Abrahamsen 2002 | 1.34          | 0.225 | 4.4%  | 3.82 [2.46, 5.94] 2002 |     |
| Ng 2002            | 1.9            | 0.158 | 4.5%  | 6.69 [4.91, 9.11] 2002 |     |
| Wahnner-Roessler 2003 | 1.06        | 0.189 | 4.5%  | 2.89 [1.99, 4.18] 2003 |     |
| Bhata 2003         | 4.02           | 0.167 | 4.5%  | 55.70 [40.15, 77.27] 2003 |     |
| Kenney 2004        | 2.88           | 0.152 | 4.5%  | 17.81 [13.22, 24.00] 2004 |     |
| Behringer 2004     | 0.64           | 0.486 | 3.7%  | 1.90 [0.73, 4.92] 2004 |     |
| Guibout 2005       | 4.26           | 0.512 | 3.6%  | 70.81 [25.96, 193.16] 2005 |     |
| Basu 2008          | 3.62           | 0.195 | 4.5%  | 37.34 [25.48, 54.72] 2008 |     |
| Howell 2009        | 1.06           | 0.627 | 3.3%  | 2.89 [0.84, 9.86] 2009 |     |
| Aim El-Din 2009    | 2.28           | 0.347 | 4.1%  | 9.78 [4.95, 19.30] 2009 |     |
| O’Brien 2010       | 4.28           | 0.454 | 3.8%  | 72.24 [29.67, 175.88] 2010 |     |
| Castellino 2011    | 2.83           | 0.112 | 4.6%  | 16.95 [13.61, 21.11] 2011 |     |
| **Subtotal (95% CI)** | **79.1%** | **8.86 [5.26, 14.94]** |          |                 |
| **Heterogeneity:** | Tau² = 1.24; | Chi² = 479.65, df = 18 (P < 0.00001); I² = 96% | Test for overall effect: Z = 8.19 (P < 0.00001) |     |
| Coleman 1987 | -0.69 | 0.691 | 3.1%  | 0.50 [0.13, 1.94] 1987 |     |
| Sankila 1996       | 2.83           | 0.265 | 4.3%  | 16.95 [10.08, 28.49] 1996 |     |
| Taylor 2007        | 2.44           | 0.264 | 4.3%  | 11.47 [6.84, 19.25] 2007 |     |
| Hodgson 2007       | 1.81           | 0.123 | 4.6%  | 6.11 [4.80, 7.78] 2007 |     |
| De Bruin 2009      | 1.72           | 0.1  | 4.6%  | 5.58 [4.59, 6.79] 2009 |     |
| **Subtotal (95% CI)** | **20.9%** | **6.70 [4.07, 11.03]** |          |                 |
| **Heterogeneity:** | Tau² = 0.25; | Chi² = 33.97, df = 4 (P < 0.00001); I² = 88% | Test for overall effect: Z = 7.47 (P < 0.00001) |     |
| Total (95% CI)     | **100.0%** | **8.11 [5.41, 12.17]** |          |                 |
| **Heterogeneity:** | Tau² = 0.92; | Chi² = 537.11, df = 23 (P < 0.00001); I² = 96% | Test for overall effect: Z = 10.11 (P < 0.00001) |     |
| **Test for subgroup differences:** | Chi² = 0.58, df = 1 (P = 0.45), I² = 0% |                 |     |

Figure 3 Summary statistics and corresponding forest plot for the relative risk (RR) of second breast cancer in institutional vs. population-based studies. RRs were calculated using a random-effects model.
have provided enough data about the nature of CT offered. The current meta-analysis showed that the use of CT only was not associated with significant risk (RR = 1.19; [95% CI, 0.50-2.82], $I^2 = 87\%$).

To explore the heterogeneity of the RR vs. therapeutic modalities, we performed a univariate analysis that showed an inverse association between lnRR and age at HL diagnosis, positive interaction with latency, and no significant effect for study size. The multivariate meta-regression analysis, however, only showed that younger age at diagnosis retained a significant independent risk (Table 3).

**RR and additional contributing factors**

Comparing HL patients diagnosed from 1960s to the early 1970s, late 1970s to early 1980s, and more recent years the reported RRs were 3.7, 5.9, and 10.7, respectively [23,28,48,51,55].
Table 4 shows data related to potential contributing factors. Pooled analysis was not attempted due to the small number of studies with sufficient data. Table 4 shows that HL patients who presented with mediastinal mass had higher risk compared with those without mediastinal mass. Table 4 also shows the inconsistency of the reported RR among those who had splenectomy versus those who did not, however, the findings were based on three studies only. Table 4 also shows the potential protective role of pelvic RT as reported by De Bruin et al. [55], where patients receiving that modality showed a risk that was not as high compared with those who did not. HL survivors who received RT had a higher risk of developing estrogen receptor (ER)-negative/progesterone receptor (PR)-negative SBC as compared with ER-positive/PR-positive tumors [57].

Discussion

HL has been a successful model for the development of effective treatment approach in clinical oncology. Long-term survivors of that disease have also allowed better recognition and understanding of the late effects of therapy. In a large cohort of 25,305 women with HL, and with 957 incidences of SBC reported from North American and European institutions, the current meta-analysis quantified the risk of SBC. The overall pooled analysis showed that there was an approximate 9-fold increase in the risk of SBC incidence (pooled RR = 8.23), and AER of 23 patients per 10,000 person-years.

Patients included in this meta-analysis developed HD at a median age of 23.7 years. There has been incongruity about the influence of younger age at HL diagnosis and the higher risk of SBC, where some studies have failed to prove that effect [39,42]. The current meta-analysis clearly showed that younger age at HL diagnosis was associated with increased risk of SBC (pooled RR = 8.23), and the risk remained after adjusting for other covariates. Moreover, we demonstrated that the RR of SBC for women who developed HL above the age of 40 years was not significant. It is presumed that the higher risk associated with
Figure 6 Summary statistics and corresponding forest plot for the relative risk (RR) of second breast cancer based on follow-up latency since Hodgkin’s lymphoma diagnosis. RRs were calculated using a random-effects model.
young age at HD diagnosis is attributed to the effect of RT delivered at a time when breast tissue is proliferating. RT used as the sole therapeutic modality was associated with a 5-fold (RR = 4.70) increase in risk and a 14-fold (RR = 14.08) increase among young (< 30 years of age). Almost all SBC arose within or at the margin of the RT field. The RR of combined RT and any CT was slightly higher than that associated with RT only (5.65

### Figure 7 Summary statistics and corresponding forest plot for the relative risk (RR) of second breast cancer vs. treatment modalities.

RRs were calculated using a random-effects model. (R radiotherapy, C chemotherapy, RC combined radiotherapy and chemotherapy).

| Study or Subgroup | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|--------|--------------|--------------|
|                   |        | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| **7.1.1 R only**  |        |              |      |                      |
| Wolden 2000       | 5.0%   | 4.30 [3.03, 6.11] | 2000 |                      |
| Swerdlow 2000     | 4.8%   | 2.51 [1.48, 4.24] | 2000 |                      |
| Cellai 2001       | 4.6%   | 2.89 [1.57, 5.32] | 2001 |                      |
| Foss Abrahamsen 2002 | 4.8% | 5.00 [2.96, 8.46] | 2002 |                      |
| Hodgson 2007      | 5.1%   | 6.62 [5.16, 9.01] | 2007 |                      |
| Alm El-Din 2009   | 4.7%   | 9.09 [5.16, 16.01] | 2009 |                      |
| **Subtotal (95% CI)** | 28.9% | **4.70 [3.28, 6.75]** |      |                      |
| Heterogeneity: Tau² = 0.14; Chi² = 19.43, df = 5 (P = 0.002); I² = 74% |
| Test for overall effect: Z = 8.41 (P < 0.00001) |

| **7.1.2 RC**       |        |              |      |                      |
| Wolden 2000       | 4.9%   | 6.17 [4.03, 9.46] | 2000 |                      |
| Green 2000        | 3.5%   | 7.77 [2.54, 23.79] | 2000 |                      |
| Cellai 2001       | 3.2%   | 1.40 [0.38, 5.13] | 2001 |                      |
| Foss Abrahamsen 2002 | 3.7% | 1.40 [0.48, 4.07] | 2002 |                      |
| Bhatia 2003       | 2.5%   | 1.86 [0.35, 9.76] | 2003 |                      |
| Kenney 2004       | 4.6%   | 1.11 [0.61, 2.02] | 2004 |                      |
| Hodgson 2007      | 5.0%   | 7.46 [5.05, 11.02] | 2007 |                      |
| Alm El-Din 2009   | 3.3%   | 11.02 [3.25, 37.38] | 2009 |                      |
| Alm El-Din 2009   | 4.0%   | 11.91 [4.89, 28.99] | 2009 |                      |
| De Bruin 2009     | 4.2%   | 1.99 [0.89, 4.46] | 2009 |                      |
| O’Brien 2010      | 4.0%   | 72.24 [29.67, 175.88] | 2010 |                      |
| O’Brien 2010      | 4.0%   | 72.24 [29.67, 175.88] | 2010 |                      |
| Swerdlow 2011     | 5.0%   | 2.41 [1.65, 3.51] | 2011 |                      |
| **Subtotal (95% CI)** | 52.0% | **5.65 [2.94, 10.88]** |      |                      |
| Heterogeneity: Tau² = 1.23; Chi² = 134.15, df = 12 (P < 0.00001); I² = 91% |
| Test for overall effect: Z = 5.19 (P < 0.00001) |

| **7.1.3 C only**   |        |              |      |                      |
| Hancock 1993      | 3.4%   | 2.10 [0.65, 6.81] | 1993 |                      |
| Cellai 2001       | 2.3%   | 0.50 [0.08, 3.01] | 2001 |                      |
| Foss Abrahamsen 2002 | 1.4% | 1.00 [0.07, 14.60] | 2002 |                      |
| Kenney 2004       | 1.5%   | 0.83 [0.07, 10.36] | 2004 |                      |
| Taylor 2007       | 1.5%   | 0.83 [0.07, 10.41] | 2007 |                      |
| Hodgson 2007      | 4.8%   | 3.39 [2.09, 5.49] | 2007 |                      |
| Swerdlow 2011     | 4.0%   | 0.50 [0.20, 1.23] | 2011 |                      |
| **Subtotal (95% CI)** | 19.0% | **1.19 [0.50, 2.82]** |      |                      |
| Heterogeneity: Tau² = 0.71; Chi² = 17.21, df = 6 (P = 0.009); I² = 65% |
| Test for overall effect: Z = 0.40 (P = 0.69) |

| **Total (95% CI)** | 100.0% | **3.98 [2.76, 5.75]** |      |                      |
| Heterogeneity: Tau² = 0.67; Chi² = 192.94, df = 25 (P < 0.00001); I² = 87% |
| Test for overall effect: Z = 7.37 (P < 0.00001) |
| Test for subgroup differences: Chi² = 9.37, df = 2 (P = 0.009), I² = 78.6% |
Table 4 Relative risk of second breast cancer vs. selected risk variables

| Variable                        | RR (95% CI)       |
|--------------------------------|-------------------|
| Mediastinal mass +             | 4.22 (2.71, 6.57) |
| Wahner-Roedler 2003 [44]       | 4.70 (2.87, 7.69) |
| Alm El-Din 2009 [54]           | 9.86 (5.42, 17.92)|
| Splenectomy -                  | 1.90 (1.05, 3.45) |
| Wahner-Roedler 2003 [44]       | 9.67 (4.87, 19.20)|
| Mantle RT, no pelvic RT        | 3.71 (1.38, 9.97) |
| De Bruin 2009 [55]             | 8.20 (6.62, 10.15)|
| Medialstinal RT, no pelvic RT   | 3.71 (1.38, 9.97) |
| Mantle RT + pelvic RT          | 2.70 (1.11, 6.56) |
| ER-/PR-                       | 9.30 (7.00, 12.36)|
| Dores 2010 [57]                | 4.95 (3.84, 6.39) |
| O’ confidence interval, ER estrogen receptors, PR progesterone receptors, RR relative risk, RT radiotherapy. |

vs. 4.70). An even higher, was the RR associated with the combination of RT and alkylating CT (RR = 6.59), thus, the potential protective effect of gonado-toxic alkylating CT was not demonstrated. Several studies showed an inverse association between the use of alkylating CT in HL and SBC risk [24,65], however, other investigators reported increased risk [30,66]. In this meta-analysis and based on data reported from three studies, the risk associated with the combination of RT and non-alkylating CT was not significant [37,54,58], also found insignificant, was the risk related to the use of CT only.

Analysis of potential additional risk factors was limited due to lack of sufficient data and/or inability to compute missing information, therefore, cautions should be exerted in interpreting results. Two studies [24,54], reported on the mantle field RT dose where there was only a small difference in RR between dose < 40 Gy and ≥ 40 Gy (5.99, and 6.13, respectively). While some studies showed that subjects with SBC were found to be significantly more likely to have received higher doses of mantle RT [52], this observation was complicated by the fact that patients treated with higher radiation doses have had longer follow-up. Guibout et al. [46], did not find a significant association between RT dose and SBC, suggesting that the increased risk after HL may indicate a specific susceptibility for developing SBC, or a particular susceptibility to radiation and/or chemotherapy, or both. Conversely, De Bruin et al. showed that the risk of SBC is related to the RT volume [55], where mantle field irradiation was associated with a 2.7-fold increased risk of SBC compared with mediastinal irradiation alone. Besides, the meta-analysis reported by Franklin et al. showed a RR of 3 comparing extended field versus involved field RT [14].

The reason for failing to show a convincing evidence of RT dose—response effect associated with SBC risk is at best divisive. There is evidence for a strongly linear radiation dose response, but only in the lower dose range (up to 5 or 10 Gy) [67,68]. It has been suggested that cell killing tends to decrease the carcinogenic effect of RT along an exponential curve at doses above 10 Gy [69]. However, it is known that BC is a known complication of low-dose breast radiation [67], thus BC may remain a risk among adolescent women who receive any dose of thoracic irradiation for HL.

Although new RT techniques and treatment strategies have the potential to reduce the future burden of late effects, nevertheless, we have shown that an even higher risk was reported in more recent years suggesting that there remains a significant cohort at an increased risk of SBC.

Pelvic RT was found to be associated with a protective effect as reported by De Bruin et al. [55]. The same effect was also noted by Basu et al., where 3.4% of patients who developed SBC received pelvic RT as compared with 26.3% among those who did not [52]. It is presumed that the protective effect of pelvic RT is attributed to the induction of premature menopause and the role played by hormone stimulation in RT-induced breast carcinogenesis [43,70]. The influence of splenectomy on SBC risk has been controversial. While some studies reported a modest higher risk [71], other studies failed to show that effect [30,52].

Only one study examined the receptor status of SBC [57]. The RR of ER-negative/PR-negative SBC was 66% higher than ER-positive/PR-positive SBC among 5-year HL survivors, and nearly two-fold higher among 15-year survivors. Conversely, other studies of small numbers of SBC patients have not found a significant variation in hormone-receptor status when compared with primary BC controls [72,73]. While the incidence of hormone receptor-positive BC in the general population exceeds that of ER-negative/PR-negative BC, it is postulated, however, that young women treated for HL may experience premature ovarian failure related to HL therapy,
and therefore, their hormonal BC risk factors may differ from those in the general population.

The present meta-analysis has several limitations. First, it is not possible to completely exclude the possibility that the HL itself carries with it an increased risk of second malignancy including SBC. Second, it is very difficult to quantify the possible effect of confounding factors such as lifestyle factors, personal risk, family history, etc. For example, Landgren et al. found increased RR (1.81) of breast cancer among HL patient with positive (vs. negative) family history of cancer [50]. Third, the analyses showed significant heterogeneity in risk estimate, nevertheless, investigating heterogeneity using meta-regression technique showed the dominant role of age at HL diagnosis. Other limitations include the lack of comprehensive treatment data including information on RT dose and additional treatments, and the lack of sufficient data to model the protective effect of endogenous hormone ablation against the risk associated with exposure to exogenous hormones. Moreover, it is not clear if a similar magnitude of risk is to be expected in a different patient population where the incidence of sporadic BC is low. Finally, the meta-analysis lacks the analysis of SBC outcome. However, SBC incidence rather its mortality was the main objective of the meta-analysis. Moreover, not all studies reported on mortality, besides, analysis of SBC mortality would be confounded by the mortality from HL itself or its therapy-related effect, ascertainment of the cause of death, age of diagnosis of HL or SBC, and length of follow-up.

Conclusions

We conclude that the current meta-analysis provided the most recent comprehensive estimate of the risk of SBC in a broad-range of HL survivors with inclusive analysis of relevant clinical and treatment variables. Based on the derived data where the median age at the diagnosis of SBC was 35.0 years and at a median latency of 17.7 years, screening recommendations for HL survivors need to be reemphasized. The results from the current meta-analysis support the favorable outcome of the risk-guided BC screening for such patients according to three prospective studies [74-76]. It is probably more appropriate that female patients with HL who are at a higher risk for developing SBC to be screened annually and at an earlier age rather than biennially starting at the age of 50 years as currently recommended for general population [77]. Our data also support the recent trend of risk-adapted management of HL to reduce the risk of short- and long-term adverse events associated with needless overtreatment [78].

Competing interests

All authors declare that they have no competing interests.

Author details

1 Oncology Center of Excellence, International Medical Center, PO Box 2172, Jeddah 21451, Saudi Arabia. 2 Princess Noorah Oncology Center, Abdulaziz Medical City, P.O. BOX 9515, Jeddah 21423, Saudi Arabia.

Authors’ contributions

EMI, KMA, GAK, OAA, and MA Concept and design of the meta-analysis. EMI Study coordination and tasks’ assignment, KMA, and GAK Initial literature search. EMI KMA, GAK, OAA, and MA Review of all potential studies. EMI, KMA, GAK, OAA, and MA Data extraction. EMI, KMA, GAK, OAA, and MA Assessing quality of included studies. EMI Statistical analysis. EMI, KMA, and GAK Investigating heterogeneity. EMI, KMA, GAK, OAA, and MA Preparation of the manuscript. EMI, KMA, GAK, OAA, and MA Reading the final manuscript. EMI, KMA, GAK, OAA, and MA Approval of the final manuscript. All authors read and approved the final manuscript.

Received: 2 November 2011 Accepted: 28 May 2012 Published: 28 May 2012

References

1. Herbst C, Rehan FA, Skoetz N, Bohlius J, Brillant C, Schulz H, Monsef I, Specht L, Engert A: Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma. Cochrane Database Syst Rev 2011, 2CD007110.
2. Rathore B, Kadin ME: Hodgkin's lymphoma therapy: past, present, and future. Expert Opin Pharmacother 2010, 11(7):2891–2906.
3. Evers AM, Hutchings M, Diehl V: Treatment of Hodgkin lymphoma: the past, present, and future. Nat Clin Pract Oncol 2008, 5(9):543–556.
4. Weiner MA, Loventhal B, Blecher ML, Marcus RB, Cantor A, Giner PW, Teremb LL, Behm FG, Wharam MD Jr, Chauvenet AR: Randomized study of intensive MOPP-ABVD with or without low-dose total-t nal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. J Clin Oncol 1997, 15(2):2769–2779.
5. Hodgson DC, Hudson MM, Constine LS: Pediatric Hodgkin lymphoma: maximizing efficacy and minimizing toxicity. Semin Radiat Oncol 2007, 17(3):230–242.
6. Canellios GP: Letter: second malignancies complicating Hodgkin's disease in remission. Lancet 1975, 1(7919):1294.
7. Baxi SS, Matasar MJ: State-of-the-art issues in Hodgkin's lymphoma survivorship. Curr Oncol Rep 2010, 12(6):366–373.
8. Miller AB, Howe GR, Sherman GJ, Lindsay JP, Yaffe MJ, Dinne PJ, Risch HA, Preston DL: Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. N Engl J Med 1984, 321(19):1285–1289.
9. Tokunaga M, Land CE, Yamamoto T, Asano M, Tokuoka S, Ezaki H, Nishimori I, Hiroshima and Nagasaki, 1950–1980. Radiat Res 1987, 112(2):243–272.
10. Neugut AI, Weinberg MD, Ahsan H, Rescigno J: Cancerogenetic effect of radiotherapy for breast cancer. Oncol (Williston Park) 1999, 13(9):1261–1245. discussion 1257.
11. Wolf J, Schellong G, Diehl V: Breast cancer following treatment of Hodgkin's disease–more reasons for less radiotherapy? Eur J Cancer 1997, 33(14):2293–2294.
12. Reche K: Carcinogenicity of antineoplastic agents in man. Cancer Treat Rev 1984, 11(1):39–67.
13. Dorf FA, Cottman CA Jr: Second cancers following antineoplastic therapy. Curr Probl Cancer 1985, 9(2):1–43.
14. Franklin J, Pluechtrow A, Paas M, Specht L, Anselmo AP, Aviles A, Biti G, Bogatyrev A, Bonadonna G, Brilliant C, et al: Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. Ann Oncol 2005, 17(12):1749–1760.
15. Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, Diller LR, Constine LS, Smith RA, Mahoney MC, et al: Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. Ann Intern Med 2010, 152(7):444–455. W144–454.
16. Vandenbroucke JP, Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M: Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Epidemiology 2007, 18(6):805–835.
Second malignancies after Hodgkin's disease: long-term analysis of risk factors and outcome. Blood 1996, 87(9):3625–3632.

Sankila R, Garwicz S, Olsen JH, Doller H, Hertz H, Kreugler A, Langmark F, Lanning M, Moller T, Tulinhus H: Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence; a population-based cohort study in the five Nordic countries. Association of the Nordic Cancer Registries and the Nordic Society of Pediatric Hematology and Oncology. J Clin Oncol 1996, 14(5):1442–1446.

Aisenberg AC, Finkelstein DM, Dopke KP, Koerner FC, Boivin JF, Willett CG: Increased mortality after successful chemotherapy: long-term risks and risk factors. Blood 2003, 102(16):4753–4757.

Wahner-Roedder DL, Nelson DF, Croghan IT, Achenbach SJ, Crowson CS, Hartmann LC, O'Fallon WM: Risk of breast cancer and breast cancer characteristics in women treated with supradiaphragmatic radiotherapy for Hodgkin lymphoma: Mayo Clinic experience. Mayo Clin Proc 2003, 78(8):708–715.

Kenney LB, Yasui Y, Inskip PO, Hammond S, Neglia JP, Mertens AC, Hammond S, Stovall M, Langmark F, Pukkala E, Andersson M, Wiklund T, Lynch CF, et al.: Malignant breast tumors and its consequences for the overall survival of Hodgkin's disease patients and for the choice of their treatment at presentation: analysis of a series of 1524 cases consecutively treated at the University Hospital. Int J Radiat Oncol Biol Phys 2001, 49(5):1327–1337.

Margolis KL, Wright JK, Wagner JS, Poplack D, Mertens AC, Stovall M, Goldin LR, Travis LB, Bandfield A, et al.: Risk of breast cancer in female survivors with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 2003, 21(23):4386–4394.

Travis LB, Hill DA, Dires GM, Gospodorwicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, et al.: Breast cancer following radiotherapy and chemotheraphy among young women with Hodgkin disease. JAMA 2003, 290(4):465–475.

Taylor AJ, Winter DL, Stoller CA, Murphy M, Hawkins MM: Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: a population-based study. Int J Cancer 2007, 120(2):384–391.

Basu SK, Schwartz C, Fisher SG, Hudson MM, Tarbell N, Muhs A, Marcus KC, Mendenhall N, Mauch P, Kun LE, et al.: Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin's disease. Int J Radiat Oncol Biol Phys 2008, 71(1):34–40.

Constine LS, Tarbell N, Hudson MM, Schwartz C, Fisher SG, Muhs AG, Basu SK, Kun LE, Ng A, Mauch P, et al.: Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. Int J Radiat Oncol Biol Phys 2008, 72(1):24–33.

Attn El-Din MA, Hughes KS, Finkelstein DM, Betts KA, Yock TJ, Tarbell NJ, Aisenberg AC, Taghian AG: Breast cancer after treatment of Hodgkin's lymphoma: risk factors that really matter. Int J Radiat Oncol Biol Phys 2009, 73(1):69–74.

De Bruin ML, Sparerands J, Van't Veer MB, Noordijk EM, Louwman MW, Zijlstra JM, Van Den Berg H, Russell NS, Broeks A, Baaijens MH, et al.: Breast
Ibrahim et al. BMC Cancer 2012, 12:197
http://www.biomedcentral.com/1471-2407/12/197
Page 19 of 19

Submit your next manuscript to BioMed Central and take full advantage of:

• Convenient online submission
• Thorough peer review
• No space constraints or color figure charges
• Immediate publication on acceptance
• Inclusion in PubMed, CAS, Scopus and Google Scholar
• Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit