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Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma

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ABSTRACT

BACKGROUND

Survivors of Hodgkin's lymphoma are at increased risk for treatment-related subsequent malignant neoplasms. The effect of less toxic treatments, introduced in the late 1980s, on the long-term risk of a second cancer remains unknown.

METHODS

We enrolled 3905 persons in the Netherlands who had survived for at least 5 years after the initiation of treatment for Hodgkin's lymphoma. Patients had received treatment between 1965 and 2000, when they were 15 to 50 years of age. We compared the risk of a second cancer among these patients with the risk that was expected on the basis of cancer incidence in the general population. Treatment-specific risks were compared within the cohort.

RESULTS

With a median follow-up of 19.1 years, 1055 second cancers were diagnosed in 908 patients, resulting in a standardized incidence ratio (SIR) of 4.6 (95% confidence interval [CI], 4.3 to 4.9) in the study cohort as compared with the general population. The risk was still elevated 35 years or more after treatment (SIR, 3.9; 95% CI, 2.8 to 5.4), and the cumulative incidence of a second cancer in the study cohort at 40 years was 48.5% (95% CI, 45.4 to 51.5). The cumulative incidence of second solid cancers did not differ according to study period (1965–1976, 1977–1988, or 1989–2000) ($P=0.71$ for heterogeneity). Although the risk of breast cancer was lower among patients who were treated with supradiaphragmatic-field radiotherapy not including the axilla than among those who were exposed to mantle-field irradiation (hazard ratio, 0.37; 95% CI, 0.19 to 0.72), the risk of breast cancer was not lower among patients treated in the 1989–2000 study period than among those treated in the two earlier periods. A cumulative procarbazine dose of 4.3 g or more per square meter of body-surface area (which has been associated with premature menopause) was associated with a significantly lower risk of breast cancer (hazard ratio for the comparison with no chemotherapy, 0.57; 95% CI, 0.39 to 0.84) but a higher risk of gastrointestinal cancer (hazard ratio, 2.70; 95% CI, 1.69 to 4.30).

CONCLUSIONS

The risk of second solid cancers did not appear to be lower among patients treated in the most recent calendar period studied (1989–2000) than among those treated in earlier periods. The awareness of an increased risk of second cancer remains crucial for survivors of Hodgkin's lymphoma. (Funded by the Dutch Cancer Society.)

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Since the late 1960s, when combination chemotherapy and high-energy radiation therapy were introduced for the treatment of Hodgkin's lymphoma, survival has increased dramatically. Cure has come at a price, however, because the treatment of Hodgkin's lymphoma has been shown to increase the risk of subsequent malignant neoplasms and other late effects considerably.[1-22] Although very high relative risks have been observed for leukemia (especially among patients who were treated with alkylating agents) and non-Hodgkin's lymphoma (which was not previously associated with a particular type of therapy), second solid cancers, the occurrence of which is related primarily to radiation therapy, contribute most to the absolute excess risk of a second cancer among survivors of Hodgkin's lymphoma.

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At 5 to 10 years after treatment, the relative risk of solid cancer is significantly higher among survivors of Hodgkin's lymphoma than in the general population, and this higher risk persists for at least 25 years.[11,19,20] Few studies have investigated the evolution of a risk of a second solid cancer beyond 25 years after treatment.[7,11,13,16] On the basis of increased knowledge of late effects, the treatment of Hodgkin's lymphoma has changed, with a trend toward the use of smaller radiation target volumes, lower radiation doses, and more effective, generally less toxic chemotherapy schemes.[23,24] However, the effect of these changes on the risk of a second cancer is still unknown.

In this study, we investigated the long-term risk of a second cancer and changes in risk over time in a large cohort of survivors of Hodgkin's lymphoma in the Netherlands. These patients had been treated between 1965 and 2000 and had detailed information on primary and relapse treatment and complete follow-up for second cancers.

METHODS

STUDY DESIGN AND PATIENTS

This study included 3905 persons in the Netherlands who had first been treated for Hodgkin's lymphoma between 1965 and 2000, when they were between 15 and 50 years of age, and who had survived for at least 5 years after receiving treatment. Patients were treated at seven academic centers or in nonacademic hospitals that were located within the region of three population-based cancer registries. The selection of the patients and the methods for data collection have been described previously.[3,8,10,12,19,22] Detailed information regarding radiation fields, chemotherapy regimens, and number of cycles, including treatment for relapse, was collected from medical files.

We used the estimated cumulative dose of procarbazine as a measure of the dose of alkylating chemotherapy, because procarbazine was nearly always administered in patients with Hodgkin's lymphoma in a combination chemotherapy regimen that included alkylating agents. For patients for whom the number of cycles of a specific regimen was unknown, the median number of cycles administered for either the initial treatment or relapse treatment within a specific treatment period (1965–1976, 1977–1988, or 1989–2000) was imputed.

Information on second cancers, including dates of diagnosis, morphologic features, topographic features, and treatment, was collected by a review of medical records, by responses to questionnaires sent to general practitioners (the response regarding second cancers was 96% complete until 1989),[8] and by record linkage with the Netherlands Cancer Registry since 1989, when the Netherlands Cancer Registry reached nationwide coverage. Information on second cancers and vital status was complete up to at least January 1, 2010.

STATISTICAL ANALYSIS

The time at risk started 5 years after the initiation of treatment and ended at the date of diagnosis of the second cancer, the date of death, or the data-censoring date. The calculation of the expected numbers of solid cancers was based on age- sex-, calendar period–, and site-specific cancer-incidence rates in the Dutch population, multiplied by the corresponding number of person-years at risk. From the observed and expected numbers of second cancers, we used standard methods to compute the standardized incidence ratios (SIRs), the absolute excess risk per 10,000 person-years, and the corresponding 95% confidence intervals.[25]

Tests for homogeneity and trend of SIRs according to sex, age, follow-up interval, attained age, and treatment (handled as a time-dependent variable to account for relapse treatment) were

performed within collapsed person-time Poisson regression models. We performed tests for linear trends in SIRs by evaluating the likelihood function of a model with a variable representing the follow-up interval or attained age as discrete values against the likelihood of a model without that variable. Tests for trend with respect to absolute excess risks were performed in additive Poisson regression models.[26]

Basal-cell skin cancers were excluded from all the analyses. The myelodysplastic syndrome was included only in the analyses of cumulative incidence, because no population reference rates were available for this disease. All second cancers that were diagnosed within 5 years after the start of treatment for Hodgkin's lymphoma were excluded from the analyses; any subsequent second cancer was included in the analyses. Patients in whom multiple second cancers developed were counted only once in the analysis of all second cancers combined; in this analysis, the time at risk ended on the date the first second cancer was diagnosed. In cancer site–specific analyses, patients with multiple second cancers contributed data regarding a second cancer of interest, regardless of whether this cancer was preceded by one at another site.

The cumulative incidence of second cancers was estimated with death treated as a competing risk, and trends over time were evaluated in competing-risk models, with adjustment for the effects of sex, age, and smoking status when appropriate.[27] The expected cumulative incidence was derived from the expected cancer incidence and expected overall mortality in the general population, which was estimated with the use of the conditional method.[28] Factors affecting the cumulative incidence of second cancers were assessed with the use of a multivariable Cox regression analysis, with treatment handled as a time-dependent variable. All reported P values are two-sided; P values of less than 0.05 were considered to indicate statistical significance. All the analyses were performed with the use of Stata statistical software, version 13 (StataCorp).

Table 1. Characteristics of the Patients.

Characteristic	Patients (N=3905)
	no. (%)
Sex	
Male	2207 (56.5)
Female	1698 (43.5)
Treatment period	
1965–1976	808 (20.7)
1977–1988	1195 (30.6)
1989–2000	1902 (48.7)
Age at first treatment for Hodgkin's lymphoma	
15–24 yr	1410 (36.1)
25–34 yr	1326 (34.0)
35–50 yr	1169 (29.9)
Maximum follow-up	
5–9 yr	349 (8.9)
10–14 yr	819 (21.0)
15–19 yr	945 (24.2)
20–24 yr	716 (18.3)
25–29 yr	464 (11.9)
30–34 yr	330 (8.5)
35–39 yr	180 (4.6)
≥40 yr	102 (2.6)
Treatment category*	
Radiation therapy only	1068 (27.3)
Chemotherapy only	473 (12.1)
Radiation therapy and chemotherapy	2364 (60.5)

* Data include treatment for recurrence. Percentages may not total 100 because of rounding.

RESULTS

PATIENTS

The cohort included 2207 male and 1698 female patients who had survived for at least 5 years after the start of treatment for Hodgkin's lymphoma (Table 1; and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Treatment (including treatment for relapse) consisted of radiation therapy only in 27.3% of the patients, chemotherapy only in 12.1%, and both therapies in 60.5%. Treatment changed over time; patients who were treated in the period from 1989 through 2000 received smaller radiation target volumes, anthracycline-containing chemotherapy, lower doses of alkylating agents, and less frequent infradiaphragmatic irradiation than those who were treated in the two earlier periods (Table S2 in the Supplementary Appendix).

The median age of the patients at the start of treatment was 28.6 years, and the median follow-up was 19.1 years (range 5.0 to 47.2), with 27.5% of patients being followed for at least 25 years. The median age of the patients at the end of follow-up was 50.4 years.

OBSERVED RISK OF SECOND CANCER AS COMPARED WITH THE GENERAL POPULATION

During follow-up, 1055 second cancers were diagnosed in 908 patients; a third cancer developed in 130 patients, and a fourth developed in 17. The risk of a second cancer among patients who had been treated for Hodgkin's lymphoma was higher than the incidence of cancer in the general population (SIR, 4.6; 95% confidence interval [CI], 4.3 to 4.9), which resulted in 121.8 excess cancers per 10,000 person-years (Table 2).

SIRs were significantly higher in the study cohort than in the general population for cancers at all sites at which at least 10 second cancers were observed, with the exception of prostate cancer. Risks that were more than 10 times as high as those observed in the general population were seen for thyroid cancer, soft-tissue sarcoma, mesothelioma, and non-Hodgkin's lymphoma, whereas SIRs were 5 to 10 times as high for esophageal, stomach, pancreatic, and lung cancer as well as leukemia. The significantly higher relative risks of thyroid cancer, mesothelioma, and soft-tissue sarcoma were associated with low absolute risks (30-year cumulative incidence, 0.8%, 0.6%, and 0.7%, respectively), owing to low background risks in the population.

Breast cancer contributed most to the overall absolute excess risk (24.9 cases of breast cancer per 10,000 person-years among men and women), representing 20.4% of the excess risk of any second cancer (121.8 cases per 10,000 person-years) in the cohort; the absolute excess risk of breast cancer among women was 54.3 cases per 10,000 person-years, representing 40.5% of the excess risk of any second cancer (134.0 cases per 10,000 person-years) among women in the cohort. Lung cancer was the next most common (absolute excess risk, 24.6 cases per 10,000 person-years, representing 20.2% of the excess risk in the cohort), followed by gastrointestinal tract cancer (19.7% of the excess risk) and non-Hodgkin's lymphoma (13.1% of the excess risk). The absolute excess risk of leukemia accounted for only 5.0% of the absolute excess risk of any second cancer.

RELATIVE AND ABSOLUTE EXCESS RISK ACCORDING TO SEX, AGE, AND FOLLOW-UP

The SIR for any second cancer remained high for at least 35 years after the start of treatment for Hodgkin's lymphoma (SIR for ≥35 years, 3.9; 95% CI, 2.8 to 5.4) (Fig. 1A), whereas the absolute excess risk increased steadily over time ($P<0.001$ for trend) (Fig. 1B). After 35 years or more of follow-up, survivors of Hodgkin's lymphoma had 364 excess cancers per 10,000 person-years. SIRs did not differ appreciably between men and women.

The SIRs for second solid cancers decreased with increasing age at the time of diagnosis of Hodgkin's lymphoma ($P<0.001$ for trend) (Table S3 in the Supplementary Appendix), rose over the first 15 years of follow-up, and remained stable thereafter. The absolute excess risk of solid cancers increased with attained age in the cohort ($P<0.001$ for trend, regardless of age at start of treatment), but SIRs decreased with older attained ages ($P<0.001$ for trend). Survivors of Hodgkin's lymphoma who were in their 60s had 1.7 excess cancers per 100 person-years and those in their 70s had 3.1 excess cancers per 100 person-years, on top of a background incidence of 1.3 and 2.1 cancers per 100 person-years, respectively.

The SIRs for lung cancer did not decrease with increasing age at the time of treatment for Hodgkin's lymphoma as strongly as they did for breast cancer and gastrointestinal tract cancer. As compared with the incidence in the general population, the SIR for lung cancer was 5.2 among patients who had been treated for Hodgkin's lymphoma when they were 35 to 50 years of age. In addition, higher SIRs became apparent earlier (5 to 9 years after the first treatment) for lung cancer than for breast cancer and gastrointestinal tract cancer.

CUMULATIVE INCIDENCE ACCORDING TO TREATMENT PERIOD

At 30 years after the start of treatment for Hodgkin's lymphoma, the cumulative incidence of any second cancer, including the myelodysplastic syndrome, was 33.2% (95% CI, 31.1 to 35.3%), as compared with the expected cumulative incidence of cancer of 9.6% in the general population.

Table 2. Standardized Incidence Ratios, Absolute Excess Risks, and 30-Year Cumulative Incidences of Selected Subsequent Malignant Neoplasms.*

Second Cancer or Cancer Site	ICD Code	No. of Patients	Standardized Incidence Ratio (95% CI)	Absolute Excess Risk	30-Yr Cumulative Incidence (95% CI)
				no./10,000 person-yr (95% CI)	
Any cancer, excluding MDS†	—	884	4.6 (4.3 to 4.9)	121.8 (111.8 to 132.4)	32.5 (30.4 to 34.6)
Any solid cancer	C00–C80	757	4.2 (3.9 to 4.5)	100.5 (91.3 to 110.2)	28.5 (26.4 to 30.5)
Lip, oral cavity, or pharynx	C00–C14	20	3.2 (2.0 to 4.9)	2.3 (1.0 to 4.1)	0.5 (0.3 to 0.9)
Gastrointestinal tract	C15–C26	184	4.6 (3.9 to 5.3)	24.0 (19.7 to 28.7)	7.0 (5.9 to 8.3)
Esophagus	C15	38	9.5 (6.7 to 13.1)	5.6 (3.8 to 8.0)	1.5 (1.0 to 2.1)
Stomach	C16	39	7.4 (5.3 to 10.1)	5.6 (3.7 to 8.0)	1.6 (1.1 to 2.3)
Colon	C18	42	2.9 (2.1 to 3.9)	4.6 (2.6 to 7.0)	1.5 (1.0 to 2.1)
Rectum or rectosigmoid junction	C19–C20	25	2.6 (1.7 to 3.9)	2.6 (1.1 to 4.5)	1.0 (0.6 to 1.5)
Pancreas	C25	23	5.7 (3.6 to 8.5)	3.1 (1.7 to 5.0)	1.0 (0.6 to 1.6)
Lower respiratory system	C33, C34, and C45	193	6.7 (5.8 to 7.8)	27.3 (22.9 to 32.1)	7.1 (6.0 to 8.3)
Lung or bronchus	C34	176	6.4 (5.5 to 7.4)	24.6 (20.5 to 29.3)	6.4 (5.4 to 7.6)
Mesothelioma	C45	17	15.1 (8.8 to 24.2)	2.6 (1.5 to 4.3)	0.6 (0.3 to 1.1)
Skin					
Melanoma	C43	34	2.8 (1.9 to 3.9)	3.6 (1.9 to 5.9)	1.1 (0.7 to 1.5)
Nonmelanoma	C44	26	3.4 (2.2 to 5.0)	3.1 (1.6 to 5.1)	0.7 (0.4 to 1.2)
Soft-tissue sarcoma	C47–C49	22	12.0 (7.5 to 18.2)	3.3 (2.0 to 5.2)	0.7 (0.4 to 1.1)
Female breast‡	C50	183	4.7 (4.0 to 5.4)	54.3 (44.7 to 65.0)	16.6 (14.1 to 19.2)
Female genital organ					
Any	C51–C58	34	2.8 (1.9 to 3.9)	3.6 (1.9 to 5.9)	2.9 (2.0 to 4.2)
Corpus uteri	C54	16	3.6 (2.1 to 5.8)	1.9 (0.8 to 3.6)	1.6 (0.9 to 2.6)
Male genital organ					
Any	C60–C63	22	1.1 (0.7 to 1.7)	0.3 (–1.0 to 2.2)	1.8 (1.1 to 2.8)
Prostate	C61	18	1.0 (0.6 to 1.7)	0.1 (–1.1 to 1.9)	1.4 (0.8 to 2.4)
Urinary tract	C64–C68	39	3.5 (2.5 to 4.7)	4.6 (2.7 to 7.0)	1.3 (0.9 to 2.0)
Kidney	C64	12	2.3 (1.2 to 4.1)	1.1 (0.2 to 2.6)	0.4 (0.2 to 0.8)
Urinary bladder	C67	22	4.1 (2.6 to 6.2)	2.8 (1.4 to 4.6)	0.6 (0.3 to 1.1)
Thyroid gland	C73	23	14.0 (8.9 to 21.0)	3.5 (2.1 to 5.5)	0.8 (0.5 to 1.2)
Primary site unknown or ill defined	C76–C80	29	4.9 (3.3 to 7.0)	3.8 (2.2 to 5.9)	1.3 (0.8 to 1.9)
Blood, bone marrow, or lymphatic system	C82–C96	147	10.4 (8.8 to 12.2)	22.2 (18.4 to 26.5)	5.0 (4.1 to 6.0)
Non-Hodgkin's lymphoma	C82–88	104	13.4 (10.9 to 16.2)	16.0 (12.9 to 19.7)	3.7 (3.0 to 4.6)
Leukemia	C91–96	41	9.5 (6.8 to 12.9)	6.1 (4.2 to 8.5)	1.3 (0.9 to 1.7)

* The standardized incidence ratios and absolute excess risks are for the comparison of the incidence of second cancer observed in the study cohort with the expected incidence of that cancer in the general population. The listed cancers are those of which at least 10 cases were observed in the cohort. ICD denotes *International Classification of Diseases, 10th Revision*, and MDS the myelodysplastic syndrome.

† Data include the first subsequent malignant neoplasm after Hodgkin's lymphoma. Besides the specific sites noted in the table, we observed the following cancers: three cancers of the tongue (C02), six oral cavity cancers (C03–C06), seven salivary gland cancers (C07–C08), two oropharynx cancers (C01, C09–C10), two nasopharyngeal cancers (C11), two hypopharyngeal cancers (C12–C13), four small intestine cancers (C17), six anal cancers (C21), eight liver cancers (C22), one gallbladder cancer (C23), four extrahepatic biliary tract cancers (C24), two other or ill-defined gastrointestinal cancers (C26), three larynx cancers (C32), one intrathoracic (mediastinal) cancer (C38), five bone cancers (C40–C41), four male breast cancers (C50), two vulva cancers (C51), eight cervical cancers (C53), eight ovarian cancers (C56), one placenta cancer (C58), three penis cancers (C60), one testis cancer (C62), one renal pelvis cancer (C65), one ureter cancer (C66), three unspecified urinary system cancers (C68), four meningiomas (C70), six brain tumors (C71), seven other central nervous system tumors (C72), and three multiple myelomas (C90).

‡ Only women were included in the denominator. For breast cancer, women accumulated 26,517.1 person-years, in which 39.0 breast cancers were expected (rounded data). An additional 30 women received a diagnosis of an in situ breast carcinoma.

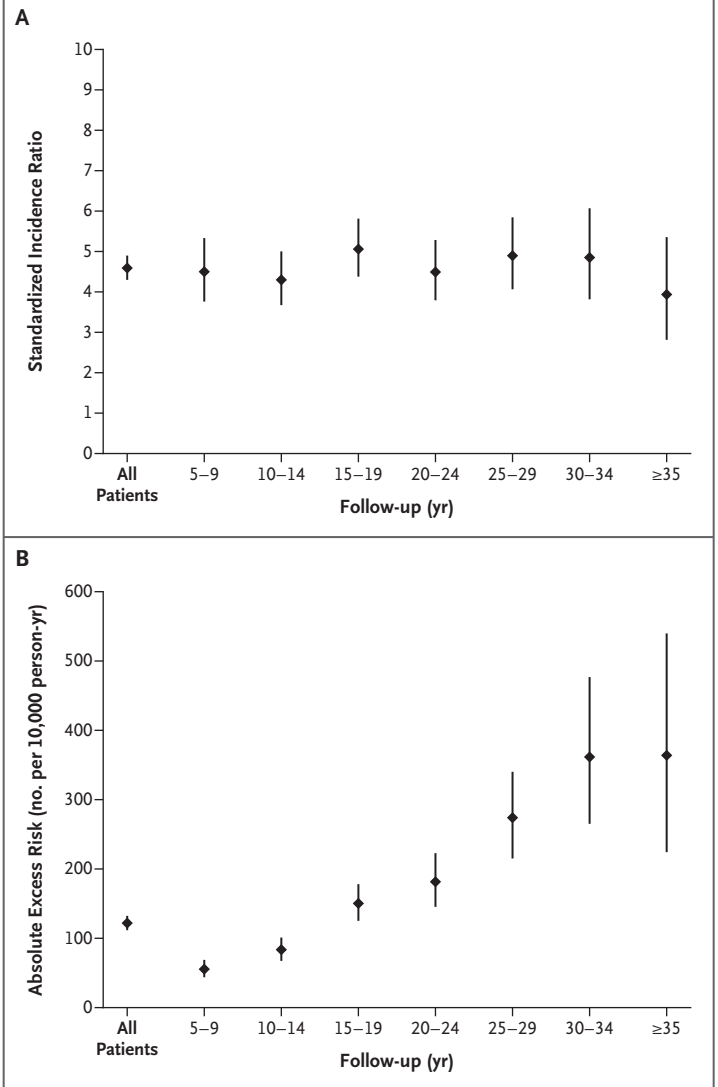

Figure 1. Standardized Incidence Ratios and Absolute Excess Risks of Any Subsequent Malignant Neoplasm after Treatment for Hodgkin's Lymphoma, According to Follow-up Interval.

The standardized incidence ratio is a comparison of the incidence of second cancer observed in the study cohort with the expected incidence in the general population. Vertical lines indicate 95% confidence intervals.

At 40 years, the cumulative incidence was 48.5% (95% CI, 45.4 to 51.5), as compared with the expected cumulative incidence of 19.0% in the general population. At 30 years, the cumulative incidence of breast cancer among women in the study cohort was 16.6% (95% CI, 14.1 to 19.2), and the cumulative incidence of lung cancer was 8.3% (95% CI, 6.7 to 10.0) among men and 4.1% (95% CI, 2.9 to 5.6) among women.

Figure 2, and Figure S1 in the Supplementary Appendix, show the cumulative incidence of selected second cancers according to the period of diagnosis of Hodgkin's lymphoma. In a multivariable analysis, with adjustment for sex, age, and smoking status, the cumulative incidence of any second cancer was lower among patients treated in the period from 1989 through 2000 than among those treated in the period from 1965 through 1976 (subdistribution hazard ratio, 0.79; 95% CI, 0.65 to 0.95; P=0.02 for trend) (Fig. 2A, and Table S4 in the Supplementary Appendix). The cumulative incidence of second solid cancers did not differ significantly among the treatment periods (P=0.71 for heterogeneity), nor did the cumulative incidence of breast cancer (P=0.17 for heterogeneity) or gastrointestinal cancer (P=0.22 for heterogeneity) (Fig. 2B and 2D, and Fig. S1B in the Supplementary Appendix).

The trend in the cumulative incidence of lung cancer according to period of treatment differed between men and women (P=0.02 for interaction). Although the cumulative incidence was lower among men treated in the period from 1989 through 2000 than among those treated in the two earlier periods (P=0.001 for trend) (Fig. S1A in the Supplementary Appendix), the incidence among women increased over time (P=0.14 for trend) (Fig. 2C).

The cumulative incidence of non-Hodgkin's lymphoma more than halved between the period of 1965 through 1976 and the period of 1989 through 2000 (P=0.003 for trend, with adjustment for sex and age) (Fig. S1C in the Supplementary Appendix). Similarly, the cumulative incidence of leukemia (and the myelodysplastic syndrome) was much lower among patients who were treated in the period from 1989 through 2000 than among those who were treated in the period from 1965 through 1976 (subdistribution hazard ratio, 0.24; 95% CI, 0.12 to 0.49; P<0.001 for trend) (Fig. S1D in the Supplementary Appendix).

ASSOCIATIONS OF TREATMENT WITH STANDARDIZED INCIDENCE RATIOS

As compared with the incidence of cancer in the general population, the SIR for supradiaphragmatic second solid cancers was 6.3 (95% CI, 5.7 to 6.9) among patients treated with supradiaphragmatic irradiation. Patients who were not treated with supradiaphragmatic irradiation also

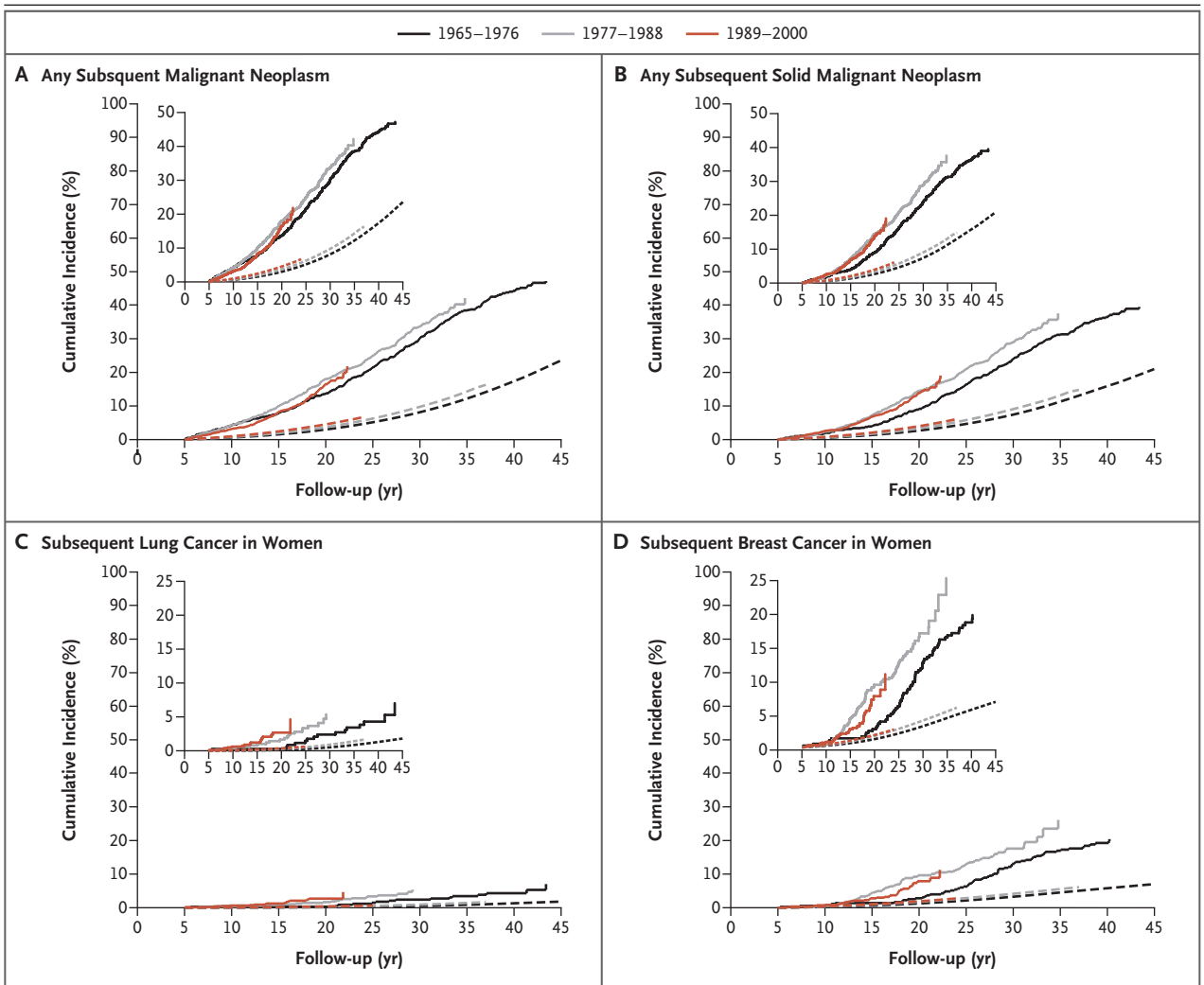

Figure 2. Cumulative Incidence of Subsequent Malignant Neoplasms, According to Treatment Period, with Death as a Competing Risk.
Solid lines represent the observed incidence, and dashed lines the expected incidence in the general population. The insets show the same data on enlarged y axes.

had a higher risk of second solid cancers above the diaphragm (SIR, 2.1; 95% CI, 1.4 to 2.9; P<0.001 for heterogeneity) (Table S5 in the Supplementary Appendix).

All but five of the patients in whom breast cancer developed had received supradiaphragmatic radiation therapy (SIR, 5.4, vs. 1.0 among patients treated without supradiaphragmatic radiation therapy; P<0.001 for heterogeneity). The risk of breast cancer decreased with increasing procarbazine dose among patients treated with supradiaphragmatic irradiation; the SIRs were 3.8 among patients who received procarbazine-containing chemotherapy and 6.8 among those who did not receive such chemotherapy (P=0.001 for heterogeneity).

The SIR for lung cancer was 7.7 (95% CI, 6.5 to 9.0) among patients treated with supradiaphragmatic irradiation. However, it was also elevated among patients treated with procarbazine-containing chemotherapy without supradiaphragmatic irradiation (SIR, 3.2; 95% CI, 1.8 to 5.3).

Of the 230 patients in whom a second solid cancer developed below the diaphragm, 146 (63.5%) had received infradiaphragmatic radiation therapy (SIR, 4.6; 95% CI, 3.9 to 5.4). The SIR was 1.7 (95% CI, 1.3 to 2.1) among patients who had been treated without infradiaphrag-

matic radiation therapy (P<0.001 for heterogeneity). SIRs were higher with increasing procarbazine dose (P<0.001 for trend), regardless of treatment with infradiaphragmatic irradiation. The risk of gastrointestinal cancer was highest among patients treated with infradiaphragmatic irradiation and procarbazine-containing chemotherapy (SIR, 8.6; 95% CI, 6.4 to 11.4) (Table S5 in the Supplementary Appendix).

ASSOCIATIONS OF TREATMENT WITH RISK OF SECOND CANCER IN THE COHORT

In the comparison of treatments within the cohort, multivariable analysis showed that patients who received supradiaphragmatic field radiotherapy not including the axilla had a much lower risk of a second solid cancer than patients who received complete mantle-field radiotherapy (hazard ratio, 0.63; 95% CI, 0.49 to 0.83) (Table 3). This finding is due largely to the significantly lower risk of breast cancer among patients who received supradiaphragmatic field radiotherapy not including the axilla than among those who received complete mantle-field radiotherapy (hazard ratio, 0.37; 95% CI, 0.19 to 0.72). The risk of breast cancer was also lower with higher cumulative procarbazine doses (hazard ratio for a cumulative procarbazine dose of ≥4.3 g per square meter of body-surface area vs. no chemotherapy, 0.57; 95% CI, 0.39 to 0.84; P=0.002 for trend). Patients who were treated with mantle-field irradiation had a risk of lung cancer that was similar to the risk among those who were treated with less-extensive supradiaphragmatic field irradiation (hazard ratio, 1.04; P=0.84).

The risk associated with smoking appeared to multiply the elevated lung-cancer risk associated with supradiaphragmatic irradiation. As compared with nonsmokers who did not receive supradiaphragmatic radiotherapy, the largest risk was observed among persons who were former or current smokers and who received supradiaphragmatic radiotherapy (hazard ratio, 14.38; 95% CI, 6.99 to 29.58). The hazard ratio among nonsmokers who received supradiaphragmatic radiotherapy was 2.96 (95% CI, 1.76 to 4.97), and the hazard ratio among former or current smokers who did not receive supradiaphragmatic radiotherapy was 4.86 (95% CI, 2.97 to 7.95).

The risk of stomach, pancreatic, or colorectal cancer was higher after infradiaphragmatic radiotherapy (P<0.001 for heterogeneity); the risks were also higher with procarbazine-containing chemotherapy than with no chemotherapy (hazard ratio for procarbazine dose ≥4.3 g per square meter, 2.70; 95% CI, 1.69 to 4.30). Patients who had undergone splenectomy had a higher risk of non-Hodgkin's lymphoma than did those who had not undergone splenectomy (hazard ratio, 1.76; 95% CI, 1.09 to 2.84). Also, mantle-field or supradiaphragmatic irradiation including the axilla, as compared with no radiotherapy, and a cumulative dose of procarbazine that was greater than 8.4 g per square meter, as compared with no chemotherapy, were associated with a higher risk of non-Hodgkin's lymphoma, although the absolute risk was small. The 30-year cumulative incidence of non-Hodgkin's lymphoma was 4.8% (95% CI, 3.8 to 6.0) among patients who received mantle-field radiotherapy and a cumulative procarbazine dose of more than 8.4 g per square meter, as compared with 2.0% (95% CI, 1.0 to 3.6) among patients who did not receive mantle-field radiotherapy and high-dose procarbazine. Results did not differ substantially according to the number of cycles with alkylating chemotherapy (Table S6 in the Supplementary Appendix).

DISCUSSION

This large cohort study with long-term and complete follow-up showed that the risk of second solid cancers did not change appreciably among patients with Hodgkin's lymphoma who were treated during the 1990s (study period 1989–2000), as compared with those who were treated during earlier decades. However, the risk of hematopoietic second cancers has clearly decreased among 5-year survivors who were treated in the most recent study period, which correlates with the declining use of alkylating agent–based chemotherapy. During follow-up, the SIR for second solid cancers remained remarkably stable, resulting in strongly increasing excess rates of a second cancer when survivors of Hodgkin's lymphoma reached ages at which background cancer rates were substantial. Even 40 years after treatment, survivors of Hodgkin's lymphoma were at increased risk for second cancers, with the cumulative incidence reaching 48.5%.

Breast cancer accounted for more than 40% of the excess risk of a second cancer among

women in our cohort. As compared with mantle-field irradiation, radiation therapy with less-extensive supradiaphragmatic fields was associated with a substantially lower risk of breast cancer, which confirms our previous results, which were based on smaller numbers.[9] Nonetheless, although a larger proportion of more recently treated female survivors of Hodgkin's lymphoma had received less-extensive supradiaphragmatic irradiation, there was little evidence that these women had a lower risk of breast cancer than those who were treated in the two earlier periods.

The interpretation of the surprising absence of a decline in the rate of second breast cancers with less radiation exposure is complicated. It was expected that lower volumes of supradiaphragmatic radiation therapy would result in lower rates of breast cancer. It is possible, however, that the changes in radiation-therapy policies were not yet applied widely enough to reduce the risk of breast cancer. It is also possible that the absence of a decrease in the incidence of breast cancer is due in part to the earlier detection of breast cancer in more recently treated women because of higher rates and earlier starts of screening, as compared with the earlier treatment cohorts.[29] We evaluated methods of breast-cancer detection at four participating hospitals. Before 2001, a total of 29.7% of the breast cancers (11 of 37 cases) were detected by means of breast-cancer screening (routine palpation, mammography, or magnetic resonance imaging); the rate is 60.8% (48 of 79) since 2001.

Furthermore, our data indicate that the introduction of less-gonadotoxic chemotherapy may have influenced the risk of breast cancer. In the two earlier periods, high doses of alkylating agents were frequently used, often causing premature menopause, which has been associated with a lower risk of radiation-associated breast cancer, as compared with lower doses of alkylating agents (≤4.2 g of procarbazine per square meter) or no chemotherapy.[5,6,9,14] The survival rate after the diagnosis of breast cancer appeared to be similar among patients with Hodgkin's lymphoma who received a diagnosis of breast cancer before 2001 and those who received the diagnosis since 2001 (overall survival at 5 years, 80.0% and 77.5%, respectively).

Although male survivors of Hodgkin's lymphoma who were treated in the period from 1989 through 2000 had a lower risk of lung cancer than those who were treated in the period from 1965 through 1976, the risk of lung cancer increased over time among female survivors — a finding that mirrors trends in smoking rates and lung-cancer incidence over the past decades in the general population. Supradiaphragmatic radiotherapy was associated with a higher risk of lung cancer than the risk among patients who were not treated with supradiaphragmatic radiotherapy, and the risk did not differ significantly between patients treated with mantle-field irradiation and those treated with irradiation of other supradiaphragmatic fields. Apparently, the latter, less-extensive radiation fields are still associated with considerable radiation exposure of the lungs.

Previously, a higher risk of lung cancer was found among patients treated with alkylating chemotherapy than among those who had not received alkylating chemotherapy, with higher risks observed with increasing number of chemotherapy cycles.[17,18] Our data do not support an association of lung-cancer risk with a higher dose of procarbazine-containing chemotherapy nor with an increasing number of cycles of alkylating chemotherapy. Although patients who received procarbazine-containing chemotherapy and did not receive supradiaphragmatic radiotherapy had a risk of lung cancer that was 3.2 times as high as that in the general population, chemotherapy did not appear to affect lung-cancer risk in the multivariable analysis — a finding that is consistent with the results of a previous case–control study conducted by our group.[21]

The cumulative incidence of gastrointestinal second cancers (stomach, pancreatic, or colorectal cancers) did not change appreciably over time. This finding is remarkable because considerably fewer patients who were treated in the period from 1989 through 2000 than who were treated in the two earlier periods received infradiaphragmatic radiotherapy. Infradiaphragmatic radiotherapy was significantly associated with the risk of gastrointestinal second cancer in our analyses and in previous studies.[1,4,10] Procarbazine-containing chemotherapy was associated with an overall risk of gastrointestinal second cancer that was 2.5 times as high as the risk without chemotherapy, without a clear effect of number of cycles. This finding confirms results

Table 3. Multivariable Cox Analyses of Treatment as Risk Factor for Selected Subsequent Malignant Neoplasms.*

Variable	All Solid Cancers			Lung Cancer			Breast Cancer in Women		
	No. of Cancers	Hazard Ratio (95% CI)	P Value	No. of Cancers	Hazard Ratio (95% CI)	P Value	No. of Cancers	Hazard Ratio (95% CI)	P Value
Radiation therapy			<0.001			<0.001			<0.001
Full mantle field	530	1.00		117	1.00		159	1.00	
Other supradiaphragmatic field with axilla	46	0.98 (0.72–1.35)		15	1.45 (0.83–2.52)		5	0.41 (0.17–1.01)	
Other supradiaphragmatic field	72	0.63 (0.49–0.83)		22	0.85 (0.52–1.39)		10	0.37 (0.19–0.72)	
Other radiotherapy and field unknown	65	0.70 (0.54–0.92)		8	0.27 (0.13–0.57)		5	0.35 (0.14–0.85)	
No radiotherapy	44	0.39 (0.28–0.55)		14	0.46 (0.25–0.83)		4	0.24 (0.09–0.67)	
Infradiaphragmatic radiotherapy			0.001			—			—
No infradiaphragmatic radiotherapy	374	1.00		—	—		—	—	
Infradiaphragmatic radiotherapy with spleen	202	1.39 (1.16–1.67)		—	—		—	—	
Other infradiaphragmatic field	181	1.04 (0.86–1.26)		—	—		—	—	
Procarbazine			0.09			0.43			0.03
No chemotherapy	283	1.00		67	1.00		97	1.00	
No procarbazine	79	0.94 (0.73–1.22)		18	0.75 (0.44–1.29)		22	0.75 (0.47–1.20)	
≤4.2 g/m^2	104	1.07 (0.84–1.35)		26	0.93 (0.58–1.51)		22	0.84 (0.52–1.36)	
4.3–8.4 g/m^2	157	1.22 (0.99–1.49)		33	0.96 (0.62–1.48)		31	0.71 (0.47–1.07)	
>8.4 g/m^2	93	1.36 (1.07–1.74)		25	1.32 (0.81–2.15)		8	0.33 (0.16–0.68)	
Chemotherapy but unknown whether procarbazine	41	1.06 (0.76–1.49)		7	0.62 (0.28–1.38)		3	0.42 (0.13–1.34)	
Smoking at end of follow-up†			<0.001			<0.001			—
Never smoked	248	1.00		19	1.00		—	—	
Former smoker	219	1.23 (1.02–1.48)		64	3.68 (2.19–6.19)		—	—	
Recent smoker	155	1.80 (1.47–2.21)		57	7.66 (4.51–13.0)		—	—	
Unknown	135	1.43 (1.15–1.79)		36	4.63 (2.60–8.24)		—	—	

	Gastrointestinal Cancer‡			Leukemia or MDS§			Non-Hodgkin's Lymphoma		
	No. of Cancers	Hazard Ratio (95% CI)	P Value	No. of Cancers	Hazard Ratio (95% CI)	P Value	No. of Cancers	Hazard Ratio (95% CI)	P Value
Radiation therapy			0.004			0.73			0.02
Full mantle field	78	1.00		39	1.00		74	1.00	
Other supradiaphragmatic with axilla	12	2.11 (1.12–3.97)		5	1.26 (0.48–3.28)		9	1.39 (0.68–2.85)	
Other supradiaphragmatic field	8	0.57 (0.27–1.22)		9	0.75 (0.34–1.65)		7	0.38 (0.17–0.85)	
Other radiotherapy and field unknown	22	1.42 (0.87–2.33)		6	0.65 (0.26–1.62)		9	0.72 (0.35–1.49)	
No radiotherapy	5	0.37 (0.14–0.99)		8	0.72 (0.29–1.78)		6	0.34 (0.14–0.83)	
Infradiaphragmatic radiotherapy			<0.001			0.10			0.77
No infradiaphragmatic radiotherapy	40	1.00		28	1.00		52	1.00	
Infradiaphragmatic radiotherapy with spleen	42	3.11 (1.93–5.00)		16	1.73 (0.86–3.48)		24	1.13 (0.66–1.92)	
Other infradiaphragmatic fields	43	2.26 (1.40–3.64)		23	2.00 (1.01–3.97)		29	0.89 (0.53–1.50)	
Procarbazine			<0.001			<0.001			0.01
No chemotherapy	30	1.00		11	1.00		34	1.00	
No procarbazine	12	1.68 (0.84–3.36)		2	0.64 (0.14–2.98)		14	1.68 (0.87–3.21)	
≤4.2 g/m^2	18	2.04 (1.12–3.73)		10	1.78 (0.72–4.35)		14	1.23 (0.64–2.35)	
4.3–8.4 g/m^2	32	2.74 (1.65–4.56)		20	3.86 (1.80–8.28)		18	1.23 (0.68–2.35)	
>8.4 g/m^2	18	2.63 (1.44–4.79)		22	7.23 (3.38–14.5)		22	2.73 (1.56–4.78)	
Chemotherapy but unknown whether procarbazine	15	4.61 (2.42–8.75)		2	1.30 (0.28–6.10)		3	0.74 (0.22–2.44)	
Splenectomy			—			0.65			0.03
No	—	—		37	1.00		56	1.00	
Yes	—	—		24	1.25 (0.66–2.35)		46	1.76 (1.09–2.84)	
Unknown	—	—		6	1.40 (0.56–3.49)		3	0.56 (0.17–1.82)	

* Radiation therapy and dose of procarbazine-containing chemotherapy were included as time-varying variables. Six cycles of a hybrid regimen of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) plus doxorubicin, bleomycin, and vinblastine (ABV) or six cycles of a regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) counted as three MOPP-equivalent cycles. One cycle of MOPP contains 1.4 g of procarbazine per square meter of body-surface area; one cycle of MOPP–ABV or one cycle of BEACOPP (baseline or dose-escalated) contains 0.7 g of procarbazine per square meter. P values are for heterogeneity of hazard ratios. Analyses were adjusted for age and sex and were stratified in the case of nonproportional hazard ratios.

† Recent smokers included current smokers and survivors who quit smoking within 5 years before the end of follow-up.

‡ Data include stomach cancer (C16), pancreatic cancer (C25), and colorectal cancer (C18–C20).

§ Data include 24 patients with MDS.

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that showed a higher risk of stomach cancer after procarbazine, as compared with no procarbazine, with a strong interaction with radiation dose.[4,10] A considerably larger proportion of patients with Hodgkin's lymphoma who were treated in the period from 1989 through 2000 than who were treated in the earlier calendar periods received chemotherapy.

Several previous studies have shown a higher risk of non-Hodgkin's lymphoma among survivors of Hodgkin's lymphoma than in the general population, the cause of which remains unclear.[7,15,16,19,20] Besides the possibility that the primary Hodgkin's lymphoma was misclassified (i.e., was actually non-Hodgkin's lymphoma), immunosuppression in survivors has been suggested as a possible explanation for this higher risk of non-Hodgkin's lymphoma.[30,31] Our finding of a higher risk of non-Hodgkin's lymphoma associated with splenectomy, as compared with no splenectomy, seems to support this hypothesis. Fortunately, splenectomy is now rarely a component of the care of patients with Hodgkin's lymphoma. However, mantle-field irradiation and high cumulative doses of procarbazine were also associated with a high risk of non-Hodgkin's lymphoma.

The strengths of our study include complete, long-term follow-up and the availability of detailed treatment data. We acknowledge that we present the results of many tests of statistical significance, and we therefore caution against overinterpretation of our findings, especially when they are based on P values of more than 0.001.

In conclusion, even 40 years after treatment for Hodgkin's lymphoma, survivors remain at increased risk for second cancers. The risk of solid cancer after treatment for Hodgkin's lymphoma was not lower among more recently treated patients than among those who were treated in earlier time periods, despite changes in treatment. Our results suggest that reducing the incidence of second cancers can best be achieved by a substantial reduction in the radiation exposure of healthy organs and tissues and by avoidance of high-dose procarbazine. Current common practice in radiation oncology, including involved-node or involved-site radiotherapy, three-dimensional conformal radiation treatment planning (in which multiple beams of radiation are shaped to match the target volume), and radiation doses of less than 36 Gy, was not applied in our study population. It is hoped that these changes may reduce the risk of solid cancer among patients treated after 2000.[23,32] At present, we are unable to conclude that changes made before 2000 had a measurable effect on the risk of a second solid cancer.

For patients with newly diagnosed Hodgkin's lymphoma, the risks of both radiation-related and chemotherapy-related late toxic effects must be carefully balanced against the risk of failing to control the primary disease. Awareness of the increased risk of subsequent malignant neoplasms remains of great importance for survivors of Hodgkin's lymphoma and for their physicians.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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