The Breast Journal

ORIGINAL ARTICLE

Breast Cancer Following Hodgkin's Disease: The Experience of the University of Florence

Icro Meattini, MD,* Lorenzo Livi, MD,* Calogero Saieva, MD,‡ Livia Marrazzo, PhD,† Andrea Rampini, MD,* Carmine Iermano, MD,* Maria Grazia Papi, MD,* Beatrice Detti, MD,* Silvia Scoccianti, MD,* and Giampaolo Biti, MD*

*Departments of *Radiation-Oncology and †Medical Physics, University of Florence, Florence, Italy; and ‡Molecular and Nutritional Epidemiology Unit ISPO – Cancer Prevention and Research Institute, Florence, Italy*

■ **Abstract:** The advent of effective chemo-radiotherapy has made Hodgkin Disease (HD) a highly curable malignancy, but the great improvement in survival rates allowed the observation in long-term survivors of several treatment complications. Secondary malignancies are the most serious complications and breast cancer (BC) represents the most common solid tumor among female survivors. The aim of our analysis is to describe the clinico-pathological characteristics and management of BC occurred after HD treatment. Between 1960 and 2003, 2,039 patients were treated for HD at the Department of Radiotherapy-Oncology of the Florence University. In this study we considered 1,538 patients on whom a minimum follow up of 6 months had been obtained. Of these, 725 were women. The most represented histological subtype was nodular sclerosis (50.6%). Supradiaphragmatic alone or with subdiaphragmatic complementary extended field radiotherapy was delivered to 83.1% of patients while supradiaphragmatic involved field radiotherapy was delivered to 10.7% of patients. Concerning the characteristics and incidence of BC, we focused our analysis exclusively on the female group. We found that BC occurred in 39, with an overall incidence of 5.4%. The mean interval after Hodgkin treatment was 19.5 years (SD ± 9.0). The median age of BC diagnosis was 50.8 years (SD ± 13.3) while the median age of Hodgkin diagnosis was 31.2 years (SD ± 14.5). Thirty-seven women received mediastinal irradiation. We observed a decreasing trend of the secondary BC incidence with increasing age of Hodgkin treatment with the maximum incidence registered in women treated at age 20 or younger. In Our Institute we perform a whole life follow up and recommend that annual mammography begins 10 years after HD treatment or, in any case, not later than age 40. ■

[Abstract amended after online publication date May 5, 2010]

Key words: breast cancer, Hodgkin's disease, late effects, screening, secondary malignancies

The advent of effective radiotherapy (RT) first and later of combined chemo-radiotherapy has made Hodgkin Disease (HD) a highly curable malignancy. This has been one of the most relevant success of oncology (1–3). The great improvement in survival rates after therapy for HD allowed the observation in long-term survivors of several treatment complications. In these patients, treatment-related toxicity surpasses HD as the greatest contributor to overall mortality (4). Secondary malignancies (SM) are the most serious complications characterized by important morbidity and mortality. Many studies have demonstrated a significant increasing risk of secondary acute non-lymphocytic leukemia, non-Hodgkin's lymphoma and solid tumors (ST) among HD patients (5–7). In particular, breast cancer (BC) remains the most common SM among female survivors, especially in those treated at young ages with supradiaphragmatic RT (8–13). Anyhow, at the present time, combined chemo-radiotherapy seems to be optimal both for most early stage HD patients and for advanced stages (14–16). The aim of our analysis is to quantify the overall incidence and to describe the clinico-pathological characteristics and management of BC occurred after HD treatment in female patients at the Department of Radiation-Oncology of the Florence University.

Address correspondence and reprint requests to: Icro Meattini, MD, Department of Radiation-Oncology, University of Florence, Viale Morgagni 85, 50134 Florence, Italy, or e-mail: icro.meattini@unifi.it.

DOI: 10.1111/j.1524-4741.2010.00904.x

Table 1. Distribution of 1,538 Cases of Hodgkin Disease (HD) According to Selected Clinical and Pathologic Characteristics

Characteristic	*n* (%)
Gender	
Female	725 (47.1)
Male	813 (52.9)
Age groups (years)	
≤30	706 (45.9)
30.1–40	322 (20.9)
>40	510 (33.2)
Clinical stage	
I	248 (16.1)
II	840 (54.6)
III	363 (23.6)
IV	87 (5.7)
Histological type*	
Nodular sclerosis	655 (50.6)
Mixed cellularity	445 (34.4)
Lymphocyte predominance	139 (10.7)
Lymphocyte depletion	55 (4.3)
General symptoms	
A	1150 (74.8)
B	388 (25.2)
ESR	
Normal	637 (41.4)
Abnormal	901 (58.6)
Site of presentation	
Mediastinum	860 (63.4)
Supradiaphragmatic without mediastinum	577 (37.8)
Subdiaphragmatic	90 (5.9)
Extranodal	2 (0.1)
Extension	
No	1333 (86.7)
Yes	205 (13.3)
Site of extension	
Lung	76 (37.2)
Bone	46 (22.4)
Cutaneous	29 (14.2)
Liver	21 (10.2)
Pleura	6 (2.9)
Multiple	6 (2.9)
Others	21 (10.2)
Staging laparotomy	
No	861 (56.0)
Yes	677 (44.0)
Primary treatment	
Only RT	833 (54.3)
RT–CHT	573 (37.2)
Only CHT	132 (8.5)
RT treated volumes	
Submantle	85 (6.1)
Mantle	897 (63.8)
Subdiaphragmatic EF	76 (5.4)
Mediastinal IF	62 (4.4)
Cervical and/or axillary IF	88 (6.3)
Subdiaphragmatic IF	17 (1.2)
Total nodal irradiation	181 (12.9)
Radiotherapy	
Supradiaphragmatic EF	1163 (82.7)
Supradiaphragmatic IF	150 (10.7)
Subdiaphragmatic alone	93 (6.6)
Chemotherapy	
MOPP	361 (23.4)
ABVD	296 (19.2)
Other regimens	48 (3.1)
No CHT	833 (54.3)
Number of cycles of CHT†	
1–3	138 (20.1)
4–6	450 (65.7)
7+	97 (14.2)

RT, radiotherapy; CHT, chemotherapy; EF, extended field; IF, involved field; ESR, erythrocyte sedimentation rate.
*Histological data not available for 244 cases.
†Data on CHT cycles not available for 20 cases subjected to CHT.

MATERIALS AND METHODS

In this retrospective study, we analyzed the development of BC in patients previously treated for HD at the Department of Radiation-Oncology of the Florence University. Between 1960 and 2003, 2,039 patients were treated for HD. The patients' data were obtained from the Institute clinical database. All parameters were not always exhaustive, especially in older cases. Moreover, we considered only patients with a minimum follow up of 6 months. The statistical analysis was conducted on 1,538 patients; among them, 725 were women. The BC incidence data relate to the female group only. In the whole group, according to Ann Arbor's classification, we registered early stages (Stage I-II) in the 70.7% of the patients and advanced stages (Stage III-IV) in the 29.3%. The most represented histological subtype was nodular sclerosis (50.6%). At presentation 54.3% of the patients received exclusive RT and 37.2% combined chemoradiotherapy. Supradiaphragmatic alone or with subdiaphragmatic complementary extended field radiotherapy (EFRT) was delivered to 82.7% of patients; the delivered dose was in the range of 36–40 Gy with conventional fractionation. Supradiaphragmatic involved field radiotherapy (IFRT) was delivered to 10.7% of patients; the maximum dose to the involved nodal regions was 30 Gy, with conventional fractionation. The median age at diagnosis of HD for the women was 30.3 years (range 10–85 years). The complete patients HD characteristics and management are summarized in Table 1. Patients were followed up from the diagnosis until death; during the first year after the end of the treatment, they received a clinical examination every 3 months, and thereafter every 6 months until the fifth year. Then, they have been asked to come for follow up visits every 2 years. At time of writing, at a median follow up of 15.6 years (range 0.5–48 years), 1,141 patients had no evidence of HD. The complete distribution of

Table 2. Distribution of 1,538 Cases of Hodgkin Disease (HD) According to Relapse Occurrence and Vital Status

Characteristic	*n* (%)
Relapse	
No	958 (62.3)
Yes	580 (37.7)
Type of relapse	
True	221 (38.1)
Marginal	52 (9.0)
Extended	144 (24.8)
Dissemination	142 (24.5)
Unknown	21 (3.6)
Time occurrence of relapse (years)	
<1	165 (28.4)
1–2	160 (27.6)
2.1–3	85 (14.7)
3.1–4	50 (8.6)
4.1–5	29 (5.0)
>5	91 (15.7)
Vital status	
Alive	1141 (74.2)
Died of HD	397 (25.8)

HD, Hodgkin disease.

our series according to relapse occurrence and vital status is summarized in Table 2.

Statistical analyses

Clinico-pathological data collected for each patient was linked to vital status information. For the survival analysis, the date of HD diagnosis was used as the start of observation. Survival time was calculated from the date of HD diagnosis to the date of last follow-up or date of death. Disease free survival time is defined as survival without HD relapse, and was calculated from the date of HD diagnosis to the date of HD relapse. We also calculated the time of BC occurrence from the date of HD diagnosis to the date of BC occurrence. The crude cumulative probability of BC occurrence at the end of follow-up was estimated by using the Kaplan–Meier method and differences between patient groups were assessed by the log-rank test. Cumulative probability comparisons were carried out using Cox proportional hazard regression models. Estimated relative risks of BC occurrence were expressed as cumulative probability (CP) and corresponding 95% confidence intervals (95% CI). Univariate models were performed to evaluate the effect of each specific parameter. Multivariate regression models were used to test the independent effect of the parameters included in the Cox models. Statistical results were considered significant at a p-value <0.05. All statistical tests were performed by SAS software (Statistical Analysis Software, Cary, NC).

RESULTS

We found that, among the female group, BC occurred in 39 patients, with an incidence of 5.4%. No cases of BC were observed in 813 male patients. The incidence for the entire group is 2.5%. Concerning these 39 female patients, the mean interval after HD treatment was 19.5 years (SD ± 9.0). The median age of BC was 50.8 years (SD ± 13.3), while the median age of HD diagnosis was 31.2 years (SD ± 14.5). Thirty-seven women received mediastinal RT, all, except one, with EFRT. Most of the patients developed BC after more than 20 years from HD diagnosis (48.8%). Three patients had bone metastasis at diagnosis of BC. In more than two-third of cases BC's histotype is ductal infiltrating. HER-2 receptor status was available only for fifteen patients and was negative in all cases. The main clinico-pathological features of patients are summarized in Table 3. Concerning BC outcome, at the time of writing, at a median follow up of 2.5 years (range 0.5–25 years), 21 patients have no disease evidence. Six patients developed local recurrence and twelve patients developed distant metastasis; all these patients died for BC after advanced BC multimodality treatment. The main results of BC cumulative probability at the end of the follow-up of 725 HD female cases according to selected individual characteristics are summarized in Table 4. Despite Cox regression univariate analysis does not reach any statistical significance for any of the parameters evaluated, we observed a decreasing trend of the secondary BC incidence with increasing age of HD treatment. The maximum incidence is observed in women treated at age 20 or younger (CP: 50.8; 95% CI: 19.8–91.3). In addition, multivariate analysis do not reach statistical significance (data not shown).

DISCUSSION

Improvements in the management of HD have resulted in a large number of long-term survivors, with an increased risk of treatment-induced SM, which are currently the primary cause of mortality among these patients (4,17–21).

Several different factors are involved in the development of SM, such as exposure to radiation therapy (7,13,22), selected chemotherapy agents (23–25),

Table 3. Characteristics of 39 Breast Cancer (BC) Diagnosed During the Hodgkin Disease (HD) Follow-up

Characteristic	*n* (%)
Time occurrence of BC after HD (years)	
<5	2 (5.1)
5–10	4 (10.3)
10.1–15	7 (17.9)
15.1–20	7 (17.9)
>20	19 (48.8)
HD treatment	
RT	29 (74.4)
RT + CHT	8 (20.5)
CHT	2 (5.1)
Radiotherapy for HD	
Supradiaphragmatic IF	1 (2.7)
Supradiaphragmatic EF	36 (97.3)
Infradiaphragmatic	–
Histotype	
Ductal infiltrating	26 (66.7)
Lobular infiltrating	6 (15.4)
Ductal in situ	4 (10.3)
Lobular in situ	3 (7.7)
T stage	
Tis	7 (17.9)
1	13 (33.3)
2	14 (35.9)
3	4 (10.3)
4	1 (2.6)
Node involved	
0	31 (79.5)
1–3	6 (15.4)
>3	2 (5.1)
Hormonal receptors	
ER+/PgR+	20 (62.5)
ER–/PgR+	3 (9.3)
ER–/PgR–	9 (28.2)
Surgery	
Conservative	17 (43.6)
Mastectomy	22 (56.3)
Adjuvant RT	
No	29 (74.4)
Yes	10 (25.6)
Adjuvant CHT	
No	25 (64.1)
Yes	14 (35.9)
Adjuvant HT	
No	17 (43.6)
Yes	22 (56.4)

BC, breast cancer; HD, Hodgkin disease; RT, radiotherapy; CHT, chemotherapy; HT, hormonotherapy; EF, extended field; IF, involved field; ER, estrogen receptor; Pgr, progesterone receptor.

Table 4. Breast Cancer (BC) Cumulative Probability in the Follow-up of 725 Hodgkin Disease (HD) Female Cases According to Selected Individual Characteristics: Number of Patients at Risk, Number of BC, Cumulative Probability (CP) at the End of Follow-up and Corresponding 95% Confidence Intervals (95% CI), and Log Rank Test

Variable	At start	BC	CP	95% CI	Log rank test
Age at HD diagnosis (years)					
≤20	140	10	50.8	19.8–91.3	0.33
20.1–30	217	15	30.7	17.2–50.9	
30.1–40	161	5	8.0	3.2–19.5	
>40	207	9	17.8	8.1–36.4	
HD treatment					
RT	408	29	31.1	17.5–51.4	0.82
RT + CHT	266	8	25.2	8.9–59.3	
CHT	51	2	7.6	1.8–27.9	
Radiotherapy					
Supradiaphragmatic IF	79	1	3.6	0.5–22.8	0.32
Supradiaphragmatic EF	575	36	39.1	20.2–66.3	
Infradiaphragmatic	20	–			
CHT†					
No CHT	408	29	31.1	17.5–51.4	0.99
ABVD	136	7	20.0	7.6–46.6	
MOPP	166	2	3.2	0.7–14.0	
Total	725	39	31.2		

BC, breast cancer; HD, Hodgkin disease; RT, radiotherapy; CHT, chemotherapy; EF, extended field; IF, involved field; CP, cumulative probability.
†Excluding other CHT.

hormonal factors (26,27) or genetic influences (28). The majority of previous studies proved that supradiaphragmatic nodal region RT is one of the most important risk factors for BC among women treated for HD (8–10,29–32).

Breast cancer is the most common ST among HD survivors women (33). In our analysis we showed a median interval after HD diagnosis of 19.5 years, a median age at BC diagnosis of 50.8 years and the most represented BC histotype was ductal infiltrating, in agreement with what previously reported (9,22,27,34,35).

One of the most important prognostic factor seems to be the patients' age at HD treatment. Our data show a clear decreasing trend of the secondary BC incidence with increasing age of HD treatment, even though not statistically significant. The largest excesses of BC are observed among women diagnosed with HD at age 30 or younger, especially those younger than 20 (2,9,10,25,26,31,35–37), a pattern that is consistent with the known radiosensitivity of the breast at young ages (38). There is no significant increase of BC risk, compared to general population, in women treated after 35 years of age (33,39).

Breast cancer is the most frequently diagnosed malignancy amongst women in the United States, with a lifetime risk in the general population of 13.4% (40). The age-standardized rates for the incidence of BC in the general population is 66.2 per 100,000 for France, 65.4 per 100,000 for Italy and 63.4 per 100,000 for UK (41).

In a relevant review, Horwich and Swerdlow (42) examined the evidences in order to understand factors contributing to the risk and to develop a logical and efficient method for medical management of patients

at higher risk. They concluded that, for those women requiring supradiaphragmatic radiotherapy at ages less than 30 years, it is important to minimize dose and limit volume of breast tissue in the field.

In some recent works (43,44) an attempt was made to quantify the reduction in dose to normal tissues associated with modern RT practice for patients with mediastinal HD and the subsequent expected reduction in SM using radiobiological cancer-risk models (45–47). Hodgson et al. (43) demonstrated that the median predicted 20-year excess relative risk (ERR) of BC for women treated at age 20 with 35 Gy mantle EFRT was 4.8 and this risk was predicted to decline to 1.8 after 35 Gy IFRT. The transition to IFRT was predicted to cause similar proportional reductions in the ERR of BC among women treated at age 30, where the median 20-year ERR of BC declined from 2.1 to 0.8. Koh et al. (44) underlined how compared to 35 Gy mantle RT, the median mean breast doses from 35 Gy IFRT were significantly reduced by 64% and this fact is predicted to reduce the ERR for female BC by approximately 65%. The significant decrease estimated for radiation-induced SM risk associated with modern RT, caused EFRT for HD to have been largely replaced by IFRT. New clinical trials are investigating even smaller treatment volumes with involved-node RT (48). Our data do not allow to compare the role of modern RT techniques to the standard treatment, since only one of the 37 patients treated with radiation therapy received IFRT and in our Institution IFRT has been delivered only in the last 10 years. It will be possible to draw a conclusion about this point only at a longer follow up of these patients.

Considering the correlation between secondary BC and HD treatment, to identify the optimal screening strategy for HD survivors appears to be a key point. This is still not well established and practice guidelines vary widely in the recommended use of screening mammography (31,49,50). A large volume of literature showed that the increased rate of secondary BC emerges following a latency of 10 years and persists beyond 25 years of follow-up (8,9,19,20,34). Evaluating the radiation risk from mammography versus the benefit from breast screening (51,52), the majority of Authors suggests that annual mammography screening should begin within 10 years after HD treatment (8,9,12,13,31–35,53). Contrast-enhanced MRI is a new and sensitive modality in detecting BC in young women and women with dense breasts. MRI's role may become even more important, as MRI developments improve sensitivity of this imaging modality (50,54–58).

In conclusion, despite techniques of administering RT have become more refined over time in an effort to reduce treatment-related damages, it should be remembered that BCs seen today reflect the treatment methods for HD of more than 20 years ago. In Our Institute we perform a whole life follow up. We suggest frequent breast self-examination and we recommend that annual mammography screening begins 10 years after HD treatment or, in any case, not later than age 40.

REFERENCES

1. Noordijk EM, Carde P, Dupouy N, *et al.* Combined modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *J Clin Oncol* 2006;24:3128–35.

2. Van Leeuwen FE, Klokman WJ, van't Veer MB, *et al.* Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence of young adulthood. *J Clin Oncol* 2000;18:487.

3. Matasar MJ, Zelenetz AD. Overview of lymphoma diagnosis and management. *Radiol Clin North Am* 2008;46:175–98.

4. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, *et al.* Longterm cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol* 2003;21:3431–9.

5. Biti G, Cellai E, Magrini SM, Papi MG, Ponticelli P, Boddi V. Second solid tumours and leukemia after treatment for Hodgkin's disease: an analysis of 1121 patients from a single institution. *Int J Radiat Oncol Biol Phys* 1994;29:25–31.

6. Parker RG. Radiation-induced cancer as a factor in clinical decision making (the 1989 ASTRO Gold Medal address). *Int J Radiat Oncol Biol Phys* 1990;18:993–1000.

7. Swerdlow AJ, Barber JA, Vaughan Hudson G, *et al.* Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. *J Clin Oncol* 2000;18:498–509.

8. Cutuli B, Dhermain F, Borel C, *et al.* Breast cancer in patients treated for Hodgkin's disease: clinical and pathological analysis of 76 cases in 63 patients. *Eur J Cancer* 1997;33:2315–20.

9. Cutuli B, Borel C, Dhermain F, *et al.* Breast cancer occurred after treatment for Hodgkin's disease: analysis of 133 cases. *Radiother Oncol* 2001;59:247–55.

10. Aisenberg AC, Finkelstein DM, Doppke KP, Boivin JF, Willet CG. High risk of breast carcinoma after irradiation of young women with Hodgkin's disease. *Cancer* 1997;79:1203–10.

11. Cook KL, Adler DD, Lichter AS, Ikeda DM, Helvie MA. Breast carcinoma in young women previously treated for Hodgkin's disease. *AJR Am J Roentgenol* 1990;155:39–42.

12. Peters MH, Sonpal IM, Batra MK. Breast cancer in women following mantle irradiation for Hodgkin's disease. *Am Surg* 1995;61:763–6.

13. Travis LB, Hill DA, Dores GM, *et al.* Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003;290:465–75.

14. Laskar S, Gupta T, Vimal S, *et al.* Consolidation radiation after complete remission in Hodgkin's disease following six cycles of ABVD chemotherapy: is there a need? *J Clin Oncol* 2004;22:62–8.

15. Franklin J, Pluetschow A, Paus M, *et al.* Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Ann Oncol* 2006;17:1749–60.

16. Biti GP, Cimino G, Cartoni C, *et al.* Extended-field radiotherapy is superior to MOPP chemotherapy for the treatment of pathologic stage I–IIA Hodgkin's disease: eight-year update of an Italian prospective randomized study. *J Clin Oncol* 1992;3:378–82.

17. Arseneau JC, Sponzo RW, Levin DL, *et al.* Nonlymphomatous malignant tumors complicating Hodgkin's disease: possible association with intensive therapy. *N Engl J Med* 1972;287:1119–22.

18. Boice JD Jr. Second cancer after Hodgkin's disease: the price of success? *J Natl Cancer Inst* 1993;85:4–5.

19. Mauch PM, Kalish LA, Marcus KC, *et al.* Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. *Cancer J Sci Am* 1995;1:33–42.

20. Dores GM, Metayer C, Curtis RE, *et al.* Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol* 2002;20:3484–94.

21. Anonymous. Cancer survivors: living longer, and now, better. *Lancet* 2004;364:2153–4.

22. Tinger A, Wasserman TH, Klein EE, *et al.* The incidence of breast cancer following mantle field radiation therapy as a function of dose and technique. *Int J Radiat Oncol Biol Phys* 1997;37:865–70.

23. Cellai E, Magrini SM, Masala G, *et al.* The risk of second malignant 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 Florence University Hospital. *Int J Radiat Oncol Biol Phys* 2001;49:1327–37.

24. Valagussa P, Santoro A, Fossati-Bellani F, *et al.* Second acute leukemia and other malignancies following treatment for Hodgkin's disease. *J Clin Oncol* 1986;4:830–7.

25. Tucker MA, Coleman CN, Cox RS, *et al.* Risk of second cancers after treatment for Hodgkin's disease. *N Engl J Med* 1988;318:76–81.

26. Hill DA, Gilbert E, Dores GM, *et al.* Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. *Blood* 2005;106:3358–65.

27. van Leeuwen FE, Klokman WJ, Stovall M, *et al.* Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst* 2003;95:971–80.

28. M'Kacher R, Girinsky T, Koscielny S, *et al.* Baseline and treatment-induced chromosomal abnormalities in peripheral blood lymphocytes of Hodgkin's lymphoma patients. *Int J Radiat Oncol Biol Phys* 2003;57:321–6.

29. Deniz K, O'Mahony S, Ross G, Purushotham A. Breast cancer in women after treatment for Hodgkin's disease. *Lancet Oncol* 2003;4:207–14.

30. Foss Abrahamsen A, Andersen A, Nome O, *et al.* Long-term risk of second malignancy after treatment of Hodgkin's disease: the influence of treatment, age and follow-up time. *Ann Oncol* 2002;13:1786–91.

31. Travis LB, Hill D, Dores GM, *et al.* Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* 2005;97:1428–37.

32. van Leeuwen FE, Somers R, Taal BG, *et al.* Increased risk of lung cancer, non-Hodgkin's lymphoma, and leukemia following Hodgkin's disease. *J Clin Oncol* 1989;7:1046–58.

33. Wolden SL, Hancock SL, Carlson RW, *et al.* Management of breast cancer after Hodgkin's disease. *J Clin Oncol* 2000;18:765–72.

34. Janov AJ, Tulecke M, O'Neill A, *et al.* Clinical and pathologic features of breast cancers in women treated for Hodgkin's disease: a case–control study. *Breast J* 2001;7:46–52.

35. Yahalom J, Petrek JA, Biddinger PW, *et al.* Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathologic analysis of 45 events in 37 patients. *J Clin Oncol* 1992;10:1674–81.

36. Travis LB, Curtis RE, Boice JD Jr. Late effects of treatment for childhood Hodgkin's disease. *N Engl J Med* 1996;335:352–3.

37. Bhatia S, Robison LL, Oberlin O, *et al.* Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* 1996;334:745–51.

38. Preston DL, Mattsson A, Holmberg E, *et al.* Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res* 2002;158:220–35.

39. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 1993;85:25–31.

40. Ries LAG, Eisner MP, Kosary C, *et al.*, eds. SEER Cancer Statistics Review, 1973–2001. Bethesda, MD: National Cancer Institute, 2004. Available at: http://seer.cancer.gov/publicdata (accessed January 15 2009).

41. Parkin DM, Muir CS. IARC, cancer incidence in five continents. Comparability and quality of data. *IARC Sci Publ* 1992;120:45–173.

42. Horwich A, Swerdlow AJ. Second primary breast cancer after Hodgkin's disease. *Br J Cancer* 2004;90:294–8.

43. Hodgson DC, Koh ES, Tran TH, *et al.* Individualized estimates of second cancer risks after contemporary radiation therapy for Hodgkin lymphoma. *Cancer* 2007;110:2576–86.

44. Koh ES, Tran TH, Heydarian M, *et al.* A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk. *Radiat Oncol* 2007;2:13.

45. Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. *Proc Natl Acad Sci USA* 2005;102:13040–5.

46. Mole RH. Ionizing radiation as a carcinogen: practical questions and academic pursuits The Silvanus Thompson Memorial lecture delivered at The British Institute of Radiology on April 18, 1974. *Br J Radiol* 1975;48:157–69.

47. Sacher GA, Trucco E. Theory of radiation injury and recovery in self-renewing cell populations. *Radiat Res* 1966;29:236–56.

48. Girinsky T, van der Maazen R, Specht L, *et al.* Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. *Radiother Oncol* 2006;79:270–7.

49. Ralleigh G, Given-Wilson R. Breast cancer risk and possible screening strategies for young women following supradiaphragmatic irradiation for Hodgkin's disease. *Clin Radiol* 2004;59:647–50.

50. Lee L, Pintilie M, Hodgson DC, Goss PE, Crump M. Screening mammography for young women treated with supradiaphragmatic radiation for Hodgkin's lymphoma. *Ann Oncol* 2008;19:62–7.

51. Dershaw DD, Yahalom J, Petrek JA. Breast carcinoma in women previously treated for Hodgkin's disease: mammographic evaluation. *Radiology* 1992;184:421–3.

52. Tabar L, Yen MF, Vitak B, *et al.* Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *Lancet* 2003;361:1405–10.

53. Kwong A, Hancock SL, Bloom JR, *et al.* Mammographic screening in women at increased risk of breast cancer after treatment of Hodgkin's disease. *Breast J* 2008;14:39–48.

54. Mariano MN, van den Bosch MA, Daniel BL, *et al.* Contrast-enhanced MRI of ductal carcinoma *in situ*: characteristics of a

new intensity-modulated parametric mapping technique correlated with histopathologic findings. *J Magn Reson Imaging* 2005;22: 520–6.

55. Lehman CD, Blume JD, Weatherall P, *et al.* Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer* 2005;103:1898–905.

56. Boyd NF, Guo H, Martin LJ, *et al.* Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007;356:227–36.

57. Kriege M, Brekelmans CT, Boetes C, *et al.* Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 2004;351:427–37.

58. Saslow D, Boetes C, Burke W, *et al.* American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2007;57:75–89.