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SOLID CANCERS AFTER BONE MARROW TRANSPLANTATION

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ABSTRACT

Background The late effects of bone marrow transplantation, including cancer, need to be determined in a large population at risk.

Methods We studied 19,229 patients who received allogeneic transplants (97.2 percent) or syngeneic transplants (2.8 percent) between 1964 and 1992 at 235 centers to evaluate the risk of the development of a new solid cancer. Risk factors relating to the patient, the transplant, and the course after transplantation were evaluated.

Results The transplant recipients were at significantly higher risk of new solid cancers than the general population (observed cases, 80; ratio of observed to expected cases, 2.7; $P < 0.001$). The risk was 8.3 times as high as expected among those who survived 10 or more years after transplantation. The cumulative incidence rate was 2.2 percent (95 percent confidence interval, 1.5 to 3.0 percent) at 10 years and 6.7 percent (95 percent confidence interval, 3.7 to 9.6 percent) at 15 years. The risk was significantly elevated ($P < 0.05$) for malignant melanoma (ratio of observed to expected cases, 5.0) and cancers of the buccal cavity (11.1), liver (7.5), brain or other parts of the central nervous system (7.6), thyroid (6.6), bone (13.4), and connective tissue (8.0). The risk was higher for recipients who were younger at the time of transplantation than for those who were older (P for trend, < 0.001). In multivariate analyses, higher doses of total-body irradiation were associated with a higher risk of solid cancers. Chronic graft-versus-host disease and male sex were strongly linked with an excess risk of squamous-cell cancers of the buccal cavity and skin.

Conclusions Patients undergoing bone marrow transplantation have an increased risk of new solid cancers later in life. The trend toward an increased risk over time after transplantation and the greater risk among younger patients indicate the need for lifelong surveillance. (N Engl J Med 1997;336:897-904.)

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BONE marrow transplantation is an increasingly effective treatment for leukemia and several other malignant and nonmalignant diseases. However, there is growing concern about possible late consequences of compromised immune function and of treatment, particularly new cancers resulting from the total-body irradiation and high-dose chemotherapy used as conditioning regimens for transplantation. Few studies have assessed the risk of cancer among long-term survivors of bone marrow transplantation.¹⁻⁷ Some studies have shown a high risk of lymphoproliferative disorders after allogeneic bone marrow transplantation and statistically significant excesses of myelodysplastic syndromes and leukemia after autologous transplantation for lymphoma.^{2,7} Earlier studies of solid cancers that occurred after transplantation have been based on relatively small numbers of cases, and little information was available on individual cancers. Using a multi-institution data base that includes almost 20,000 recipients of allogeneic transplants, we conducted a study to determine the risk of new solid cancers after bone marrow transplantation.

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METHODS

Patients

A total of 19,229 patients who received allogeneic or syngeneic bone marrow transplants (97.2 percent and 2.8 percent, respectively) were identified from the International Bone Marrow Transplant Registry (IBMTR) and the Fred Hutchinson Cancer Research Center in Seattle. Data from the IBMTR, which covers 234 transplantation centers, included transplantations for the period from 1964 to 1990, with follow-up through 1991; the Seattle data were for the period from 1969 to 1992. The risk of new cancers in 1980 among the patients from Seattle² and several centers covered by the IBMTR^{4,6,7} have been published previously. From the original cohort of 19,430, we excluded 201 patients with Fanconi's anemia and 376 with primary immunodeficiency diseases, because they have an inborn susceptibility to cancer.^{8,9}

Most of the patients (75 percent) received transplants for leukemia, and most (79 percent) received bone marrow from an HLA-identical sibling. The median age at the time of transplantation was 25.5 years. Overall, 91 percent of the recipients were followed through the end date of the study. Among the 9501 patients who survived for at least 1 year after transplantation, the median duration of follow-up was 3.5 years (mean, 4.5; maximum, 25). Pathology reports and selected slides were reviewed centrally for 95 percent of the patients with new solid tumors.

Treatment and Risk Factors

The characteristics of the patients are shown in Table 1. For patients with second cancers, information on prior therapy for the primary disease was abstracted from the transplantation center's records, but such data were generally unavailable for the other patients. Conditioning regimens for 14,000 patients (73 percent of the cohort) consisted of total-body irradiation combined with cyclophosphamide-based regimens (65 percent) or other drugs (8 percent). Another 656 patients (most of whom had aplastic anemia) received limited-field irradiation (total nodal, total lymphoid, or thoracoabdominal irradiation), without total-body irradiation. Patients who did not undergo irradiation typically received cyclophosphamide (22 percent), with or without other drugs.

Prophylaxis against graft-versus-host disease included T-cell depletion of bone marrow; drug therapy with cyclosporine, methotrexate, corticosteroids, or other drugs; and combined therapies. Acute graft-versus-host disease was commonly treated with cyclosporine, antithymocyte or antilymphocyte globulin, corticosteroids, or a combination of these agents. Fewer than 550 patients were treated with methotrexate, azathioprine, or monoclonal antibodies for acute graft-versus-host disease. Information on drugs used to treat chronic graft-versus-host disease was incomplete and therefore not evaluated.

Statistical Analysis

For each transplant recipient, the number of person-years at risk was calculated from the date of transplantation until the date of last contact, death, diagnosis of a new cancer, or completion of the study, whichever occurred first. Age-, sex-, year-, and region-specific incidence rates for all solid cancers combined and for cancers at specific anatomical sites were applied to the appropriate person-years at risk to compute the expected numbers of cancers. Incidence rates for all invasive cancers (except nonmelanoma skin cancers) were obtained from selected registries in the United States, England and Wales, Europe, and Asia.¹⁰⁻¹² Ratios of observed to expected cases and 95 percent confidence intervals were calculated on the assumption that the observed number of cancers followed a Poisson distribution.¹³ The absolute excess risk was calculated as the observed number of cancers minus the expected number of cancers per 10,000 transplant recipients per year. The cumulative probability of a new invasive solid cancer was estimated by the Kaplan-Meier method.¹⁴

Univariate and multivariate analyses were used to compare risks for various subgroups of transplant recipients who survived for at

least one year after transplantation, with the use of Poisson regression methods for grouped survival data^{13,15} and Cox proportional-hazards regression techniques.¹⁶ These two approaches had nearly identical results, and only the results of the Poisson analyses are presented here. Since the risk of cancer may differ according to the disease for which the transplantation was performed, the data were stratified according to the primary disease in six categories: acute lymphoblastic leukemia, acute nonlymphocytic leukemia, chronic myelogenous leukemia, severe aplastic anemia, lymphoma, and other. The data were also stratified according to the interval since transplantation (with cutoff points at 2.5, 5, 7.5, 10, and 12.5 years). Analyses were further adjusted for the cohort (Seattle or IBMTR) and the age at the time of transplantation. Age was entered into the model with the use of three continuous variables: less than 10, 10 to 39, and 40 or more years. Occurrences of acute graft-versus-host disease (grades II to IV) and chronic graft-versus-host disease (moderate or severe disease in the IBMTR cohort and clinically extensive disease in the Seattle cohort) were entered as time-dependent covariates. Except where noted, Poisson regression analyses were performed for all invasive solid cancers except non-melanoma skin cancer (71 cases among patients who survived for at least one year after transplantation); invasive squamous-cell skin cancers (8 cases) were considered separately.

RESULTS

Among the 19,229 patients who underwent bone marrow transplantation, 80 new cases of invasive solid cancers were observed as compared with 29.8 expected cases in the general population (ratio of observed to expected cases, 2.7; $P < 0.001$) (Table 2). The risk of cancer was similar in the IBMTR cohort (observed cases, 49; ratio of observed to expected cases, 2.4) and the Seattle cohort (observed cases, 31; ratio of observed to expected cases, 3.2). The risks were significantly elevated for cancers of the buccal cavity (ratio of observed to expected cases, 11.1), liver (7.5), brain and other parts of the central nervous system (7.6), thyroid (6.6), bone (13.4), and connective tissue (8.0) and for melanoma (5.0). There was little increase in the risk of common adult cancers, such as breast cancer in women or digestive, respiratory, or genitourinary tract cancers in women or men. The overall risk rose steeply over time after transplantation, with a risk that was eight times as high as expected among patients who survived 10 or more years after transplantation (P for trend, < 0.001). The cumulative incidence rate of new solid cancers 5, 10, and 15 years after transplantation was 0.7 percent (95 percent confidence interval, 0.4 to 0.9 percent), 2.2 percent (95 percent confidence interval, 1.5 to 3.0 percent), and 6.7 percent (95 percent confidence interval, 3.7 to 9.6 percent), respectively; the corresponding values for the general population were 0.3, 0.6, and 0.8 percent. Only 104 patients were followed for more than 15 years. The risks of cancers of the buccal cavity, brain, and thyroid tended to be highest five or more years after transplantation, whereas the risks of melanoma and cancers of bone and connective tissue were elevated throughout the follow-up period.

Several unusual cancers were diagnosed. Two of the three liver cancers were malignant fibrous histiocyto-

mas, which are extremely rare in the general population. One patient had Kaposi's sarcoma of the visceral organs (unrelated to the acquired immunodeficiency syndrome), and one patient had neuroblastoma of the nasal cavities. Bone and connective-tissue cancers included chondrosarcoma (three cases), osteosarcoma (one), rhabdomyosarcoma (two), fibrosarcoma (two), and unspecified bone sarcoma (one). Brain and spinal cord cancers included astrocytoma (four cases), glioblastoma (six), and primitive neuroectodermal cancer (one). Ten of the 11 brain cancers developed in patients with acute leukemia. Of the 11 invasive melanomas, 7 occurred in patients with acute nonlymphocytic leukemia; 5 were early-stage lesions (<0.6 mm in diameter, Clark level II), 5 were Clark level III or IV lesions (0.9 to 3.8 mm in diameter), and 1 was unclassified. All three salivary gland cancers were mucoepidermoid carcinomas.

Of the 80 patients with new cancers, 36 died. The new cancer was the primary cause of death in 26 (including 10 with brain tumors).

A strong relation was found between the patient's age at the time of transplantation and the risk of cancer. The risk for children who were under 10 years of age at the time of transplantation was 36.6 times as high as expected; the risk was 4.6 times as high as expected for those who were 10 to 29 years old at the time of transplantation and nearly normal for those who were 30 years or older (P for trend, <0.001) (Table 3). The inverse association between risk and age persisted when the risk was evaluated with use of the absolute excess risk (P for trend, 0.002). Over half the excess solid tumors in the youngest age group were cancers of the brain (observed cases, 9; expected cases, 0.22) or thyroid (observed cases, 4; expected cases, 0.02), with 9 of these 13 tumors occurring in children who had undergone cranial irradiation before transplantation. When brain and thyroid cancers were excluded from the analysis, there was no difference in the absolute excess risk among the patients who were less than 10, 10 to 19, or 20 to 29 years old at the time of transplantation.

The risk of solid cancer also varied according to the primary disease (Table 4) and tended to be highest for patients with acute leukemia. Significantly elevated risks were also found for patients with acute nonlymphocytic leukemia, acute lymphoblastic leukemia, or chronic myelogenous leukemia who had undergone transplantation before the age of 30 years. Among the patients who were 30 years or older at the time of transplantation, only those with acute nonlymphocytic leukemia had a significantly increased risk of solid cancer (ratio of observed to expected cases, 2.3), and the excess risk of solid tumors for older patients was similar to that for the patients who underwent transplantation at a younger age (21.0 and 26.6, respectively).

Table 5 shows the results of multivariate regression

TABLE 1. CHARACTERISTICS OF 19,229 PATIENTS UNDERGOING BONE MARROW TRANSPLANTATION.*

CHARACTERISTIC	NO. OF PATIENTS (%)
Cohort	
IBMTR	14,798 (77.0)
Seattle	4,431 (23.0)
Male sex	11,378 (59.2)
Primary disease	
Acute lymphoblastic leukemia	4,245 (22.1)
Acute nonlymphocytic leukemia	5,208 (27.1)
Chronic myelogenous leukemia	4,885 (25.4)
Non-Hodgkin's lymphoma	729 (3.8)
Other cancers†	561 (2.9)
Severe aplastic anemia	2,159 (11.2)
Myelodysplastic syndrome or myeloproliferative disorder	643 (3.3)
Other‡	799 (4.2)
Donor-recipient relationship and histocompatibility	
Identical twin	533 (2.8)
HLA-identical sibling	15,217 (79.1)
HLA-mismatched sibling or other relative§	2,265 (11.8)
Unrelated donor	1,079 (5.6)
Other or uncertain	135 (0.7)
Conditioning regimen	
TBI and cyclophosphamide, with or without other drugs	12,426 (64.6)
TBI without cyclophosphamide, with or without other drugs	1,574 (8.2)
LFI with or without cyclophosphamide or other drugs	656 (3.4)
Busulfan and cyclophosphamide with or without other drugs	2,859 (14.9)
Cyclophosphamide with or without other drugs	1,435 (7.5)
Other	279 (1.5)
T-cell depletion of marrow	2,580 (13.4)
Drugs given for GVHD prophylaxis	
Cyclosporine, no methotrexate	5,953 (31.0)
Methotrexate, no cyclosporine	4,378 (22.8)
Cyclosporine and methotrexate	7,003 (36.4)
Other or no drugs	1,895 (9.8)
Acute GVHD (grades II-IV)	7,310 (38.0)
Chronic GVHD¶	3,262 (17.0)
TBI dose (Gy)	
Single dose	
<10	1,594 (11.4)
≥10	2,097 (15.0)
Fractionated doses	
<12	2,054 (14.7)
12	4,861 (34.7)
13	1,213 (8.7)
≥14	1,944 (13.9)
Unknown	237 (1.7)

*TBI denotes total-body irradiation, LFI limited-field irradiation, and GVHD graft-versus-host disease. Percentages do not always add to 100 because of rounding.

†Other cancers included Hodgkin's disease (in 175 patients), multiple myeloma (in 225), chronic lymphoblastic leukemia (in 34), and solid cancers (in 127).

‡Other primary diseases included inherited disorders of metabolism (in 158 patients), hemoglobinopathies (in 315), and other, primarily nonmalignant, diseases (in 326).

§This category includes 251 HLA-matched relatives other than siblings.

¶Chronic GVHD was defined as moderate or severe graft-versus-host disease for the IBMTR cohort and clinically extensive disease for the Seattle cohort.

||Percentages for TBI-dose categories are for the subgroup of 14,000 patients who underwent TBI.

TABLE 2. RATIO OF OBSERVED TO EXPECTED CASES OF NEW INVASIVE SOLID CANCERS ACCORDING TO THE TIME SINCE TRANSPLANTATION.*

SITE OF CANCER	TIME AFTER TRANSPLANTATION										95% CI
	<1 YR		1-4 YR		5-9 YR		≥10 YR		TOTAL		
No. of patients (person-yr)	19,229 (12,476)		9501 (22,778)		3234 (8386)		690 (1724)		19,229 (45,364)		
	Obs	Obs:Exp	Obs	Obs:Exp	Obs	Obs:Exp	Obs	Obs:Exp	Obs	Obs:Exp	
All solid tumors	9	1.2	34	2.3†	24	4.1†	13	8.3†	80	2.7†	2.1-3.3
Buccal cavity or pharynx	0	0.0	3	3.9	9	32.4†	5	77.9†	17	11.1†	6.5-17.8
Lip	0	0.0	1	19.5	1	51.7	0	0.0	2	18.9†	2.1-68.2
Tongue	0	0.0	1	6.4	2	35.8	3	238.2†	6	19.5†	7.1-42.4
Salivary gland	0	0.0	0	0.0	3	117.2†	0	0.0	3	23.2†	4.7-67.7
Gum or other site in mouth	0	0.0	1	5.1	2	26.9†	2	107.4†	5	12.5†	4.0-29.2
Pharynx	0	0.0	0	0.0	1	9.7	0	0.0	1	1.7	0.0-9.5
Colon	0	0.0	1	1.4	0	0.0	0	0.0	1	0.7	0.0-3.8
Rectum	0	0.0	1	2.3	0	0.0	1	20.6	2	2.2	0.3-7.9
Liver	1	9.2	1	5.0	0	0.0	1	54.4	3	7.5†	1.5-22.0
Lung	1	1.3	1	0.8	0	0.0	0	0.0	2	0.7	0.1-2.6
Breast (female)	1	0.6	4	1.2	1	0.8	1	2.9	7	1.1	0.4-2.2
Cervix	0	0.0	1	1.4	0	0.0	0	0.0	1	0.7	0.0-3.9
Uterine corpus	0	0.0	0	0.0	1	6.8	0	0.0	1	1.4	0.0-7.9
Testis	0	0.0	2	2.5	0	0.0	0	0.0	2	1.2	0.1-4.4
Brain or other CNS site	1	2.5	3	4.2	7	26.0†	0	0.0	11	7.6†	3.8-13.5
Thyroid	1	3.2	2	3.4	2	8.1	3	42.1†	8	6.6†	2.8-12.9
Bone	0	0.0	3	16.0†	1	14.0	1	77.7†	5	13.4†	4.3-31.3
Connective tissue	1	7.3	2	8.2	1	10.7	0	0.0	4	8.0†	2.2-20.5
Melanoma of the skin	2	3.5	7	6.7†	1	2.2	1	7.4	11	5.0†	2.5-8.9
Other‡	1	0.4	3	0.9	1	0.8	0	0.0	5	0.8	0.2-1.8

*Data include all invasive solid tumors except nonmelanoma skin cancer. The analysis included patients receiving allogeneic or syngeneic transplants; patients with a primary disease of Fanconi's anemia or an immunodeficiency disease were excluded. Obs denotes observed cases, Exp expected cases, CI confidence interval, and CNS central nervous system.

†P<0.05.

‡Other new cancers included cancer of the penis (in one patient), Kaposi's sarcoma (in one), neuroblastoma of the nasal passages (in one), and metastatic cancer with an unknown primary site (in two).

TABLE 3. RATIO OF OBSERVED TO EXPECTED CASES AND ABSOLUTE EXCESS RISK OF NEW INVASIVE SOLID CANCERS ACCORDING TO AGE AT TRANSPLANTATION.*

AGE AT TRANSPLANTATION	NO. OF PATIENTS	PERSON-YEARS AT RISK	OBS	EXP	OBS:EXP (95% CI)	EXCESS RISK†
<10 yr	2745	7,989	22	0.6	36.6 (22.9-55.4)	26.8
10-19 yr	4178	12,008	8	1.7	4.6 (2.0-9.1)	5.2
20-29 yr	4948	11,996	21	4.6	4.6 (2.8-7.0)	13.7
30-39 yr	4474	8,914	13	9.4	1.4 (0.7-2.4)	4.1
≥40 yr	2884	4,457	16	13.5	1.2 (0.7-1.9)	5.7

*Obs denotes observed cases, Exp expected cases, and CI confidence interval.

†The absolute excess risk is the number of observed cases minus the number of expected cases per 10,000 patients per year.

TABLE 4. RATIO OF OBSERVED TO EXPECTED CASES AND ABSOLUTE EXCESS RISK OF NEW INVASIVE SOLID CANCERS ACCORDING TO AGE AT TRANSPLANTATION AND PRIMARY DISEASE.*

PRIMARY DISEASE	AGE AT TRANSPLANTATION							
	<30 YR				≥30 YR			
	Obs	Exp	Obs: Exp	Excess Risk†	Obs	Exp	Obs: Exp	Excess Risk†
Acute nonlymphocytic leukemia	24	2.1	11.6‡	26.6	14	6.1	2.3‡	21.0
Acute lymphoblastic leukemia	15	1.2	12.2‡	17.5	1	1.3	0.8	-3.0
Chronic myelogenous leukemia	6	1.4	4.3‡	9.7	8	10.5	0.8	-4.1
Severe aplastic anemia	5	1.7	3.0	4.6	3	1.9	1.6	10.5
Lymphoma or other	1	0.6	1.7	1.0	3	3.0	1.0	-0.2
Total	51	7.0	7.3‡	13.8	29	22.8	1.3	4.6

*Obs denotes observed cases, and Exp expected cases.

†The absolute excess risk is the number of observed cases minus the number of expected cases per 10,000 patients per year.

‡P<0.05.

analyses for patients who survived for at least one year after transplantation. Ten potential risk factors were evaluated with adjustment for age, time since transplantation, and primary disease (model 1 in Table 5). Patients who underwent pretransplantation conditioning with radiation had an increased risk of cancer as compared with those who did not receive radiotherapy. The risk of cancer in transplant recipients who underwent limited-field irradiation was 18.4 times as high as the risk for those who did not undergo irradiation. The doubling of the risk among patients given total-body irradiation either as a single dose or in multiple fractions was not statistically significant. However, the risk increased significantly with increasing doses of radiation for both the patients who received a single dose and those who received multiple doses (model 2 in Table 5) (P for trend, 0.006 and 0.001, respectively). Among patients undergoing total-body irradiation with a single dose of 10 Gy or higher or fractionated doses totaling 13 Gy or higher, the risk was three to four times that among the patients who did not undergo irradiation. A similar dose-response pattern was found when we compared the risk with that in the general population: the ratio of observed to expected cases was 6.7 for patients receiving a single dose of 10 Gy or higher and 6.1 for those receiving fractionated doses totaling 13 Gy or higher. In these groups, the risk of a new cancer was highest among the patients who had survived for five or more years (9.3 and 14.4, respectively).

Table 6 shows the results of univariate and multivariate regression analyses for individual sites of invasive cancer among the patients surviving for at least one year after transplantation. Patients who received

TABLE 5. MULTIVARIATE ANALYSIS OF RISK FACTORS FOR NEW INVASIVE SOLID CANCERS AMONG PATIENTS WHO SURVIVED FOR AT LEAST ONE YEAR AFTER TRANSPLANTATION.*

VARIABLE	CASES (N=71)	RELATIVE RISK (95% CI)
Model 1: General risk factors†		
TBI, single fraction	25	2.1 (0.6-7.5)
TBI, multiple fractions	35	2.1 (0.6-7.1)
Limited-field irradiation	5	18.4 (3.7-90.5)
Acute GVHD (grades II-IV)	19	0.8 (0.4-1.3)
Chronic GVHD	18	1.1 (0.6-2.0)
T-cell depletion	6	1.0 (0.4-2.5)
HLA mismatched or unrelated donor	4	0.6 (0.2-1.8)
Twin donor	3	0.5 (0.2-1.9)
Male sex	41	1.2 (0.7-1.9)
Seattle cohort	28	1.3 (0.7-2.3)
Model 2: Radiation dose‡		
None	6	1.0 —
TBI, single fraction		
<10 Gy	3	0.9 (0.2-4.4)
≥10 Gy	22	2.7 (0.7-10.1)
		P for trend, 0.006§
TBI, multiple fractions		
<12 Gy	4	1.2 (0.3-5.7)
12-12.9 Gy	15	1.8 (0.5-6.6)
13-13.9 Gy	6	4.1 (1.0-17.4)
≥14 Gy	10	4.4 (1.1-17.7)
		P for trend, 0.001§
Limited-field irradiation	5	16.1 (3.2-80.7)

*CI denotes confidence interval, TBI total-body irradiation, and GVHD graft-versus-host disease.

†The model used for general risk factors was a Poisson regression model stratified according to the primary disease and time since transplantation and adjusted for age at transplantation (see the Methods section).

‡The radiation-dose model was a Poisson regression model stratified and adjusted as indicated for the general model but including the radiation-dose variables. The model excludes data on patients with unknown radiation doses.

§P values for trend are for the comparison between TBI-dose categories and no radiation.

TABLE 6. RISK FACTORS FOR NEW INVASIVE SOLID CANCERS AMONG PATIENTS WHO SURVIVED FOR AT LEAST ONE YEAR AFTER TRANSPLANTATION, ACCORDING TO THE SITE OF CANCER.*

VARIABLE	MELANOMA OF THE SKIN (N=9)		BRAIN OR OTHER CNS CANCER (N=10)		BONE OR CONNECTIVE-TISSUE CANCER (N=8)		THYROID CANCER (N=7)		SQUAMOUS-CELL CARCINOMA			
									BUCCAL CAVITY (N=14)		SKIN (N=8)	
	no. of cases	RR	no. of cases	RR	no. of cases	RR	no. of cases	RR	no. of cases	RR	no. of cases	RR
High-dose TBI†	7	8.2‡	8	4.3	2	0.6	6	5.8	6	3.0	1	0.2
Limited-field irradiation	0	0.0	0	0.0	0	0.0	0	0.0	3	136‡	0	0.0
Acute GVHD (grades II–IV)	2	0.6	2	0.4	1	0.4	3	1.9	6	1.7	4	2.1
Chronic GVHD	1	0.4	0	0.0§	1	0.6	0	0.0	9	6.0‡	7	22.6‡
T-cell depletion	3	4.5	0	0.0	0	0.0	1	4.9	0	0.0	0	0.0
HLA mismatched or unrelated donor	0	0.0	1	0.6	1	2.2	0	0.0	0	0.0	0	0.0
Twin donor	0	0.0	1	2.6	0	0.0	1	2.4	0	0.0	0	0.0
Male sex	3	0.4	8	2.5	5	1.7	2	0.4	13	9.7‡	8	∞‡
Seattle cohort	2	0.7	5	2.1	1	0.1	4	1.3	6	1.0	4	1.4

*CNS denotes central nervous system, RR relative risk, TBI total-body irradiation, and GVHD graft-versus-host disease. The results shown are for univariate Poisson regression models stratified according to the primary disease and time since transplantation and adjusted for age at transplantation. The results of multivariate analyses were similar, with the following significant risk factors: brain and other central nervous system cancers, high-dose total-body irradiation (relative risk = 4.3, P = 0.06) and chronic graft-versus-host disease (relative risk = 0.0, P = 0.03); squamous-cell carcinoma of the buccal cavity, limited-field irradiation (relative risk = 101, P = 0.003), chronic graft-versus-host disease (relative risk = 5.1, P = 0.004), and male sex (relative risk = 8.7, P = 0.006); and squamous-cell carcinoma of the skin, chronic graft-versus-host disease (relative risk = 24.1, P < 0.001) and male sex (relative risk = ∞, P = 0.003).

†High-dose total-body irradiation was defined as ≥10 Gy for a single dose and ≥13 Gy for fractionated doses and was compared with low-dose or no radiation.

‡P < 0.01.

§P < 0.05.

high doses of total-body irradiation had a significant increase in the risk of melanoma and an increased risk of cancer of the brain and thyroid. The risk of buccal cancer was particularly high after limited-field irradiation. Chronic graft-versus-host disease was associated with elevated risks of squamous-cell cancers of the buccal cavity and skin. Of the 16 cases in patients with chronic graft-versus-host disease, 11 occurred in those who had received immunosuppressive therapy for two or more years. Twenty-one of the 22 cases of squamous-cell buccal or skin cancer developed in male patients. Depletion of T cells in the donor marrow was associated with a relative risk of invasive melanoma of 4.5 (Table 6) and a relative risk of 5.9 when the two in situ cases and nine invasive cases were considered together (P = 0.02).

The immunosuppressive drugs used to prevent or treat acute graft-versus-host disease had no apparent effect on the risk of a new solid cancer in univariate or multivariate analyses. The drugs used for pretransplantation conditioning, evaluated singly and in combination, were not significantly related to the risk of solid cancer.

DISCUSSION

Our analysis of nearly 20,000 bone marrow recipients, including 3200 who survived for five or more years, revealed a high risk of specific solid cancers after transplantation. The risk increased sharply over time (to 6.7 percent at 15 years) and was highest among children who had undergone transplantation when they were less than 10 years old. Statistically significant increases in risk were confined to melanoma and cancers of the buccal cavity, brain, liver, thyroid, bone, and connective tissue. The increased risk of new solid cancers after bone marrow transplantation is likely to be related to pretransplantation conditioning with radiation, altered immune function, and prior treatment for the primary disease.

Previous studies have reported an increased incidence of new cancers after bone marrow transplantation, mainly lymphomas and hematopoietic disorders, which occurred early in the follow-up period.^{2,4-7,17-19} Lymphoproliferative disorders are the most common cancer in the first year after allogeneic bone marrow transplantation; most are related to compromised immune function and Epstein-Barr virus in-

fection.^{2,7} The estimated 10-year cumulative incidence of lymphoma in our cohort is less than 1.5 percent, with no cases of lymphoma observed 10 or more years after transplantation.

Data on post-transplantation solid cancers are sparse. The two largest studies reported small numbers of cancers at individual anatomical sites and an overall risk that was two to three times as high as that in the general population.^{2,7} Studies in animals have also linked various solid tumors to bone marrow transplantation.^{18,20}

Whole-body irradiation at the doses typically given to transplant recipients would be fatal without bone marrow transplantation. The transplantation experience is also unique because large doses of radiation are given to patients who will also have impaired immune function. In our study, the risk of a solid cancer among patients who survived for one or more years after transplantation rose with the dose of radiation, with three to four times the risk at the highest dose levels, as compared with those who did not receive radiation therapy. The elevated risks for several solid cancers are consistent with a radiogenic effect, especially for cancers of the thyroid, salivary gland, bone, connective tissue, and brain.²¹ The 18-fold risk of cancer in patients who received limited-field irradiation is almost entirely attributable to a higher-than-expected number of cancers after thoraco-abdominal irradiation among patients with severe aplastic anemia who were treated at a single center, as reported previously.^{6,22}

Radiogenic cancers generally have a long latent period, and the risk of such cancers is frequently high among patients undergoing irradiation at a young age.^{21,23} Transplant recipients routinely undergo thorough follow-up examinations, which may result in early detection of secondary cancers. We found that young children given radiotherapy as part of the conditioning regimen had a high risk of cancer of the brain or thyroid, and most of these patients had received cranial irradiation before transplantation. Radiogenic thyroid cancer has been reported in children exposed to high or low doses of radiation but not in adults.^{24,25} Higher than expected numbers of brain cancers have been reported among children treated with cranial irradiation at doses of 1 to 3 Gy for tinea capitis²⁶ and 18 to 24 Gy for acute lymphoblastic leukemia.²⁷

Studies of patients who were exposed to radiation have found increased risks of bone and connective-tissue cancers in these patients only when the radiation doses surpassed 10 Gy.²⁸⁻³⁰ We found an increased risk of salivary gland cancer after radiation therapy — three cases — which is consistent with the strong dose response of the mucoepidermoid carcinomas of the salivary gland reported among survivors of the atomic bomb.³¹

Patients with immunodeficiency diseases and those

receiving immunosuppressive therapy for organ transplants are prone to the development of cancer at certain sites.³²⁻³⁴ We found no link between immune dysfunction (i.e., HLA-mismatched marrow transplants, T-cell depletion, or graft-versus-host disease) and an elevated risk of solid cancer (all types combined), nor could we confirm an excess risk associated with the administration of antithymocyte globulin for graft-versus-host disease.³ However, the large increase in the risk of melanoma in our study and the possible association of melanoma with T-cell depletion are consistent with the findings in immunosuppressed patients with renal allografts³⁵ or malignant lymphoma.^{36,37} The mechanism of the association between melanoma and high doses of radiation is unclear, since melanoma has not previously been linked to ionizing radiation.^{21,23} Immunologic factors may also contribute to the increased risk of squamous-cell skin cancers after bone marrow or renal transplantation, especially in regions where one can be exposed to strong sunlight.³³ Immunologic alterations may predispose patients to squamous-cell cancers of the buccal cavity, particularly in view of the association between oral mucositis and chronic graft-versus-host disease. A recent study of patients with aplastic anemia who underwent transplantation at the Fred Hutchinson Cancer Research Center in Seattle or Hôpital St. Louis in Paris showed that the incidence of solid tumors, predominantly tumors of the buccal cavity and skin, was significantly increased after the administration of azathioprine for chronic graft-versus-host disease.⁴ In immunosuppressed patients, oncogenic viruses such as human papillomaviruses may contribute to squamous-cell cancers of the skin and buccal mucosa after transplantation.^{32,38} The excess risk of squamous-cell cancers of the buccal cavity and skin among male patients is unexplained, but it may indicate an interaction between ionizing radiation, immunodeficiency, and other risk factors more prevalent among men than women.

In our study, only 690 transplant recipients were followed for 10 or more years, which limited our ability to estimate the risk of cancer among long-term survivors. Follow-up of recipients surviving 10 to 20 years after transplantation should clarify the risks of breast, lung, and other cancers that may arise only after a long latent period. The experience of patients with Hodgkin's disease and others who underwent irradiation at a young age^{21,23,39,40} indicates that the risk of cancer among patients who receive transplants at a young age and survive to adulthood may be even higher than that reported in our study.

Bone marrow transplantation prolongs survival or is curative in many patients with cancer or other life-threatening diseases. These benefits clearly outweigh the risks of late complications. However, our results should alert physicians that recipients of bone marrow transplants, particularly those receiving trans-

plants at a young age, have an increased incidence of new solid cancers and that the excess risk of cancer rises sharply with time. Transplant recipients should be followed indefinitely to detect early cancer and precursor lesions (e.g., dysplastic nevi, actinic keratoses, and oral leukoplakia), and they should avoid carcinogenic exposures (e.g., exposure to tobacco), which may potentiate the risk of solid cancers.

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