Individualized Estimates of Second Cancer Risks After Contemporary Radiation Therapy for Hodgkin Lymphoma

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BACKGROUND. Estimates of radiation-related second cancer risk among Hodgkin lymphoma survivors are largely based on radiation therapy (RT) fields and doses no longer in use, and these estimates do not account for differences in normal tissue dose among individual patients. This study gives individualized estimates for the risks of lung and female breast cancer expected with contemporary involved-field RT and low-dose (20 Gy) RT for mediastinal Hodgkin lymphoma.

METHODS. Three RT plans were constructed for 37 consecutive patients with mediastinal Hodgkin lymphoma: 35 Gy mantle RT, 35 Gy involved-field RT (IFRT), and 20 Gy IFRT. For each of the 111 RT plans, individual-level dosimetry data were incorporated into a cell initiation/inactivation/proliferation model to estimate the excess relative risk (ERR) and cumulative incidence of radiation-induced second cancer.

RESULTS. ERR estimates were compatible with results of epidemiological studies. Compared with 35 Gy mantle radiation therapy, 35 Gy IFRT was predicted to reduce the 20-year ERRs of breast and lung cancer by 63% and 21%, respectively, primarily because of lower normal tissue doses with the omission of axillary RT. Low-dose (20 Gy) IFRT was associated with a 77% and 57% decrease in these ERRs. Patient-specific differences in normal tissue dose with IFRT led to 11-fold and 3.6-fold variations among individual's estimates of breast and lung cancer ERR, respectively.

CONCLUSIONS. Contemporary IFRT is predicted to substantially reduce risk of secondary breast and lung cancer compared with mantle RT, with considerable variation in risk among individuals. Individualized prospective risk estimates could facilitate patient-specific counseling and the development of more effective RT techniques. ***Cancer*** **2007;110:2576–86.** © *2007 American Cancer Society.*

KEYWORDS: Hodgkin lymphoma, radiotherapy, mantle, involved-field, extended-field, radiation dose, individualized second cancer risk, mathematical modeling, biological modeling.

Numerous studies have demonstrated increased risk of second malignancy among young cancer survivors, largely attributed to radiation therapy (RT).[1–8] However, because of the long latency required to observe second solid cancers and the rapid evolution of RT techniques, many estimates of radiation-related second cancer risk reflect outcomes of treatment no longer in use. For example, RT has been associated with significantly increased risk of second cancer among Hodgkin lymphoma survivors, but published risk estimates are largely based on patients treated with $\geq$35 Gy to mantle, extended-field, or subtotal nodal RT fields in the 1960s through the 1980s.[5–9] Since that time, Hodgkin lymphoma treatment has

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progressed to use smaller involved-field radiation therapy (IFRT) fields, and recent clinical trial results suggest that low-dose (20 Gy) RT may emerge as standard treatment for adult Hodgkin lymphoma.[10,11] Moreover, there is large variation in normal tissue exposure among individuals who are nominally receiving the same form of RT.[12,13] Consequently, published risks of second cancers are likely not generalizable to contemporary Hodgkin lymphoma patients and conceal substantial differences in risk among individual patients.

Ideally, patient-specific radiation exposure data could be used to prospectively estimate RT-related second cancer risk. This approach has the potential advantages of being patient-specific and also providing second cancer risk estimates to newly diagnosed patients undergoing treatment, thereby facilitating risk counseling and treatment decisions. Finally, modeling of second cancer risk could aid development of more effective RT techniques by helping to quantify the reduction in late toxicity expected from changes in RT practice.

Recent advances in RT planning systems and in the radiobiologic modeling of second cancer risk facilitate these goals. The radiobiologic modeling of second cancer risk has historically been hindered by uncertainty concerning the dose-to-risk relation for radiation-induced cancer at high radiation doses.[14] Early models of radiation-induced cancer had predicted that virtually all radiation-mutated cells would be sterilized by doses in the range commonly prescribed for RT, and, thus, the risk of radiation-induced cancer would be minimal.[15,16] However, such predictions are not compatible with epidemiologic evidence for Hodgkin lymphoma survivors, for whom the risk of second cancer continues to increase with increasing radiation doses above 20 Gy.[2,3,17–19] By contrast, a recently developed radiobiological model of carcinogenesis[20] takes into account cellular repopulation by proliferation that occurs both during and after fractionated RT.[21–24] In terms of carcinogenesis, repopulation largely cancels the effects of cellular inactivation, as some of the proliferating cells carry and pass on premalignant damage produced earlier in the treatment. The inclusion of cellular repopulation in models of radiation-induced cancer results in predictions of second lung cancer and breast cancer risk at high radiation doses ($\geq$20 Gy) more compatible with epidemiological evidence.[1,3,7]

Utilization of this model is facilitated by modern computed tomography (CT)-based RT planning systems that allow detailed estimates of the normal tissue radiation dose delivered during an individual's course of RT. Taken together, these advances potentially permit the prospective estimation of second cancer risk associated with changes in RT dose and treatment volumes.[25]

This study uses individual-level radiation dose data and a contemporary radiobiological model to estimate the decrease in risks of breast and lung cancer expected with RT volume and dose reductions for mediastinal Hodgkin lymphoma. We also describe the variation in second cancer risk estimates among individuals who are nominally receiving the same RT treatment.

MATERIALS AND METHODS

The study included 37 consecutive patients (16 men, 21 women) with Stage I-III Hodgkin lymphoma who received mediastinal RT at the Princess Margaret Hospital, Canada. Prepubertal patients and those receiving RT for recurrence were excluded. Patients without mediastinal involvement were excluded, because most of the radiation-related risk of second breast and lung cancer arises from irradiating the mediastinum. Thirty-one (84%) patients had disease confined to the lymph nodes within the mediastinum $\pm$ neck. Four patients (3 women, 1 man) had unilateral axillary involvement, 1 female patient had bilateral axillary involvement, and 1 female patient had a cardiac effusion. All patients received chemotherapy before RT, most commonly ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). The study was approved by the hospital's research ethics board.

Radiotherapy Technique

For each patient, 3 RT plans were constructed by using the patient's planning CT data set: 35 Gy in 20 fractions mantle RT (historical treatment), 35 Gy in 20 daily fractions IFRT (current treatment), and 20 Gy in 10 daily fractions IFRT (potential future treatment). Figure 1 shows surface projections of typical field borders for mantle RT and IFRT.

For IFRT planning, target volumes were the same as those used for the actual IFRT delivered. The clinical target volume (CTV) typically consisted of nodal regions involved with Hodgkin lymphoma at the time of diagnosis, accounting for reduction in mediastinal width due to chemotherapy. Typcially there was a 1.5 cm margin from the mediastinum to the edge of the lung shields. Adjacent nodal regions were included according to established guidelines.[26] Treatment volumes were identical for the 35 Gy and 20 Gy IFRT plans. Mantle fields were designed according to accepted anatomic landmarks,[26] and used the post-chemotherapy mediastinal width to define the med-

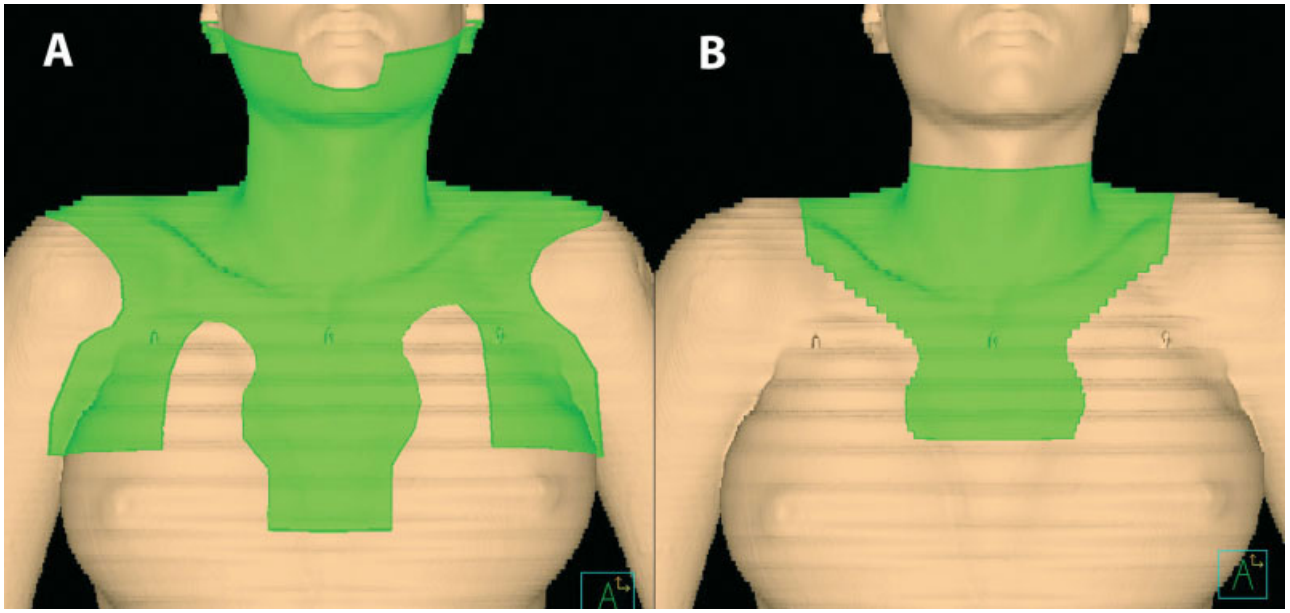

FIGURE 1. Digitally reconstructed CT planning images demonstrate surface projection of (A) anterior beam of mantle RT field, (B) mediastinal involved field RT (IFRT). Substantial reduction in breast tissue exposure can be seen with the omission of the axillae from IFRT fields.

iastinal CTV. The inferior border was placed at the bottom of thoracic vertebra 9 (T9) or more inferiorly when required to cover the intial extent of disease. The upper border of the lung shields was typically 1.5 cm below the clavicles, curved along the inferior border of the fourth rib, and then extended laterally to shield breast tissue at a level 1 cm above the inferior tip of the scapula.

For all cases, opposed anterior and posterior beams were used, ensuring coverage of the CTV within ±8% of the prescription dose, with point maximum doses no greater than 110% of the prescription dose. Dose corrections for tissue inhomogeneity were applied. Beam energy was 6 MV, with some patients also treated with 18 MV segments to improve dose homogeneity. All treatment plans were generated by using the Pinnacle planning system, version 6.2b (ADAC Laboratories, Milpitas, Calif).

Second Cancer Risk Modeling

The relation between fractionated radiation dose and cancer risk was modeled for female breast and for lung by using a cell initiation/inactivation/proliferation model described in detail previously.[20] This model extends the standard initiation/inactivation radiation cancer risk model,[16] which predicts that increased inactivation of premalignant cells with increasing radiation dose leads to negligible radiation-related cancer risk at the prescribed tumor dose (eg, at 35 Gy), a prediction incompatible with epidemiologic studies.[3,17] In contrast, the initiation/inactivation/proliferation model used here has been shown to predict second cancer risks at high doses consistent with the epidemiological data for Hodgkin lymphoma.[13,20]

The model predicts organ-specific cancer risks at high and low radiation doses based on 1) cancer risk data from atomic-bomb survivors (who were exposed to lower doses), 2) the demographic variables (age, time since exposure, sex, ethnicity) of the individual(s) of interest, and 3) organ-specific parameters describing radiation-induced cellular repopulation (which have previously been estimated both for breast and lung).[20] Ordinary differential and difference equations were used to track the time development of the mean normal stem-cell number and of the mean initiated, premalignant stem-cell number during the fractionated radiotherapy and until cellular repopulation was completed. The model assumes that the repopulation dynamics of the premalignant stem cells follows the same basic pattern as that of the normal stem cells but with the possibility that the per-cell growth rate of premalignant cells differs by a constant factor, r, from the per-cell growth rate for normal stem cells. The parameter values used in the calculation were the same as those used previously[20] except for $r = 0.825$ (for breast) and $r = 1$ (for lung), which gives slightly better agreement with earlier extended-field epidemiological data[3] than the

values $r = 0.76$ and $r = 0.96$ used previously for breast and lung.[20]

The model was used to generate organ-specific excess relative risk (ERR, where ERR = RR-1) estimates for each dose and fractionation scheme, assuming treatment delivered in daily fractions of 1.75 Gy to 2.0 Gy. For each RT plan, dose volume histograms (DVH) were calculated for bilateral lungs and female breasts. Each incremental small volume in the DVH, ΔV_j (j = 1200), is associated with a total dose of $D_j = {}_j\Delta D$. Given the associated ERR (D_j), the overall predicted ERR is the volume average of these local ERRs, ie, ERR = $(1/V)\Sigma_j$ ERR (D_j) ΔV_j, where V is organ volume. Estimated ERRs are presented for modeled ages of 20, 30, or 40 years at treatment.

The cumulative incidences of breast and lung cancer after RT were estimated, accounting for competing risks of mortality. The rate for competing risks was obtained from the survival of the Hodgkin lymphoma population using U.S. National Institutes of Health National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) data and SEER*Stat software.[27] For the calculation of breast cancer incidence, the rate of competing risks was approximated by using the overall rate of death in the Hodgkin lymphoma population, assuming that the cause of death in the Hodgkin lymphoma population was primarily due to causes other than breast cancer. The survival for female patients treated at 20, 30, and 40 years of age was calculated by using the population diagnosed at ages 15–24 years, 25–34 years, and 35–44 years, respectively. The rate of breast cancer in the female general population was estimated by using SEER incidence data[28] at 5-year age categories as follows: 20–24 years, 25–29 years, ..., 85+ years. The increase in the hazard for the Hodgkin lymphoma population compared with the general population was calculated as 1 + ERR, with ERR (scaled for time since RT) obtained from the initiation/inactivation/proliferation model described above. The rate for breast cancer in Hodgkin lymphoma population was calculated as the product between 1 + ERR and the rate of breast cancer incidence in the general population.

To estimate the competing risk of death, the survival for smoking and nonsmoking Hodgkin lymphoma patients was obtained by numerically solving the system of equations:

$$HR(t_{i+1}) = \frac{\log\left(S_s(t_i)\right) - \log\left(S_s(t_{i+1})\right)}{\log\left(S_{ns}(t_i)\right) - \log\left(S_{ns}(t_{i+1})\right)}$$

$$p_s S_s(t) + (1 - p_s) S_{ns}(t) = S(t) \quad \text{for } \forall t$$

where $S(.)$ is the survival of Hodgkin lymphoma population, HR is the increase in the hazard due to smoking, p_s is the proportion of smokers; the underscript s stands for quantities specific to smokers, and ns applies to quantities specific to nonsmokers. The proportion of smokers, age-specific and sex-specific, were obtained from statistics published by the U. S. Department of Health and Human Services[9] using estimates for white men and women ages 20, 30, and 40 years for calendar years 2000–2003. The hazard of death in smokers and nonsmokers by age group were obtained from Lew et al.[30] The survival of smokers and nonsmokers was assumed to be the same for the population in 2000–2003 as for the population in 2004 and 2005.

The rate of lung cancer in the general population was estimated by using SEER data.[28] The rates are estimated separately for men and women by using 5-year age categories, 20–24 years, 25–29 years, ..., 85+ years. For breast cancer, the increase in the hazard for the Hodgkin lymphoma population compared with the general population was calculated as 1 + ERR with time-scaled ERR obtained from the radiobiologic model. By using the proportion of smokers (p_s) in the population and the proportion of lung cancers attributed to smoking (p_l), the rate of lung cancer for smokers (r_s) and nonsmokers (r_{ns}) can be estimated as follows:

$$r_s = \frac{p_l r}{p_s}$$

and

$$r_{ns} = \frac{(1 - p_l) r}{1 - p_s}$$

where r is the rate of lung cancer in the general population. The rate of lung cancer in Hodgkin lymphoma population was then calculated as the product between 1 + ERR and the rate of lung cancer incidence in the general population by age, sex, and smoking status. Lung cancer risks are presented for nonsmokers to avoid additional assumptions of the interaction of smoking and RT on lung cancer risk and also because these results apply to the majority of contemporary Hodgkin lymphoma patients in North America.

RESULTS

Average Breast Cancer Risk

All mediastinal RT treatments were predicted to increase the risk of breast cancer, regardless of the prescribed RT dose or field size. The median pre-

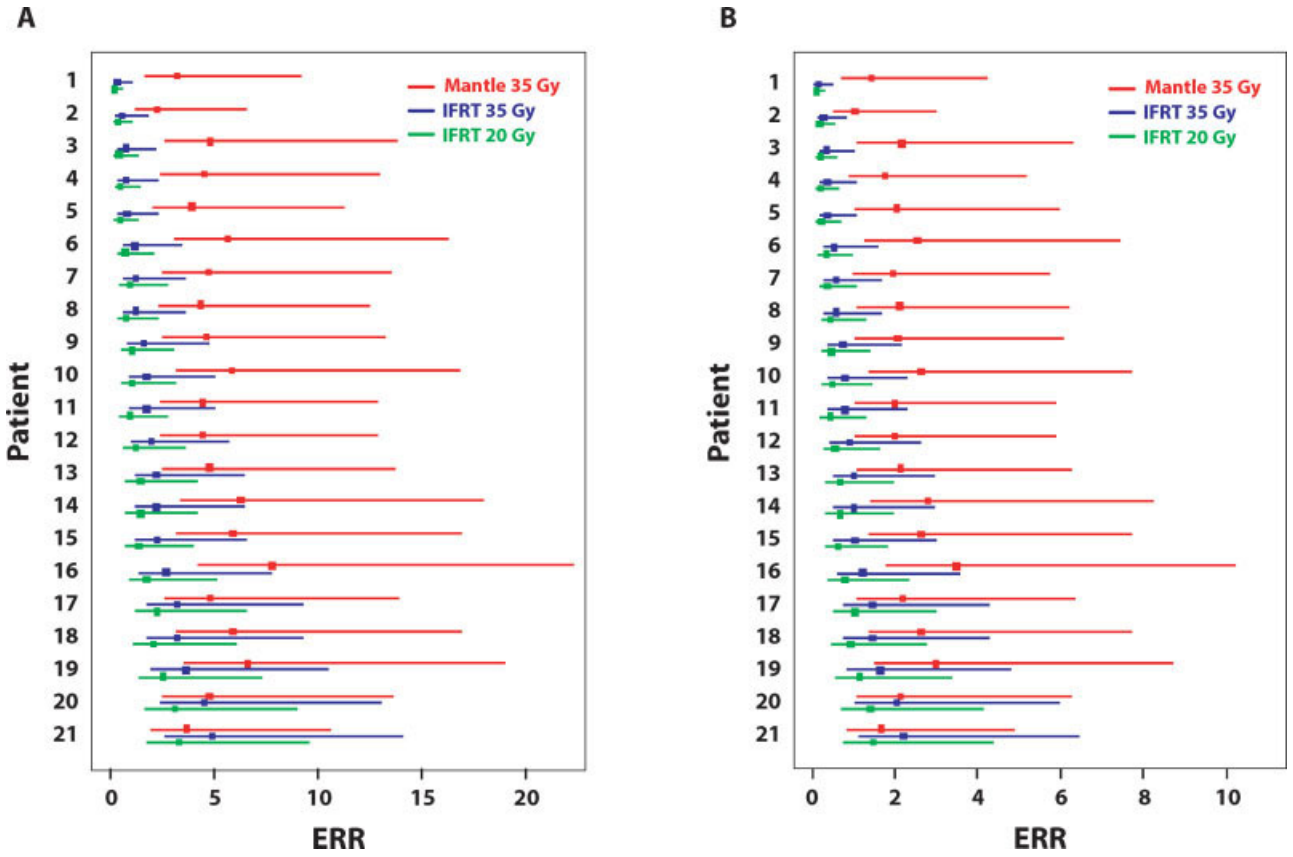

FIGURE 2. Estimated ERRs of breast cancer for 21 female HL patients. Error bars show 95% confidence intervals. Different ERR scales are use for different ages at exposure. (A) Modeled age 20 years: median ERRs were 4.8 (35 Gy mantle), 1.8 (35 Gy IFRT), and 1.1 (20 Gy IFRT). (B) Modeled age 30 or 40 years: median ERRs were 2.1 (35 Gy mantle), 0.8 (35 Gy IFRT), and 0.5 (20 Gy IFRT).

dicted 20-year ERR (=RR-1) of breast cancer for women treated at age 20 with 35 Gy mantle RT was 4.8 (Fig. 2A). This risk was predicted to decline to 1.8 after 35 Gy IFRT, and to 1.1 after 20 Gy IFRT. Consistent with epidemiologic studies, the estimated ERR of breast cancer decreased with older age at treatment. The transition to IFRT was predicted to cause similar proportional reductions in the ERR of breast cancer among women treated at age 30 years (Fig. 2B), where the median 20-year ERR of breast cancer declined from 2.1 (mantle 35 Gy) to 0.8 (IFRT 35 Gy) and 0.5 (IFRT 20 Gy).

For modeled age 20 years at RT, the medians of individual's estimated 20-year cumulative incidence of breast cancer were 3.1%, 1.5%, and 1.1% after treatment with 35 Gy mantle, 35 Gy IFRT, and 20 Gy IFRT, respectively, with an expected incidence in the general population of the same age of 0.5% (Fig. 3). Although women treated at age 30 years had lower predicted ERRs of breast cancer than younger women, their higher baseline risk led to a higher median estimated 20-year cumulative incidence after the same treatments, ie, 5.8%, 3.3%, and 2.7%, after 35 Gy mantle, 35 Gy IFRT, and 20 Gy IFRT, respectively. The expected rate in the general population is 1.8%.

Individual Breast Cancer Risk

Differences in radiation exposures to normal tissues led to significant variation in the predicted ERRs among individuals nominally receiving the same treatment. For example, among women treated at age 30 years, there was a 3.5-fold variation among individually predicted ERR of breast cancer after 35 Gy mantle RT (lowest = 1.0; 95% CI, 0.5–3.0; highest = 3.5; 95% CI, 8–10.2; Fig. 2B). This variation increased to 11-fold after 35 Gy IFRT (lowest = 0.2; 95% CI, 0.1–0.5; highest = 2.2; 95% CI, 1.1–6.4; Fig. 2B).

Individual-level differences in breast cancer risk after IFRT were largely related to the increase in breast dose in cases where axillae were irradiated in the IFRT field. For 30-year-old women with disease

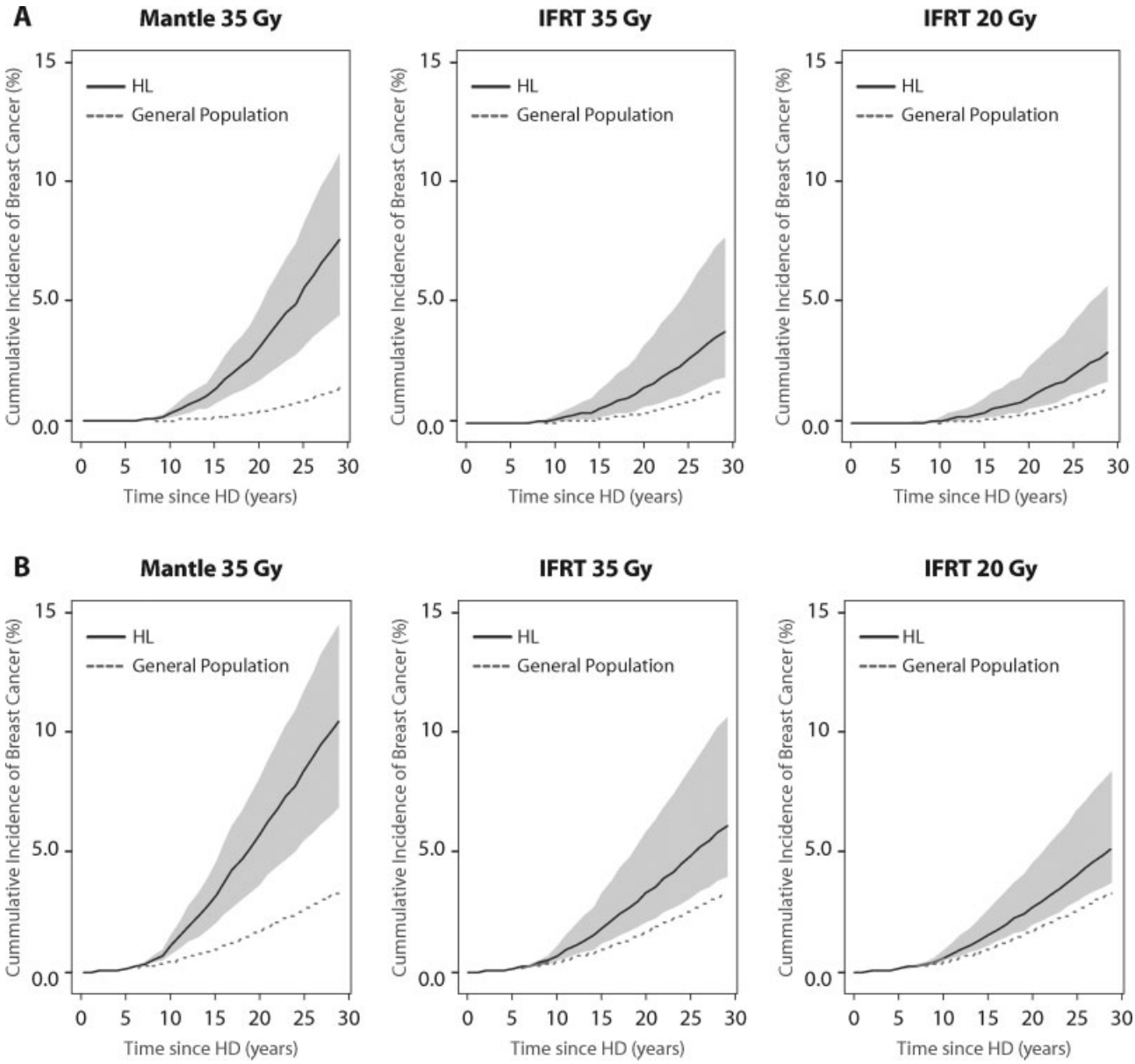

FIGURE 3. Estimated cumulative incidence of breast cancer treated at (A) age 20 years or (B) age 30 years. Shaded areas illustrate the range of estimated cumulative incidence calculated with individual patient's median ERR estimates.

limited to the mediastinum with or without neck nodes, the median estimated 20-year ERR of breast cancer with 35 Gy IFRT was 0.8, whereas if 1 axilla was treated, it was 0.9, and 1.6 if both axillae were treated (the latter estimate based on a single case). In 1 woman with unilateral axillary disease and mediastinal bulk (Patient 21 in Fig. 2), the mean breast dose with 35 Gy IFRT was 260 cGy higher than with the 35 Gy mantle plan, resulting in a slightly higher ERR of breast cancer. This was because of wider margins around the infraclavicular lymph nodes in the IFRT plan.

Average Lung Cancer Risk

Lung cancer ERRs for nonsmoking patients are shown in Figure 4. The median estimated 20-year ERRs of lung cancer for nonsmoking women treated with 35 Gy mantle at ages 20 or 30 years were 18.0 and 7.4, respectively. The transition from 35 Gy mantle to 35 Gy IFRT was predicted to lead to a 21% reduction in the median ERR of lung cancer. IFRT dose reduction to 20 Gy was estimated to reduce the 20-year ERRs of lung cancer for nonsmoking women treated at age 20 or 30 years to 7.8 and 3.2, respectively, a 57% reduction compared with 35 Gy mantle

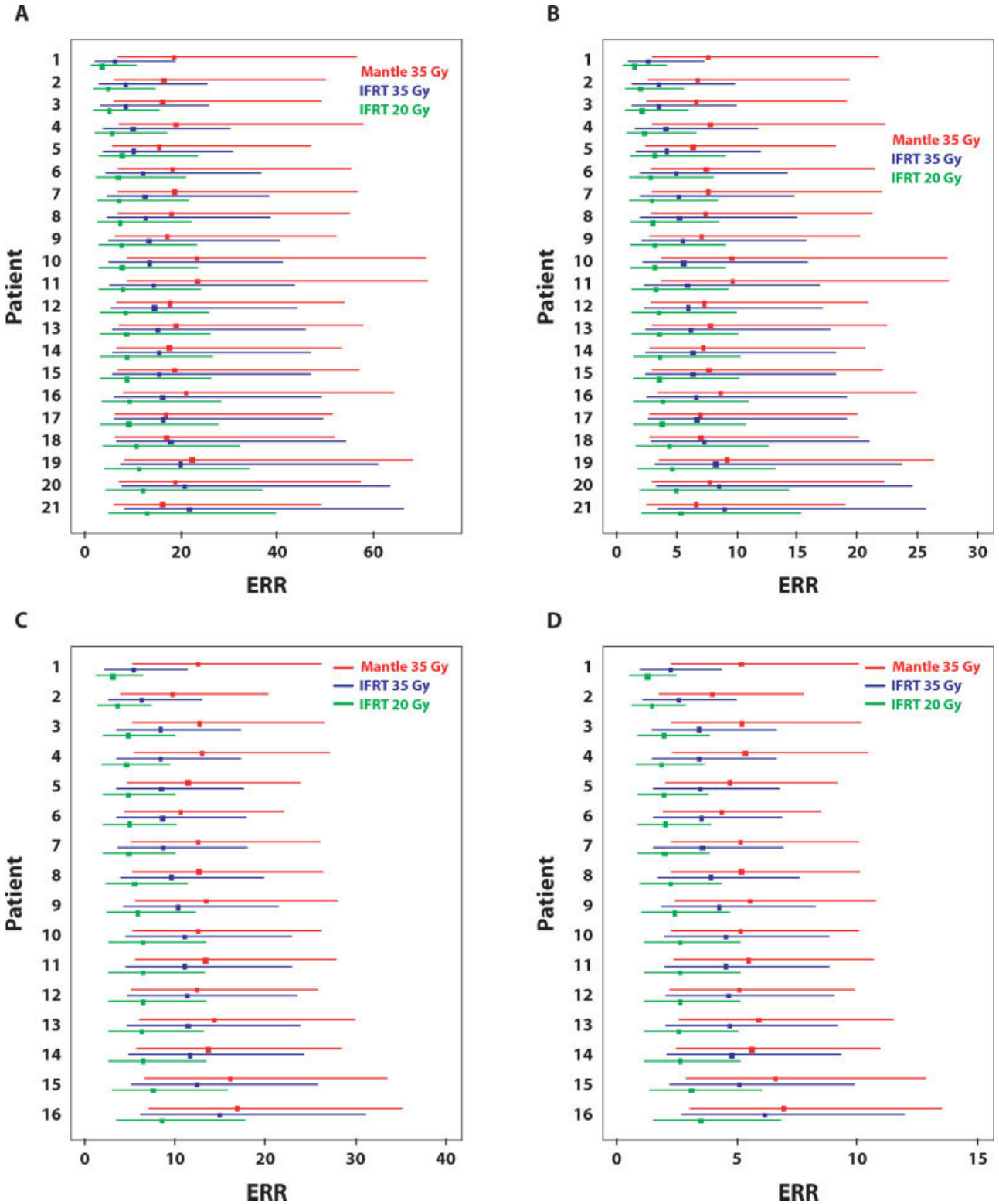

FIGURE 4. Individual patients' ERR estimates of lung cancer among nonsmoking Hodgkin lymphoma survivors. Different ERR scales are used for different sexes and ages at exposure. Error bars show 95% confidence intervals. (A) Women aged 20 years: median ERRs were 18.0 (35 Gy mantle), 14.2 (35 Gy IFRT), and 7.8 (20 Gy IFRT). (B) Women aged 30 years: median ERRs were 7.4 (35 Gy mantle), 5.8 Gy (35 Gy IFRT), and 3.2 (20 Gy IFRT). (C) Men aged 20 years: median ERRs were 12.6 (35 Gy mantle), 9.9 (35 Gy IFRT), and 5.6 (20 Gy IFRT); (D) Men aged 30 years: median ERRs were 5.2 (35 Gy mantle), 4.1 (35 Gy IFRT), and 2.3 (20 Gy IFRT).

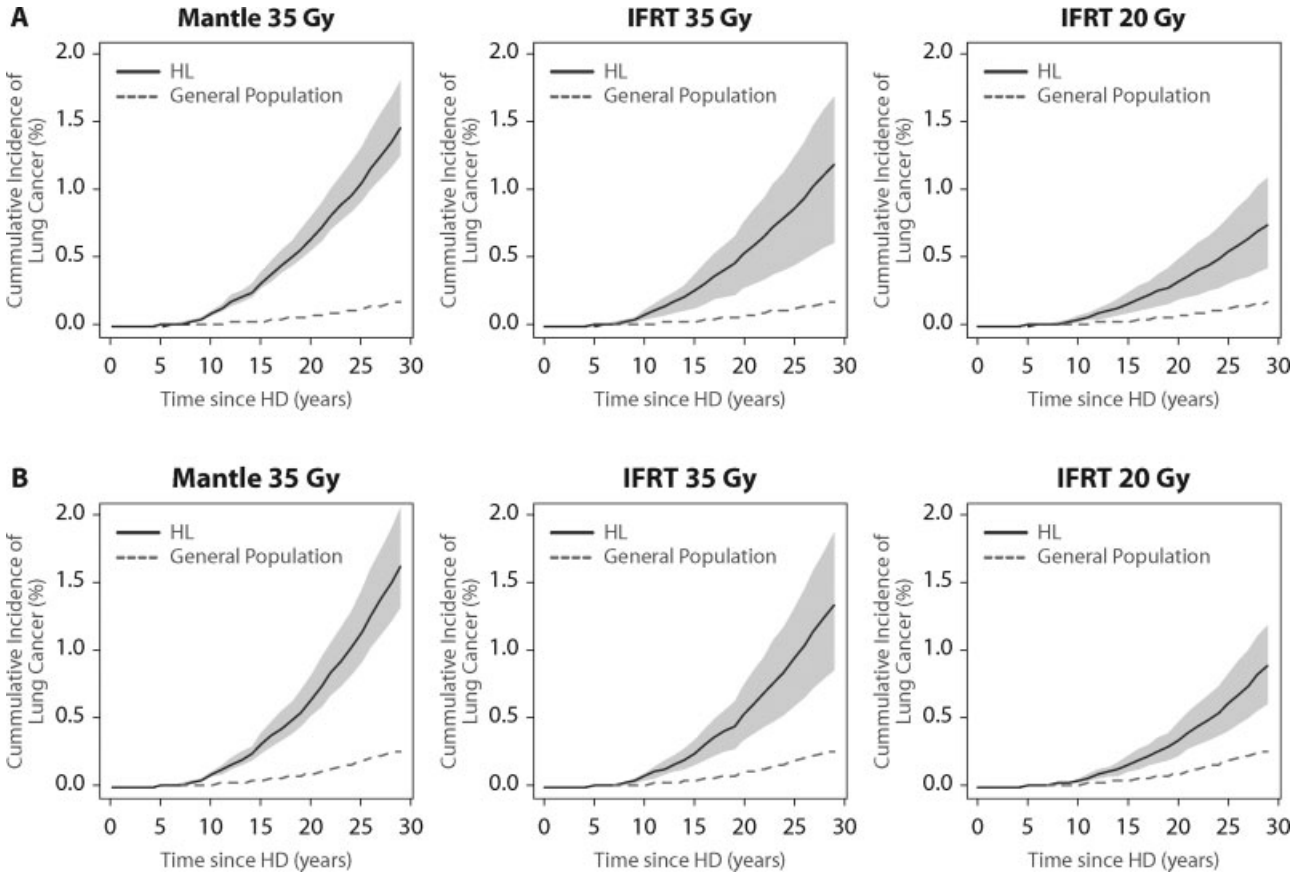

FIGURE 5. Cumulative incidence of lung cancer among nonsmoking (A) females or (B) males age 40. Shaded areas illustrate the range of estimated cumulative incidence calculated based on individual patients' median ERR estimates.

RT. The proportional reduction in the predicted ERR of lung cancer with the transition to 35 Gy IFRT and 20 Gy IFRT was the same for men. Consistent with epidemiologic studies, the 20-year ERRs of lung cancer were higher for women than men (Fig. 4).

Prior studies have shown that the excess absolute risk of lung cancer is observed primarily in patients treated at older ages.[5] Among nonsmoking men treated at age 40 years, the predicted 20-year cumulative incidence of lung cancer decreased from 2.0% (mantle 35 Gy) to 1.6% (IFRT 35 Gy), and 1.1% (IFRT 20 Gy) in contrast to an expected rate in the general population of 0.3%. Among nonsmoking women treated at age 40 years, the estimated 20-year cumulative incidence of lung cancer attributable to radiation decreased with decreasing radiation exposure from 2.0% (mantle 35 Gy) to 1.6% (IFRT 35 Gy) and 1.0% (IFRT 20 Gy), with an expected rate in the general population of 0.2% (Fig. 5). Younger nonsmoking Hodgkin lymphoma survivors were predicted to have 20-year cumulative incidence rates of lung cancer <1% and similar proportional reductions in ERR with decreasing radiation exposure. Smoking among Hodgkin lymphoma survivors treated at age 40 years was predicted to increase the 20-year cumulative incidence of lung cancer by 3.1% to 6.9%.

Individual Lung Cancer Risk

As with breast cancer, there was significant variation among individuals' estimated ERRs of lung cancer. There was a 1.5-fold variation in the estimated ERR of lung cancer among nonsmoking female patients treated at age 30 or 40 with 35 Gy mantle RT (lowest = 6.3; 95% CI, 2.48–18.16; and highest = 9.6; 95% CI, 3.77–27.60), and this variation increased to 3.6-fold with IFRT 35 Gy (lowest = 2.5; 95% CI, 0.99–7.27; and highest = 8.9; 95% CI, 3.50–25.66). A similar degree of variation in ERR estimates was seen for males (data not shown). Again, this individual-level variation in lung cancer risk after IFRT was largely related to whether axillae were included in the IFRT fields. For 30 or 40-year-old patients

with no axillary RT, the median estimated 20-year ERR of lung cancer with 35 Gy IFRT was 4.6, whereas if 1 axilla was treated, it was 5.7, and if both axillae were treated (single case), it was 8.9. There were 3 cases in which 35 Gy IFRT plans had wider margins around infraclavicular or subcarinal lymph nodes or pericardial disease than the mantle plans, resulting in mean lung doses 66–466 cGy higher and consequently higher ERRs of lung cancer with IFRT.

DISCUSSION

Second cancers are a major cause of morbidity and mortality among long-term survivors of Hodgkin lymphoma. However, published estimates of second cancer risk are largely based on outdated RT treatment. Because contemporary IFRT delivers substantially less radiation to normal tissues than mantle or extended-field RT,[13] it is difficult to apply published risk estimates when informing current patients of risks of modern therapy. To our knowledge, this is the first study to apply a contemporary radiobiological model to develop individualized prospective estimates of second cancer risk following modern IFRT for patients with Hodgkin lymphoma.

The transition from 35 Gy mantle to 35 Gy IFRT was predicted to result in 63% and 21% reductions in the median ERRs of breast and lung cancer attributable to radiation. This reduction in breast cancer risk was largely attributed to the lesser volume of normal tissue irradiated when axillary fields were omitted with IFRT. The results are compatible with the results of a recent meta-analysis that compared extended-field RT with IFRT and found a significantly greater risk of breast cancer associated with the larger fields.[31]

Early outcomes from the EORTC H9F[11] and German HD10[10] trials suggest that 20 Gy IFRT may be as effective as higher doses for selected patients, and our results provide the first estimates of the ERRs of breast and lung cancer that may be expected with the adoption of this treatment. Compared with 35 Gy mantle, 20 Gy IFRT was estimated to reduce median ERRs of breast cancer and lung cancer by 77% and 57%, respectively. These observations not only support the rationale for recent low-dose IFRT trials, but also they suggest a means of evaluating the effect of future changes in RT delivery. For example, by using the methods employed here, it would be possible to estimate the decrease in second cancer risk associated with the transition to even smaller treatment volumes with involved-node RT that has been proposed for future European trials of early stage Hodgkin lymphoma.[32]

Another advantage of dosimetric second cancer risk modeling is the capacity for greater individualization of risk estimates. Because of individual differences in patient anatomy and the location of involved sites, there was substantial variation in the radiation dose to lung and breast tissue delivered to patients receiving nominally similar treatment. Consequently, providing a single estimate of second cancer risk associated with IFRT obscures important differences among individuals' true risks, and this may be misleading for some patients. Further, we found that for 3 patients, wider RT field margins around infraclavicular, mediastinal, or pericardial disease increased the lung or breast tissue dose enough to offset the benefits of IFRT. In each case, the variation in treatment fields was thought to be consistent with variation known to occur in clinical practice,[12] and although it would have been possible to modify the IFRT (or mantle) plans post hoc to produce a reduction in normal tissue dose with IFRT, these cases illustrate how seemingly minor differences in RT planning may influence second cancer risk.

Radiation carcinogenicity has previously been modeled primarily as a balance between initiation of malignancy and cellular killing, ie, beyond a certain radiation dose, greater cell killing was thought to offset cancer induction and the risk of developing a radiation-induced cancer declined. However, this paradigm is not compatible with results of large studies of Hodgkin lymphoma survivors that demonstrate increasing risks with escalating doses well beyond 20 Gy.[3,17–19] By contrast, the model used in this study incorporates the effect of cellular proliferation that is known to occur both during and after fractionated radiotherapy.[24] As a result, the model predicts that second cancer risk continues to rise with doses exceeding 20 Gy, more consistent with results of epidemiological studies of Hodgkin lymphoma survivors.[1,3] For example, women treated with 35 Gy mantle RT at age 20 years were predicted to have a 20-year ERR of breast cancer of 4.8 (RR = 5.8), whereas cohort studies have generally reported 3-fold to 10-fold RRs of breast cancer for women treated in their 20s.[5,7,33,34] Higher RRs have been reported in some studies of young women receiving RT.[35,36] Our finding that the ERR of breast cancer declines with increasing age at treatment is also consistent with epidemiological studies.[7–9]

There are few estimates of the cumulative incidence of breast cancer associated with specific RT doses or fields that can serve as external comparators for our modeled estimates. Cohort studies have reported the 20-year cumulative incidence of breast cancer to be approximately 4% to 8% among young

adult females (ie, <age 25 years) and to be approximately 3% to 16% among older women, on average somewhat higher than our estimates.[5,34,37] In most cases, these cumulative risk estimates did not account for competing causes of death. Furthermore, many patients in published cohort studies likely received doses over 40 Gy to mantle fields that treated prechemotherapy mediastinal volumes without dose correction for tissue inhomogeneity, and, as a result, would have had higher normal tissue doses than were modeled in our 35 Gy mantle scenarios.[38,39] Consequently, we believe that our risk estimates associated with 35 Gy mantle RT are conservative, and, for many patients, the risk reduction associated with transition from historic RT to contemporary IFRT may be greater than the average modeled reduction in our patients. It is also noteworthy that many European trials employ 30 Gy as the standard RT dose, with a further proportional reduction in normal tissue exposure compared to 35 Gy.

Lung cancer risks after 35 Gy mantle RT estimated in this study are generally in keeping with published RRs that typically range from 4-fold to 12-fold.[5,7–9] Our modeled risks were also consistent with observational studies that found higher RR, but lower absolute risks, of lung cancer among those treated at younger ages.[5,7] In a study of the British National Lymphoma Investigation, the 20-year cumulative risk of lung cancer among patients treated at ages younger than 45 years was 1.4%, and it was 3.6% among all ages.[5] Similar cumulative incidence of lung cancer has been reported by others.[9] Again, radiation dose-specific and field-specific estimates of the cumulative incidence of lung cancer suitable for external comparison of our risk estimates are scarce or nonexistent.

The model used here could be refined further to incorporate other factors that influence second cancer risk. Only second cancer risks attributable to radiation exposure were modeled in this study, whereas the total risk experienced by patients is likely to be influenced by exposure to selected chemotherapy agents,[5,17–19] hormonal factors,[2] or genetic influences,[40] none of which are incorporated into our models. So, while our results incorporate radiation dose, normal tissue volume, patient age, sex, and smoking status, they nevertheless over simplify the complexity of second cancer risk. Ideally, more sophisticated models of second cancer risk would also include information on biologic predisposition and the risk associated with chemotherapy agents to allow even more patient-specific estimates. Collection of individual-level radiation exposure data in patients receiving RT and correlation with observed second cancer risks are necessary to further validate and refine the model used here. Even so, our results provide prospective estimates of second cancer risk substantially more realistic than any prior attempt and provide new insight into the risk associated with contemporary IFRT.

To summarize, our findings provide new insight into the reduction of second cancer risk expected with contemporary IFRT for Hodgkin lymphoma, as well as the possible benefits of further dose reductions. Continued refinement of such models, incorporating new epidemiologic evidence as it arises, could be used to guide the development of more effective RT techniques and could potentially be employed to counsel individual patients on their risk of second cancer after modern therapy.

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