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ORIGINAL REPORT

Parenthood in Survivors of Hodgkin Lymphoma: An EORTC-GELA General Population Case-Control Study

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ABSTRACT

Purpose
We investigated the impact of Hodgkin lymphoma (HL) on parenthood, including factors influencing parenthood probability, by comparing long-term HL survivors with matched general population controls.

Patients and Methods
A Life Situation Questionnaire was sent to 3,604 survivors treated from 1964 to 2004 in successive clinical trials. Responders were matched with controls (1:3 or 4) for sex, country, education, and year of birth (10-year groups). Controls were given an artificial date of start of treatment equal to that of their matched case. The main end point was presence of biologic children after treatment, which was evaluated by using conditional logistic regression analysis. Logistic regression analysis was used to analyze factors influencing spontaneous post-treatment parenthood.

Results
In all, 1,654 French and Dutch survivors were matched with 6,414 controls. Median follow-up was 14 years (range, 5 to 44 years). After treatment, the odds ratio (OR) for having children was 0.77 (95% CI, 0.68 to 0.87; $P < .001$) for survivors compared with controls. Of 898 survivors who were childless before treatment, 46.7% achieved post-treatment parenthood compared with 49.3% of 3,196 childless controls (OR, 0.87; $P = .08$). Among 756 survivors with children before treatment, 12.4% became parents after HL treatment compared with 22.2% of 3,218 controls with children before treatment (OR, 0.49; $P < .001$). Treatment with alkylating agents, second-line therapy, and age older than 35 years at treatment appeared to reduce the chances of spontaneous post-treatment parenthood.

Conclusion
Survivors of HL had slightly but significantly fewer children after treatment than matched general population controls. The difference concerned only survivors who had children before treatment and appears to have more personal than biologic reasons. The chance of successful post-treatment parenthood was 76%.

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INTRODUCTION

Hodgkin lymphoma (HL) has high cure rates (80% to 90%) and a predominant incidence in patients age 20 to 44 years. Many patients wish to start or complete a family after therapy.[1-3] There are few studies on parenthood after treatment specifically for HL, and most concern outdated treatment regimens[4] and/or small patient groups.[5,6] Publications on mixed cancer types often concern survivors of childhood cancer,[7,8] do not take into account whether patients attempted parenthood,[9-12] or lack a suitable general population comparison group.[4,6,13]

Since 1964, the European Organisation for Research and Treatment of Cancer (EORTC) Lymphoma Group, along with the Groupe d'Etude des Lymphomes de l'Adulte [GELA] since 1993, has uniformly treated patients with HL in successive clinical trials. From 1982 onward, these trials focused not only on efficacy but also on reduction of treatment-related toxicity. In 2009, a Life Situation Questionnaire (LSQ) with questions related to fertility and parenthood, among others, was sent to patients.

We investigated the influence of treatment for HL on successful motherhood and fatherhood in a large cohort of European long-term survivors, comparing HL survivors with matched general population controls. We also investigated factors influencing the success of attempted parenthood by comparing different treatment regimens in a nested case-control study.

PATIENTS AND METHODS

Survivors

Overall, 6,658 patients with histologically proven, newly diagnosed HL were included in nine consecutive randomized trials between 1964 and 2004 (Table 1). For detailed protocols of these trials, see Raemaekers et al,[2] Tubiana

Table 1. Case and Control Characteristics (males and females, external and internal analyses)

	Controls		Cases					
	Matched Controls External Analysis*		Included in External Analysis*		Included in Internal Analysis†		All Patients Included in H1-H9 Trials	
Characteristic	No.	%	No.	%	No.	%	No.	%
Cases	6,414		1,654	25	745	11	6,658	
Males	3,166	49	815	49	345	46	3,638	55
Country								
France	2,862	45	737	45	285	38	2,991	45
Netherlands	3,552	55	917	55	376	50	2,438	37
Other	0		0		84	11	1,229	18
Age at start treatment, years‡	Artificial		Real		Real		Real	
Median	31		30		24		31§	
Range	15-70		15-69		15-51		5-73	
< 30	2,978	46	808	49	606	81	3,202	48
30-49	2,784	43	700	42	138	19	2,646	40
≥ 50	652	10	146	9	1	< 1	805	12
Age at reply questionnaire, years								
Median	47		47		41		N/A	
Range	23-80		24-85		24-71			
Follow-up duration, years	Artificial		Real		Real			
Median	13		13		15		N/A	
Range	5-44		5-44		5-44			
Period of treatment start‡	Artificial		Real		Real		Real	
1964-1976	271	4	73	4	51	7	587	9
1977-1993	1,986	31	513	31	284	38	2,535	38
1994-2004	4,157	65	1,068	65	410	55	3,536	53
Disease stage								
I and II	N/A		1,481	90	656	88	5,719	86
III and IV			173	10	89	12	939	14
"B" symptoms present	N/A		475	29	213	29	1,987	30
Initial treatment only	N/A		1,472	89	659	88	5,342	80
Chemotherapy			1,235	75	523	70	4,298	65§
Alkylating agents			702	42	300	40	2,617	39
No alkylating agents			528	32	223	30	1,673	25
Radiotherapy			1,380	83	618	83	4,884	73§
Above diaphragm			1,048	63	463	62	3,453	52
Under diaphragm			331	20	155	21	1,430	21
Staging laparotomy			68	4	44	6	379	6
First- and second-line treatment¶	N/A		182	11	86	12	1,316	20
Education level								
Low	1,968	31	502	30	132	18	Not known	
Middle	2,070	32	534	32	258	35		
High	2,376	37	618	37	348	47		
Unknown	0		0		7	1		

NOTE. Due to rounding, percentages may exceed or fall short of 100%.
Abbreviation: N/A, not applicable.
*External analysis: matched analysis of survivors and general population controls.
†Internal analysis: nested case-control study within survivor cohort.
‡For general population controls, data on start of artificial treatment and artificial treatment period are given.
§Age at treatment was unknown for five cases of the total 6,658. Chemotherapy details were unknown for eight cases of the total, and five were included for external analysis. Radiotherapy details were unknown for one case of the total, included for external analysis.
¶Second-line treatment varied from radiotherapy to high-dose chemotherapy and bone marrow transplantation.

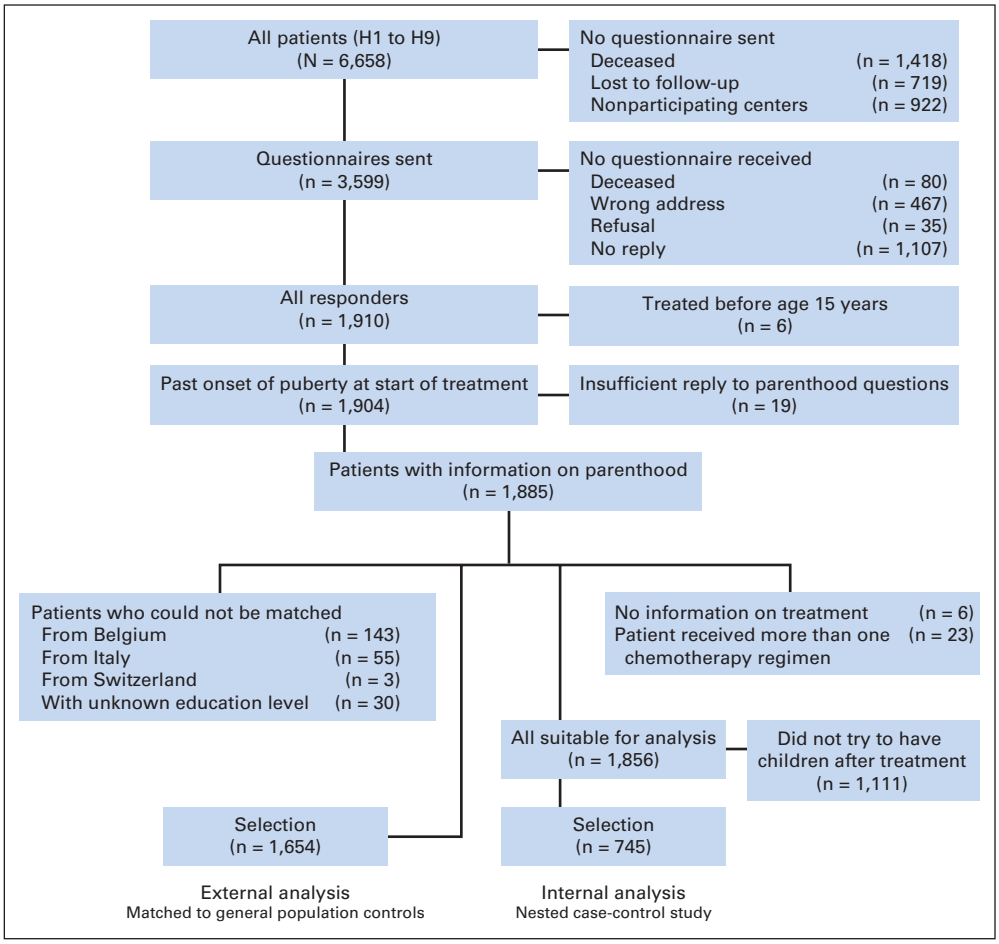

Fig 1. Study flow diagram showing selection of cases for analysis.

et al,[14] Tubiana et al,[15] Carde et al,[16] Somers et al,[17] Carde et al,[18] Noordijk et al,[19] Aleman et al,[20] Fermé et al,[21] and Thomas et al.[22] Administered treatment was recorded, including chemotherapy type, number of cycles, radiotherapy fields, and dose. In 2008, current addresses were searched for all 5,733 survivors alive at last follow-up. For 3,597 survivors, a recent address was obtained (Fig 1, CONSORT diagram).

Questionnaires

Survivors received the newly developed LSQ, which addresses issues not available in other validated questionnaires and contains the following items: parenthood after HL, education, work, insurance, survivors' health, and social situation. Because of the sensitive nature of the questionnaire, only one reminder was sent after 5 weeks.

The number of children before and after HL therapy was obtained from the following LSQ question: "How many children alive at birth have you fathered/given birth to? Please specify the numbers before and after HL." Information on artificial reproductive techniques (ARTs) used was documented for children born after HL therapy. Whether patients tried to have children after HL therapy was evaluated on the basis of the following question: "After first treatment for HL, did you conceive or try to conceive a pregnancy/have you been pregnant or tried to become pregnant?" If no children were born after HL therapy, patients were asked for their reasons for not having children. Adoption was evaluated on the basis of the following question: "After HL, have you tried to adopt a child? If yes, did you succeed?"

Of 3,597 survivors approached, 1,910 (53%) returned the questionnaires with a signed informed consent form. A nonresponders analysis was performed to compare those who did not return the questionnaires with those who did, and it indicated almost no differences. Responders more often came from less recent trials and had slightly less often been treated with nonalkylating chemotherapy and radiotherapy above the diaphragm. Disease stage distribution was similar in responders and nonresponders.

Selection of Cases and Controls

For the external analysis (comparing survivors with general population controls), we obtained data from the United Nations Economic Commission for Europe (UNECE) Generations and Gender Survey, available for France and the Netherlands.[23] Patients (cases) older than age 15 years at treatment start with a known number of children after HL and living in France (n = 737) or the Netherlands (n = 917) were matched per stratum to controls. Strata were defined by sex, country of residence, education level, and year of birth (10-year groups). Four controls were matched per case, except in one stratum in which seven cases could be matched to only three controls each. Interviews were conducted in 2009 (cases), 2005 (French controls), and 2003 (Dutch controls). To correct for year of interviewing (duration of follow-up), cases were matched to controls 4 years older for France and 6 years older for the Netherlands. After stratum matching, controls were given an artificial year of treatment start by individually matching each case to four controls. Year of treatment start was corrected for controls by subtracting six (the Netherlands) or four (France). Because controls were given an artificial year of treatment start, the expressions "children before treatment" and "children after treatment" were used for both groups. Controls younger than age 15 years or older than age 70 years at the start of fictional treatment were excluded to keep the age range of cases and controls similar. In total, 1,654 cases were compared with 6,414 controls (Fig 1).

Analysis of Treatment Effect

For the internal analysis (comparing survivors in different treatment groups), we selected all survivors who replied that they had tried to have

children after HL treatment. Analysis was done on treatment received, not on an intention-to-treat basis. Twenty-three survivors were excluded because they received several chemotherapy regimens. After exclusions, 745 survivors were suitable for internal analysis (Fig 1).

Excluding Bias From Internal Analysis

To exclude that factors associated with lower probability of post-treatment parenthood found in the internal analysis were selected by chance, we divided cases and matched controls from the external analysis into six groups on the basis of these factors. Thirty-four cases and their matched controls could not participate in the analysis because of missing treatment details.

Definitions

Survivors given chemotherapy were grouped into those treated without alkylating agents (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD][24] or epirubicin, bleomycin, vinblastine, and prednisone [EBVP][25]) and those treated with alkylating chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone [MOPP][26]; MOPP/ABV hybrid [MOPP/doxorubicin, bleomycin, and vinblastine][27]; or cyclophosphamide, doxorubicin, vincristine, bleomycin, etoposide, procarbazine, and prednisone [BEACOPP baseline][28]). Cycles given at reduced dose were considered full cycles. The number of cycles was used to estimate the amount of alkylating agents administered, counting one cycle of MOPP/ABV or BEACOPP as being equivalent to 0.5 cycles of MOPP. In two trials[14,15] maintenance chemotherapy was given for 2 years: vinblastine 6 or 10 mg or 6 mg once per week for 3 months alternating with procarbazine 150 mg once per day for 3 weeks, with a gap of 4 weeks in between. The cumulative procarbazine dose was 9 g/m^2, approximately equal to six cycles of MOPP, and was therefore considered as six cycles of MOPP equivalent.

Information on smoking and education level was obtained from the LSQ questionnaires. Education level was grouped into low, middle, and high: low comprised primary school and the lower level of secondary school (corresponding to International Standard Classification of Education [ISCED] levels 0, 1 and 2[29]), middle comprised the higher levels of secondary school (ISCED levels 3 and 4), and high comprised higher education and university (ISCED levels 5 and 6).

ART meant use of intrauterine insemination, in vitro fertilization, or intracytoplasmic sperm injection with fresh or cryopreserved semen.

Statistical Analyses

We estimated the difference in number of biologic children after treatment (primary end point) between HL survivors (cases) and general population controls. Factors associated with chances of spontaneous post-treatment parenthood were also investigated.

Conditional logistic regression analysis was used to compare cases and controls. Variables entered into the model to evaluate potential confounding were age at treatment, treatment period (1964 to 1976, 1977 to 1993, 1994 to 2004), and existing biologic children before treatment (no, yes). If the adjusted odds ratios (aORs) for biologic children after treatment changed by more than 10% on addition of any of these variables, they were retained in the model.

Univariable analysis of factors influencing spontaneous post-treatment parenthood in cases was performed by using the χ^2 test. The multivariable analysis was performed by using logistic regression analysis. Variables entered were age at treatment (15 to 24, 25 to 34, or $\geq$ 35 years), treatment period, clinical stage (I to II or III to IV), presence of "B" symptoms (no, yes), cycles of alkylating chemotherapy in MOPP equivalents (no alkylating chemotherapy, $<$ three cycles, $\geq$ three cycles MOPP equivalent), radiotherapy (above or below the diaphragm or on the iliac and inguinal region [males]/on the iliac region [females]), education level (low, middle, high), and presence of biologic children before treatment (no, yes). A stepwise selection procedure was used. Results were expressed as ORs with 95% CIs. Exact binomial 95% CIs for the proportion of male children before and after treatment were calculated. All statistical tests were two-sided; statistical significance was defined as a P value of less than .05. Data were stored at the EORTC data center in Brussels, Belgium. STATA software version 10.1 (STATA, College Station, TX) was used.

Table 2. Children Before and After Treatment in Cases and Controls (external analysis)

	No Children After Treatment		Children After Treatment		
Before Treatment	No.	%	No.	%	Total
Cases					
No children	479	53.3	419	46.7	898
Children	662	87.6	94	12.4	756
Controls					
No children	1,621	50.7	1,575	49.3	3,196
Children	2,505	77.8	713	22.2	3,218

RESULTS

External Analysis

Fewer cases (513 of 1,654; 31.0%) than controls (2,288 of 6,414; 35.7%) had at least one biologic child after treatment (Table 2). Before treatment, 45.7% of cases and 50.2% of controls had biologic children. The OR for having children after treatment was 0.77 (95% CI, 0.68 to 0.87; $P < .001$) for cases compared with controls. OR did not change with correction for presence of children before treatment, age at treatment, or treatment period. More cases (25 of 1,654; 1.5%) than controls (56 of 6,414; 0.9%) adopted after treatment (OR, 1.78; 95% CI, 1.11 to 2.87; $P = .02$). Thirteen additional cases attempted adoption but without success. Three of them reported their failure was (partly) related to their cancer history.

Females and males had different outcomes. Among females, significantly fewer cases (274 of 839; 32.7%) than controls (1,263 of 3,248; 38.9%) had biologic children after treatment. Among males, the difference between cases and controls was smaller: 239 of 815 (29.3%) of cases versus 1,025 of 3,166 (32.4%) of controls. The aOR was 0.64 (95% CI, 0.52 to 0.77; $P < .001$) for females corrected for age at treatment start; OR was 0.84 (95% CI, 0.70 to 1.00; $P = .06$) for males.

We investigated the importance of already having children before treatment. Of 898 cases who were childless before treatment, 539 (60.0%) tried to have children and 419 (46.7%) succeeded compared with 1,575 of 3,196 (49.3%) of childless controls (OR, 0.87; 95% CI, 0.74 to 1.01; $P = .08$). Among survivors with children before treatment, the difference between cases and controls was more marked: 127 of 756 cases (16.8%) attempted post-treatment parenthood and 94 (12.4%) succeeded compared with 713 (22.2%) of 3,218 controls (OR, 0.49; 95% CI, 0.38 to 0.63; $P < .001$). Results were similar when all cases (262; 15.8%) and controls (1,097; 17.1%) older than age 45 years at treatment were excluded.

Looking at cases only, 666 attempted post-treatment parenthood and 513 (77%) succeeded (Table 3). Chances of success did not differ between those with and those without children before treatment. Chances of success were also similar between males and females, but males used ARTs far more often. Approximately 40% of those who were childless but more than 80% of those with children before treatment did not try to have children after treatment. Reasons for survivors' decision to refrain from having children are listed in Table 4. Among those with children before treatment, "family was already completed" was the most frequent reply (82%). In those who were

Table 3. Parenthood in Cases From the External Analysis: Outcome According to Sex and Biological Children Before Treatment

Outcome	Sex	No Children After Treatment: Attempt No.	Attempt %	No Attempt No.	No Attempt %	Failure No.	Failure %	Children After Treatment: ART* No.	ART* %	Spontaneous No.	Spontaneous %
No children before treatment	Male	237	56	188	44	48	20	36	15	153	65
	Female	302	64	171	36	72	24	5	2	225	75
Children before treatment	Male	67	17	323	83	17	25	11	16	39	58
	Female	60	16	306	84	16	27	0		44	73
Total		666	40	988	60	153	23	52	8	461	69

NOTE. Percentages in the Failure column and beyond are calculated within the group who attempted.
*ART (assisted reproductive techniques) includes intrauterine insemination, in vitro fertilization, or intracytoplasmic sperm injection with fresh or cryopreserved semen.

childless, "personal decision" (28%), "being single" (28%), and "I plan to have children later on" (25%) were the most frequent explanations for the decision not to have children until now. Survivors could choose several reasons, but the large majority (84%) expressed one reason only, independently of sex (89% in males, 78% in females) for having (86%) or not having (80%) children before treatment.

Internal Analysis

Among males attempting post-treatment parenthood, 63% (217 of 345) succeeded spontaneously, and a further 15% (49 of 345) succeeded with the help of ARTs (Table 5). Among females, these figures were 74% (295 of 400) and only 2% (eight of 400) with ARTs. In males, age 35 years or older (OR, 0.16; $P < .001$) and second-line treatment (OR, 0.10; $P < .001$) were associated with lower probability of spontaneous post-treatment parenthood. A strong dose-response relationship was found with dose of alkylating chemotherapy administered: the OR was 0.34 ($P = .003$) for treatment with less than three MOPP-equivalent cycles of alkylating chemotherapy compared with an OR of 0.04 ($P < .001$) for treatment with three or more MOPP-equivalent cycles. In females, lower probability of post-treatment parenthood was associated with age 35 years or older (OR, 0.13; $P < .001$), treatment with three or more MOPP-equivalent cycles of alkylating chemotherapy (OR, 0.51; $P = .01$), second-line treatment (OR, 0.27; $P < .001$), and high education level (OR, 0.58; $P = .03$).

Excluding Bias From Internal Analysis

ORs for all biologic children after treatment for cases were consistently lower in females than in males (Fig 2) compared with controls. They were also lower when more aggressive treatment was given.

Sex Ratio of Children

Among 1,662 children born before treatment to 820 cases (internal control), the female:male ratio was 1.000:1.062 (proportion of boys, 0.531; 95% CI, 0.503 to 0.558). Among 995 children born after treatment to 570 cases, the ratio was similar with 1.000:1.033 (proportion of boys, 0.516; 95% CI, 0.483 to 0.550). In male cases, the before-treatment ratio was 1.000:1.074 (864 children; 423 males; proportion of boys, 0.537; 95% CI, 0.499 to 0.575) and that after treatment was 1.000:1.073 (476 children; 264 males; proportion of boys, 0.537; 95% CI, 0.489 to 0.584).

DISCUSSION

In a large cohort of long-term HL survivors, we observed survivors had significantly fewer children after treatment than general population controls. This difference was significant only in females and among those who already had biologic children before treatment. When further investigating this remarkable finding in survivors with

Table 4. Reasons Not to Have Children After Treatment in Cases Who Did Not Try and Did Not Have Children After Treatment (cases from the external analysis)

Reason*	Males (n = 511) No.	Males (n = 511) %	Females (n = 477) No.	Females (n = 477) %	Children Before Treatment: No (n = 359) No.	No (n = 359) %	Yes (n = 629) No.	Yes (n = 629) %	All (N = 988) No.	All (N = 988) %
Family completed (children before HL)	288	57	230	48	4†	1	514	82	518	53
Personal decision	66	13	105	22	102	28	69	11	171	17
Medical reasons	22	4	35	7	36	10	21	3	57	6
Plan to have children later on	45	9	44	9	88	25	1	< 1	89	9
Being single	60	12	46	10	101	28	5	1	106	11
No particular reasons	23	5	22	5	30	8	15	2	45	5
Other	33	6	38	8	33	9	38	6	71	7
No response given	18	4	34	7	22	6	30	5	52	5

Abbreviation: HL, Hodgkin lymphoma.
*Patients could give more than one reason.
†Probably due to presence of biological children from partner or a misinterpretation.

Table 5. Multivariable Analysis of Factors Influencing Survivors' Odds of Having Children Without ART (internal analysis)

Factor	Biological Children Without ART		No Biological Children Spontaneously*		No Biological Children		Biological Children With ART†		Total			Model With All Variables Adjusted			Final Model Adjusted		
	No.	%	No.	%	No.	%	No.	%	No.	%	χ^2 P‡	OR	95% CI	P‡	OR	95% CI	P‡
Males	217	63	128	37	79	23	49	14	345								
Age at start of treatment, years																	
15-24	89	41	38	27	20	25	18	37	127	37	< .001	1.00			1.00§		
25-34	112	52	66	52	39	49	27	55	178	52		0.52	0.26 to 1.02	.06			
≥ 35	16	7	24	19	20	25	4	8	40	12		0.09	0.03 to 0.27	< .001	0.16	0.07 to 0.36	< .001
Period of treatment start																	
1964-1976	17	8	5	4	5	6	0		22	6	.29	1.00			—		
1977-1993	89	41	57	45	32	41	25	51	146	42		1.33	0.34 to 5.16	.74			
1994-2004	111	51	66	52	42	53	24	49	177	51		1.26	0.32 to 4.95	.65			
Disease stage																	
I and II	207	95	92	72	57	72	35	71	299	87	< .001	1.00			—		
III and IV	10	5	36	28	22	28	14	29	46	13		1.30	0.42 to 4.03	.65			
B-symptoms																	
Absent	157	72	76	59	45	57	31	63	233	68	.11	1.00			—		
Present	59	27	52	41	34	43	18	37	111	32		0.79	0.42 to 1.51	.48			
Unknown	1	< 1	0		0		0		1								
Initial treatment only	203	96	93	73	57	72	36	73	296	86							
Chemotherapy																	
No alkylating agents	80	37	12	9	11	14	1	2	92	27		1.00			1.00		
Alkylating agents	64	29	75	59	40	51	35	71	139	40							
< 3 cycles MOPP equivalent	42	19	21	16	11	14	10	20	63	18	< .001	0.37	0.17 to 0.82	.01	0.34	0.16 to 0.70	.003
≥ 3 cycles MOPP equivalent	22	10	54	42	29	37	25	51	76	22		0.04	0.02 to 0.10	< .001	0.04	0.02 to 0.09	< .001
Radiotherapy																	
Above diaphragm	149	67	79	62	49	62	30	61	228	66	.03	1.00			—		
Below diaphragm	47	22	15	12	10	13	5	10	62	18		1.09	0.47 to 2.55	.84			
Iliac and inguinal region	12	6	16	13	8	10	8	16	28	8		0.60	0.18 to 2.02	.41			
First- and second-line treatment¶	14	6	35	27	22	28	13	27	49	14	< .001	0.10	0.04 to 0.24	< .001	0.10	0.04 to 0.23	< .001
Education level																	
Low	45	21	21	16	14	17	7	14	66	19	.17	1.00			—		
Middle	77	36	49	38	32	41	17	35	126	37		0.62	0.26 to 1.48	.29			
High	95	44	56	44	31	39	25	51	151	44		0.55	0.23 to 1.30	.17			
Unknown	0		2	2	2	3	0		2	1							
Children before treatment																	
No	168	77	97	76	58	83	39	80	665	89	.68	1.00			—		
Yes	49	23	31	24	21	27	10	20	80	23		1.23	0.58 to 2.63	.59			
Females	295	74	105	26	97	24	8	2	400								
Age at start of treatment, years																	
15-24	172	58	46	44	42	43	4	50	218	55	.001	1.00			1.00§		
25-34	118	40	49	47	45	46	4	50	167	42		0.73	0.94 to 1.29	.28			
≥ 35	5	2	10	10	10	10	0		15	4		0.11	0.03 to 0.38	< .001	0.13	0.04 to 0.43	< .001
Period of treatment start																	
1964-1976	26	9	3	3	3	3	0		29	7	.06	1.00			—		
1977-1993	105	36	33	31	28	29	5	63	138	35		0.72	0.17 to 2.96	.65			
1994-2004	164	56	69	66	66	68	3	38	233	58		0.38	0.09 to 1.53	.17			
Disease stage																	
I and II	272	92	85	81	78	80	7	88	357	89	.005	1.00			—		
III and IV	23	8	20	19	19	20	1	13	43	11		0.47	0.16 to 1.35	.16			
B-symptoms																	
Absent	222	75	67	64	63	65	4	50	289	72	.12	1.00			—		
Present	68	23	34	32	30	31	4	50	102	26		0.65	0.36 to 1.14	.13			
Unknown	5	2	4	4	4	4	0		9	2							

(continued on following page)

Table 5. Multivariable Analysis of Factors Influencing Survivors' Odds of Having Children Without ART (internal analysis) (continued)

Factor	Biological Children Without ART		No Biological Children Spontaneously*		No Biological Children		Biological Children With ART†		Total		χ^2 P‡	Model With All Variables Adjusted			Final Model Adjusted		
	No.	%	No.	%	No.	%	No.	%	No.	%		OR	95% CI	P‡	OR	95% CI	P‡
Initial treatment only	276	94	87	83	80	83	7	88	363	91							
Chemotherapy																	
No alkylating agents	98	33	33	31	29	30	4	50	131	33		1.00			1.00§		
Alkylating agents	119	40	42	40	41	42	1	13	161	40							
< 3 cycles MOPP equivalent	57	19	15	14	15	15	0		72	18	.18	1.24	0.60 to 2.56	.56			
≥ 3 cycles MOPP equivalent	62	21	27	26	26	6	1	13	89	22		0.69	0.31 to 1.50	.35	0.51	0.30 to 0.87	.01
Radiotherapy																	
Above diaphragm	213	72	67	64	63	65	4	50	280	70	.29	1.00			—		
Below diaphragm	56	19	15	14	12	12	3	38	71	18		0.92	0.44 to 1.89	.82			
Iliac region	10	3	8	8	8	8	0		18	5		0.93	0.25 to 3.41	.91			
First- and second-line treatment¶	19	6	18	17	17	17	1	13	37	9	.005	0.22	0.10 to 0.52	< .001	0.27	0.12 to 0.57	< .001
Education level																	
Low	53	18	22	21	21	12	1	13	66	17	.45	1.00			1.00§		
Middle	103	35	29	28	27	28	2	25	132	33		0.94	0.41 to 2.16	.88			
High	136	46	61	58	56	58	5	63	197	49		0.59	0.27 to 1.31	.20	0.58	0.36 to 0.93	.03
Unknown	3	1	2	2	2	2	0		5	1							
Children before treatment																	
No	245	83	85	81	77	79	8	100	330	83	.30	1.00			—		
Yes	50	17	20	19	20	21	0		70	18		1.15	0.56 to 2.35	.71			

NOTE. Due to rounding, percentages may exceed or fall short of 100%. OR (odds ratio) for iliac and/or inguinal region radiotherapy are taken together. Radiotherapy under the diaphragm was analyzed exclusive of iliac and inguinal radiotherapy.

Abbreviations: ART, assisted reproductive technique; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone.

*The column labeled "No Biological Children Spontaneously" is the sum of the "No Biological Children" and "Biological Children With ART" columns.

†ART includes intrauterine insemination, in vitro fertilization or intracytoplasmic sperm injection with fresh or cryopreserved semen.

‡For χ^2 testing, the fifth and seventh columns were analyzed separately against each other and the first column, so test results are for children conceived spontaneously (without ART) versus biological children conceived with ART and versus failure to conceive children. For logistic regression analysis, the fifth and seventh columns were taken together, see third column, and analyzed against the first column. ORs provided are ORs for having biological children without ART.

§In the final model for both males and females, age 15-24 and 25-34 years were taken together as the reference category, as were no alkylating chemotherapy and < three cycles of MOPP equivalent, and low and middle education level in the final model for females.

¶Second-line treatment varying from radiotherapy to high-dose chemotherapy and bone marrow transplantation.

children before treatment, we found the main difference was in the group who decided to refrain from having children after treatment. This suggests at least part of the parenthood outcome in HL survivors was the result of a personal decision rather than a biologic reason.

Several factors were associated with reduced probability of spontaneous success among survivors who attempted post-treatment parenthood: age ≥ 35 years at treatment, alkylating chemotherapy, and second-line treatment. The aORs for post-treatment spontaneous

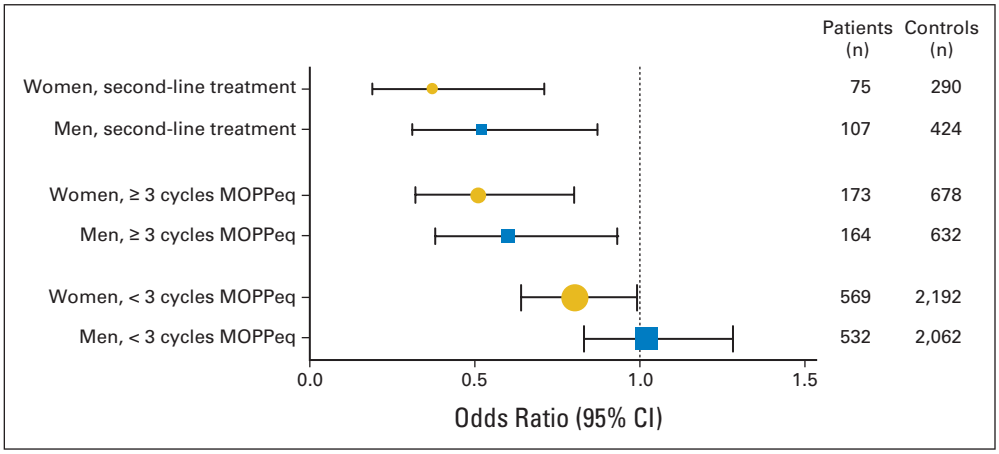

Fig 2. Odds ratios for having biologic children after treatment, in cases compared with general population controls. MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; MOPPeq, cycles of alkylating chemotherapy in MOPP equivalents.

parenthood associated with alkylating chemotherapy were extremely low, especially in men (aOR, 0.04 if alkylating chemotherapy dose was three or more cycles of MOPP equivalent), demonstrating greater impact of treatment on fertility in men than in women. Men, however, can compensate for loss of fertility by using cryopreserved semen; women have no such option readily available. This explains why the probability of biologic children (with or without ARTs) was reduced in female HL survivors.

Compared with controls, female and male HL survivors had ORs for having children after treatment similar to those reported by Cvancarova et al[10] in combined lymphoma and leukemia survivors: ORs of 0.61 and 0.88, respectively, compared with ORs of 0.64 and 0.84 in our series. They also found a remarkably reduced reproduction rate in survivors with children before treatment but gave no explanation.

Our study is by far the largest and the only one with general population controls performed among HL survivors. It is unique in presenting data on motivations for parenthood choices. Little is known about motivation for parenthood after cancer treatment. There are several reasons why survivors forgo becoming a parent: they might fear dying prematurely or suffering cancer treatment–related health complaints. They might also be afraid that cancer treatment has damaged their gametes and reproductive system, leading to more pregnancy complications and handicaps in offspring. Another reason might be fear of increased cancer risk in offspring. However, we considered it unethical to address questions like fear of carcinogenesis by mail and therefore did not investigate this in detail. One-fifth of patients did not have children after treatment because of a personal decision, and survivors considered their family complete more often than did controls at the same point in their lives. Schover et al[30,31] have analyzed in male cancer survivors that survivors' perceptions play an important role, which was also suggested by our results. They found that 6% of cancer survivors who were childless before treatment have their wish for future children decreased by cancer versus 29% of survivors who had children before treatment.

Evidence has been published of a reversed sex ratio in offspring of male childhood cancer survivors compared with their siblings with an excess of female offspring.[32] Reduced testosterone levels and Leydig cell dysfunction were considered causative factors.[33] In HL survivors, there has been limited evidence of mild Leydig cell dysfunction.[34,35] We found no difference in sex ratio before and after treatment: the female:male ratio of 0.93 observed after treatment was close to the normal population values of 0.94 to 0.95,[36-38] in agreement with previous findings.[39-41]

Of the 3,599 questionnaires sent, 1,910 (53%) were completed. Of 6,658 patients initially included in the trials, 1,498 (22%) died, 922 (14%) were included in centers that did not participate in this survey, and 719 (11%) were lost to follow-up. The explanation for the seemingly low response of 53% lies in what is also one of the strengths of this study: its scope. Much happened between trial inclusion between 1964 and 2004 and the start of this survey: physicians moved away or died, hospitals merged, and whole departments disappeared, hampering the tracing back of many patients treated in the past. Because of privacy laws, we were not allowed to track down patients directly but were required to do our tracking via their original treating physician. Many nonresponders were survivors for whom no correct address was found by their former physicians.

Overall, 25% of the control group remained childless; it was 23% (752 of 3,248) in women. This is quite high, indicating a potentially increased rate of subfertility. Among Dutch women born in 1945, 11% remained childless; for women born in 1960, it was 17%, and for women born in 1975, it was 20%.[42] In France, these figures are 10% in women born in 1950 and 15% in those born in 1980.[43] However, our control group does not appear to be subfertile when keeping in mind that controls were born between 1923 and 1982 but the distribution of year of birth was skewed toward the younger years. Higher education levels were also over-represented among HL survivors and thus among our matched controls (who remained childless more often[42]). Follow-up in our study was long-term but still incomplete, suggesting that participants might start a family in the future.

Another potential source of bias could be confounding by marital status. Two studies[44,45] reported that cancer survivors are less often married, which might lead to smaller chances of starting a family. In our study, more than 80% of survivors were currently married or living together, a high rate that limits the possible influence of this potential source of bias.

We documented that nonresponders had more likely been treated with nonalkylating chemotherapy and radiotherapy above the diaphragm only. This may contribute to an underestimation of parenthood probability in our survivors. However, given that our results found no differences between patients and controls without children before treatment, this potential underestimation is unlikely to influence our conclusions.

In conclusion, survivors of HL had significantly fewer children after treatment than did general population controls. The difference concerned only patients who already had children before treatment and was larger in females than in males. Both psychological and treatment factors contributed. Finally, three-quarters of survivors who attempted post-treatment parenthood succeeded.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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