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Supplementary appendix

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Pregnancy following chemotherapy among children treated from 1970 through 1999: a report from the Childhood Cancer Survivor Study cohort

APPENDIX TABLE 1. Overlap (%) of alkylating and related DNA inter-strand crosslinking agent exposures among the analytic cohort (n=10,938).

Exposure	Bu-sulfan	Carmu-stine	Carbo-platin	Cis-platin	Chloram-bucil	Cyclophos-phamide	Dacar-bazine	Ifos-famide	Lomu-stine	Mel-phalan	Nitrogen mustard	Procar-bazine	Temo-zolomide	Thio-tepa
Busulfan	-	0	2 (0·0)	1 (0·0)	0	107 (1·0)	3 (0·0)	2 (0·0)	0	3 (0·0)	3 (0·0)	3 (0·0)	0	4 (0·0)
Carmustine		-	9 (0·1)	13 (0·1)	4 (0·0)	241 (2·2)	14 (0·1)	11 (0·1)	6 (0·1)	2 (0·0)	13 (0·1)	29 (0·3)	0	0
Carboplatin	-	-	-	70 (0·6)	0	122 (1·1)	4 (0·0)	108 (1·0)	9 (0·1)	10 (0·1)	6 (0·1)	18 (0·2)	2 (0·0)	12 (0·1)
Cisplatin	-	-	-	-	0	571 (5·2)	56 (0·5)	230 (2·1)	15 (0·1)	13 (0·1)	21 (0·2)	32 (0·3)	0	10 (0·1)
Chlorambucil	-	-	-	-	-	3 (0·0)	2 (0·0)	0	1 (0·0)	1 (0·0)	4 (0·0)	15 (0·1)	0	1 (0·0)
Cyclophosphamide	-	-	-	-	-	-	170 (1·6)	338 (3·1)	44 (0·4)	75 (0·7)	69 (0·6)	421 (3·8)	1 (0·0)	34 (0·3)
Dacarbazine	-	-	-	-	-	-	-	13 (0·1)	34 (0·3)	10 (0·1)	173 (1·6)	211 (1·9)	0	0
Ifosfamide	-	-	-	-	-	-	-	-	0	13 (0·1)	7 (0·1)	10 (0·1)	0	6 (0·1)
Lomustine	-	-	-	-	-	-	-	-	-	5 (0·0)	15 (0·1)	106 (1·0)	1 (0·0)	2 (0·0)
Melphalan	-	-	-	-	-	-	-	-	-	-	7 (0·1)	8 (0·1)	0	7 (0·1)
Nitrogen mustard	-	-	-	-	-	-	-	-	-	-	-	458 (4·2)	0	8 (0·1)
Procarbazine	-	-	-	-	-	-	-	-	-	-	-	-	1 (0·0)	12 (0·1)
Temozolomide	-	-	-	-	-	-	-	-	-	-	-	-	-	0
Thiotepa	-	-	-	-	-	-	-	-	-	-	-	-	-	-

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APPENDIX TABLE 2. Likelihood of reporting first pregnancy and live birth (hazard ratios [HR]) among female childhood cancer survivors not exposed to pelvic or cranial radiotherapy, compared with female siblings, limited to the ages during which participants reported ongoing menses.*

Group	Pregnancy	Live birth
	HR (95% CI)	HR (95% CI)
Female siblings	1·00 (ref)	1·00 (ref)
Female survivors, all	0·90 (0·84-0·97)	0·84 (0·78-0·91)
Ages 15-29 years during follow-up	0·96 (0·89-1·04)	0·89 (0·82-0·98)
Ages 30-44 years during follow-up	0·64 (0·53-0·76) †	0·66 (0·55-0·79) †
Not exposed to any alkylator/related agents	0·93 (0·85-1·01)	0·87 (0·79-0·96)
Exposed to alkylator/related agents	0·90 (0·83-0·98)	0·85 (0·78-0·94)

*Participants enter the analysis at age 15, cohort entry, or age of menarche (whichever is latest), and exit the analysis at the time of menopause (from any cause), treating menopause as a competing risk event.

†P-value for interaction with age in relation to immediate row above, p<0·0001

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APPENDIX TABLE 3. Likelihood of reporting first pregnancy and live birth (hazard ratios [HR]) among different childhood cancer diagnosis groups not exposed to pelvic or cranial radiotherapy, compared with siblings.*

Group	Males				Females			
	Pregnancy		Live birth		Pregnancy		Live birth	
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Siblings	1·00 (ref)		1·00 (ref)		1·00 (ref)		1·00 (ref)	
Leukemia survivors								
Without alkylating/similar agents	0·76 (0·65-0·89)	‡	0·73 (0·62-0·87)	‡	1·12 (0·99-1·26)		1·07 (0·94-1·23)	
With alkylating/similar agents	0·74 (0·64-0·87)	‡	0·77 (0·65-0·91)	‡	0·85 (0·75-0·98)	†	0·87 (0·75-1·00)	
Central nervous system tumor survivors								
Without alkylating/similar agents	0·54 (0·45-0·64)	‡	0·56 (0·46-0·67)	‡	0·65 (0·56-0·76)	‡	0·61 (0·51-0·72)	‡
With alkylating/similar agents	0·62 (0·28-1·38)		0·56 (0·23-1·41)		0·38 (0·19-0·78)	‡	0·48 (0·23-1·03)	
Hodgkin lymphoma survivors								
Without alkylating/similar agents	0·86 (0·68-1·09)		0·81 (0·63-1·04)		0·97 (0·76-1·23)		1·00 (0·78-1·28)	
With alkylating/similar agents	0·37 (0·31-0·46)	‡	0·39 (0·32-0·48)	‡	0·81 (0·71-0·94)	‡	0·80 (0·69-0·92)	‡
Non-Hodgkin lymphoma survivors								
Without alkylating/similar agents	1·16 (0·80-1·69)		1·22 (0·82-1·80)		0·81 (0·44-1·52)		0·65 (0·31-1·36)	
With alkylating/similar agents	0·75 (0·65-0·86)	‡	0·77 (0·66-0·89)	‡	0·99 (0·84-1·16)		0·97 (0·81-1·16)	
Kidney tumor survivors								
Without alkylating/similar agents	0·92 (0·72-1·17)		0·89 (0·69-1·16)		0·82 (0·67-1·01)		0·82 (0·65-1·03)	
With alkylating/similar agents	0·45 (0·11-1·80)		0·52 (0·13-2·12)		0·67 (0·25-1·84)		0·61 (0·19-1·94)	
Neuroblastoma survivors								
Without alkylating/similar agents	0·75 (0·55-1·03)		0·69 (0·48-0·99)	†	1·01 (0·80-1·28)		1·00 (0·77-1·30)	
With alkylating/similar agents	0·50 (0·34-0·74)	‡	0·49 (0·32-0·75)	‡	0·81 (0·63-1·05)		0·70 (0·52-0·94)	†
Soft tissue sarcoma survivors								
Without alkylating/similar agents	0·84 (0·65-1·07)		0·92 (0·71-1·18)		0·98 (0·78-1·24)		0·93 (0·73-1·19)	
With alkylating/similar agents	0·61 (0·47-0·79)	‡	0·62 (0·47-0·81)	‡	1·04 (0·84-1·29)		1·03 (0·83-1·29)	
Bone tumor survivors								
Without alkylating/similar agents	0·78 (0·60-1·00)		0·77 (0·59-1·01)		1·03 (0·83-1·27)		0·97 (0·77-1·21)	
With alkylating/similar agents	0·47 (0·40-0·56)	‡	0·47 (0·39-0·55)	‡	0·87 (0·77-0·99)	†	0·82 (0·71-0·94)	‡

*Sex-specific models adjusted for race/ethnicity and year of birth.
†P=0·01 to <0·05
‡P<0·01

APPENDIX TABLE 4. Likelihood of reporting first pregnancy (hazard ratios [HR]) among childhood cancer survivors when adjusted by all 14 alkylating and related DNA inter-strand crosslinking agent exposures, expressed as mg/m^2.*

Exposure	Males		Females	
	HR (95% CI)		HR (95% CI)	
Busulfan, dose level†				
Lower, <450	0·45 (0·15-1·41)		0·21 (0·06-0·79)	§
Upper, ≥450	1·39 (0·77-2·53)		0·14 (0·03-0·55)	**
Carmustine, any vs. none	1·15 (0·88-1·50)		0·84 (0·64-1·11)	
Carboplatin, dose level†				
Lower, <2,112	1·46 (0·49-4·33)		1·02 (0·52-2·01)	
Middle, 2,112-4,009	1·78 (1·02-3·11)	§	0·86 (0·44-1·68)	
Upper, ≥4,100	1·41 (0·55-3·64)		0·71 (0·32-1·58)	
Chlorambucil, any vs. none	2·49 (0·59-10·4)		1·11 (0·45-2·74)	
Cisplatin, dose level†				
Lower, <355	0·85 (0·57-1·26)		1·02 (0·76-1·37)	
Middle, 355-487	0·75 (0·52-1·08)		1·17 (0·91-1·52)	
Upper, ≥488	0·56 (0·39-0·82)	**	0·94 (0·73-1·22)	
Cyclophosphamide, dose level†				
Lower, <3,625	1·21 (1·06-1·39)	**	0·92 (0·82-1·05)	
Middle, 3,625-7,411	0·89 (0·77-1·03)		1·04 (0·91-1·20)	
Upper, ≥7,412	0·60 (0·51-0·71)	**	0·99 (0·87-1·12)	
Dacarbazine or Temozolomide, any vs. none‡	1·18 (0·91-1·54)		0·89 (0·71-1·11)	
Ifosfamide, dose level†				
Lower, <26,853	0·88 (0·54-1·44)		0·92 (0·64-1·32)	
Middle, 26,853-52,999	0·57 (0·34-0·95)	§	0·82 (0·57-1·19)	
Upper, ≥53,000	0·41 (0·22-0·77)	**	1·05 (0·74-1·49)	
Lomustine, dose level†				
Lower, <411	1·03 (0·52-2·04)		0·92 (0·48-1·74)	
Upper, ≥411	0·73 (0·23-2·34)		0·42 (0·17-1·03)	
Melphalan, any vs. none	1·25 (0·72-2·18)		1·24 (0·83-1·87)	
Nitrogen mustard, dose level†				
Lower, <36	1·05 (0·62-1·77)		1·06 (0·71-1·58)	
Middle, 36-56	0·76 (0·40-1·46)		1·20 (0·81-1·77)	
Upper, ≥57	0·75 (0·40-1·43)		0·87 (0·53-1·41)	
Procarbazine, dose level†				
Lower, <3,352	0·68 (0·45-1·04)		0·95 (0·69-1·29)	
Middle, 3,352-5,059	0·42 (0·25-0·71)	**	0·91 (0·67-1·23)	
Upper, ≥5,060	0·41 (0·24-0·69)	**	0·90 (0·61-1·32)	
Thiotepa, any vs. none	0·44 (0·11-1·75)		0·96 (0·30-3·07)	

*Adjusted for all agents listed below plus age at diagnosis and race/ethnicity.
†None as referent group; levels (mg/m^2) among exposed based on tertiles, or if sample size was limited, the median.
‡Dacarbazine doses only available for survivors diagnosed 1987-1999 (n=219 exposed); in subanalyses with those survivors, no association seen with dacarbazine dose levels; only 3 survivors exposed to temozolomide.
§P=0·01 to <0·05
**P<0·01

APPENDIX TABLE 5. Association between age at initial cancer diagnosis and subsequent likelihoods (hazard ratios [HR]) of reporting pregnancy and live birth.*

Age at diagnosis	Pregnancy	Live birth
	HR (95% CI)	HR (95% CI)
Males, years		
15-20	1·00 (ref)	1·00 (ref)
10-14	0·88 (0·76-1·01)	0·86 (0·74-1·00)
5-9	0·94 (0·81-1·09)	0·90 (0·76-1·05)
<5	0·94 (0·80-1·10)	0·87 (0·74-1·03)
Females, years		
15-20	1·00 (ref)	1·00 (ref)
10-14	1·11 (0·98-1·26)	1·13 (0·99-1·29)
5-9	1·01 (0·87-1·16)	1·11 (0·96-1·29)
<5	0·92 (0·80-1·06)	0·96 (0·83-1·11)

* Estimates derived from Model 1 in Table 4 with concurrent adjustment for individual chemotherapy agent doses and race/ethnicity.