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DECREASED FERTILITY AMONG FEMALE CHILDHOOD CANCER SURVIVORS WHO RECEIVED 22 TO 27 Gy HYPOTHALAMIC/PITUITARY IRRADIATION. A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY

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Abstract

Objective—To evaluate the effect of hypothalamic/pituitary radiation dose on the occurrence of first pregnancy

Design—Retrospective cohort study of childhood cancer five-year survivors (CCS) diagnosed between 1970 and 1986 prior to 21 years of age at one of 26 North American pediatric cancer treatment centers

Setting—Self-administered questionnaire

Patient(s)—3619 female CCS who participated in the Childhood Cancer Survivor Study and received no/scatter (≤ 0.1 Gy) radiation to the ovaries and 2081 female siblings (Sibs) of the participants

Intervention(s)—None

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Main Outcome Measure(s)—Self-reported pregnancy events

Result(s)—As a group CCS were as likely to report being pregnant as Sibs (Hazard Ratio (HR), 1.07; 95% Confidence Interval (95%CI), 0.97 to 1.19). Multivariable models showed a significant decrease in the risk of pregnancy with HPT RT doses ≥ 22 Gy compared with those CCS receiving no HPT RT.

Conclusion(s)—These results support the hypothesis that exposures of 22 to 27 Gy HPT RT may be a contributing factor to infertility among female CCS.

Keywords

childhood cancer survivor; hypothalamic irradiation; pituitary irradiation; alkylating agent; pregnancy

INTRODUCTION

Survivors of childhood cancer are less likely to report pregnancy than their siblings (1,2) or population controls (3). Factors associated with decreased pregnancy and/or live birth rates have included testicular radiation dose > 7.5 Gy (2), ovarian radiation dose > 5 Gy (1), treatment with higher doses of alkylating agents (1, 2) and, for females only, hypothalamic/pituitary (HPT) irradiation dose ≥ 30 Gy (1).

Bath et al. reported that luteininzing hormone (LH) excretion, evaluated using daily early morning urine samples from day 1 of a menstrual cycle for a minimum of two cycles, was decreased in acute lymphoblastic leukemia (ALL) patients treated with 24 Gy cranial radiation therapy (CRT) compared to controls. Moreover, the luteal phase was significantly shorter in ALL patients than non-cancer controls, with a high frequency of short (≤ 11 days) luteal phases in the ALL patients (4). These data demonstrated that luteal phase deficiency occurred in some menstrual cycles of some female ALL survivors who received prophylactic CRT.

Luteal phase deficiency (LPD) is a controversial syndrome and is considered as causal or contributory in cases of failed implantation, infertility and early pregnancy loss (5). The pathophysiological basis of LPD is reported to involve disorders including those where the luteal phase is short and lasts less than 10 days. Patients diagnosed with LPD exhibit lower circulating progesterone concentrations in the 14 days following ovulation if pregnancy does not occur (5,6). In light of recent studies on the reliability and reproducibility of endometrial histology (7,8), a shortened luteal phase may be the only objective evidence of LPD.

The present analysis was conducted to determine if HPT radiation therapy (RT) < 30 Gy was associated with a lower risk of pregnancy in women who had received no or very low (< 0.10 Gy) RT doses to the ovaries.

PATIENTS AND METHODS

A cohort of 20,720 previously untreated patients (females − 9,253) who were less than 21 years of age at diagnosis, survived for at least 5 years after the date of diagnosis, and were diagnosed with an eligible cancer between January 1, 1970 and December 31, 1986 was identified at the 26 participating institutions of the Childhood Cancer Survivor Study (CCSS). The study design, cohort characteristics and baseline data collection are presented in detail elsewhere (9–11).

The CCSS collected data for all surgical procedures performed for cancer treatment. In addition, participants and siblings were asked about additional surgical procedures performed and the methods employed for contraception, including tubal ligation and vasectomy. Those participants or their partners who underwent an operation that resulted in sterilization (eg, tubal ligation, hysterectomy, vasectomy) prior to pregnancy were classified as surgically sterile as a result of contraceptive or non-contraceptive reasons and were excluded from this analysis. Because this is a questionnaire-based study, values for biological markers such as follicle stimulating hormone or anti-Mullerian hormone were not obtained.

Permission was requested from a random sample of the cohort to contact their nearest age sibling (11). Four thousand twenty-three (83%) participated among 4848 eligible siblings. These siblings were used as controls for comparisons to survivors in the CCSS cohort.

This study was approved by the Institutional Review Board at each participating institution, and informed consent for participation was obtained from all subjects who were 18 or more years of age, or their parents, if the subject was less than 18 years of age.

EXPOSURE ASSESSMENT

Detailed data regarding the chemotherapeutic agents administered to the patient for treatment of the original cancer, and for any recurrences of the cancer, the cumulative dose of drug administered for several drugs of interest, and the doses, volumes and dates of administration of all RT were abstracted from medical records for 12,954 of those who completed the baseline questionnaire (11). The distribution of cumulative doses for each of the agents was divided into tertiles. The alkylating agent dose (AAD) score was calculated by adding the tertile score (1, 2 or 3) (1) for each of the alkylating agents given to a particular patient (12). An AAD score of 0 was assigned to non-exposed patients.

RT dose to the ovaries and pituitary was determined for each patient (1). Details of the dosimetry methods are described in Stovall et al (13,14). The present analysis included only CCSS participants whose ovarian radiation dose was < 0.1 Gy.

STATISTICAL METHODS

Cox proportional hazard models with age as the time-scale were used to compare hazards of a pregnancy between same age subjects as previously described in Yasui et al.(15). Subjects entered the risk set for regression analyses at the age at which they entered the CCSS cohort (5 years after date of diagnosis of primary cancer), and were followed until the minimum age of first pregnancy, death, or completion of baseline questionnaire, whichever came first. To create a similar age-based follow-up period, siblings were assigned a pseudo diagnosis date corresponding to the age of their survivor sibling at diagnosis of their primary cancer and identical methods were used to define their time-to-event variables. Within family correlation was accounted for with the use of sandwich standard-error estimates (16). Multiple-imputation methodology for event-time imputations (17,18) was employed for those who reported one or more pregnancies, but did not report their age at first pregnancy. Age at first pregnancy was available for 89% (904/1019) of CCS and for 93% (908/979) of siblings, and was imputed for the remaining 11% (115/1019) of female CCS and for the remaining 7% (71/979) of female siblings. As spontaneous abortion might also be expected with luteal phase deficiency, we studied time to first miscarriage as an outcome. Unfortunately we were missing age at first miscarriage for one-third of the women who reported a miscarriage. When more than 20% of the values are missing, imputation is unreliable. Therefore we could not analyze the miscarriage data using the same methods that were used for the overall analysis – i.e. looking at time to first miscarriage.

Two sets of models were evaluated. The first compared fertility for CCS versus siblings, controlling for education level, marital status, age at diagnosis (or pseudo age at diagnosis), race/ethnicity and smoking status. A second set of models among CCS only, evaluated the impact of demographic and treatment variables. Candidate treatment variables evaluated included summed AAD score, HPT RT dose, and the following individual chemotherapy agents - actinomycin D, BCNU, CCNU, cyclophosphamide, cis-platinum, cytosine arabinoside, daunorubicin, doxorubicin, DTIC, nitrogen mustard, procarbazine, vinblastine, vincristine, VM-26 (Teniposide), VP-16 (Etoposide), thio-tepa, ifosfamide, and melphalan. Univariable and multivariable analyses were carried out, with final treatment variables included in the multivariable model that were significant at the 0.1 level or that markedly influenced (>10% change) the effect of another factor in the model (confounder).

RESULTS

We evaluated the occurrence of pregnancy in 3619 female CCS and 2081 females in the sibling cohorts. The CCS cohort was younger ($p < 0.001$), less likely to have a bachelor's degree or higher ($p < 0.001$), more likely to have never been married ($p < 0.001$) and more likely to have never smoked ($p < 0.001$) than the sibling cohort (Table 1).

Adjusted for age at diagnosis, marital status, educational attainment, race/ethnicity, and smoking status, the hazard ratio (HR) of a survivor ever being pregnant was 1.07 (95% CI, 0.97 to 1.19), compared to the sibling cohort. In univariable models restricted to the survivors, of the exposure variables, only the higher HPT RT categories (≥ 22 to < 27 Gy and ≥ 27 Gy), treatment with CCNU or actinomycin D were statistically significant (Table 2).

Multivariable models among survivors were developed to study the effect of HPT RT adjusted for demographic and treatment variables. Variables included in the multivariable model were significant at the 0.1 level (race, smoking status, marital status, education, age at diagnosis and VP-16) or markedly influenced (>10% change) the effect of HPT RT (Actinomycin-D). CCNU, despite being significant in univariable analyses, was not included in the final model because it did not remain significant when adjusted for other treatment variables and did not substantially influence the effect of HPT RT. The final multivariable model showed adverse effect of HPT RT on the risk of pregnancy. The effect of HPT RT was not apparent until the threshold dose of 22 Gy was exceeded (> 0 to < 15 Gy - HR, 0.88; 95%CI, 0.71 to 1.10; ≥ 15 to < 22 Gy - HR, 1.04; 95%CI, 0.79 to 1.36; ≥ 22 to < 27 Gy - HR, 0.67; 95%CI, 0.53 to 0.84; ≥ 27 Gy - HR, 0.65; 95%CI, 0.46 to 0.92) (Table 3).

DISCUSSION

We undertook the present analysis to determine if there was an effect of lower dose (< 30 Gy) HPT RT on the risk of pregnancy among female participants in the CCSS who had received no or very low (< 0.1 Gy) doses of ovarian RT. We identified a decreased risk of pregnancy among those who had received HPT RT doses of ≥ 22 Gy.

The normal menstrual cycle consists of the follicular phase and the luteal phase. The onset of the luteal phase is defined by a surge of LH release which coincides with ovulation (19). When fertilization has occurred, post-ovulatory progesterone production is maintained by pituitary LH secretion until implantation occurs, at which time placental human chorionic gonadotropin (HCG) stimulation of the corpus luteum maintains progesterone levels (20,21).

Luteal phase deficiency or delayed endometrial maturation, resulting from a subnormal mid-cycle LH "surge" and inadequate progesterone production from the corpus luteum (22–24) may be one of the causal factors for implantation failure and early pregnancy loss (5) and

recurrent miscarriage (25). Horta et al. demonstrated an increased frequency of low progesterone levels in the luteal phase, based on basal body temperature records, among women with a history of habitual abortion (25). Li et al. defined the luteal phase on the basis of basal body temperature records and reported that the mid-luteal progesterone was < 30 nmol/L in 17.4% of 144 women with a history of recurrent, consecutive, first trimester miscarriages (26). Jordan et al., utilizing the integrated serum progesterone level (sum of daily serum progesterone levels from the day after the LH surge to the day before the next menstrual period), defined luteal phase deficiency as an integrated serum progesterone level < 80 ng-days/ml. The basal body temperature record was an insensitive predictor of luteal phase deficiency in this study and timed endometrial biopsy was only modestly sensitive, identifying only 57% of those with an integrated serum progesterone level < 80 ng-days/ml (7).

It is important to note however that several studies have shown that variability in the length of the luteal phase may be normal, even among fertile women (7). Furthermore detailed data concerning endometrial histology have indicated that substantial variability in the histological characteristics of secretory phase endometrium is also normal (7) and have demonstrated that traditional histological dating of the endometrium is not a valid clinical diagnostic tool. It has not been possible in the current questionnaire based study of childhood survivors to perform evaluation of endometrial histology, which would not be indicated based on these data. The delayed endometrial morphological development reported with LPD does not reflect circulating progesterone concentrations (5). Low circulating luteal phase progesterone concentrations may however have important consequences upon subtle aspects of endometrial function at the time of required receptivity.

Bath et al. reported that LH excretion, evaluated using daily early morning urine samples from day 1 of a menstrual cycle for a minimum of two cycles, was decreased in acute lymphoblastic leukemia (ALL) patients treated with 24 Gy CRT compared to controls. Moreover, the luteal phase was significantly shorter in ALL patients than normal controls (12.2 ± 0.3 days versus 13.6 ± 0.4 days; $p = 0.01$), with a high frequency of short (≤ 11 days) luteal phases in the ALL patients (4). These data demonstrated that luteal phase deficiency occurred in some menstrual cycles of some female ALL survivors who received prophylactic CRT.

There is some evidence that female survivors of acute leukemia are less likely to have liveborn infants. Nygaard et al. reported that the cumulative percentage of female ALL survivors who reported a pregnancy by age 25 years was 41.0% (95% CI, 21.9 to 60.1) for those treated with chemotherapy only and was 18.4% (95% CI, 3.0 to 33.8) ($p = 0.043$) for those whose treatment included both chemotherapy and prophylactic CRT(18 to 24 Gy) (27). Byrne at al. reported that the unadjusted fertility rate for female survivors of ALL was significantly lower than that of their siblings. They were unable to demonstrate an effect of treatment with an alkylating agent on the first pregnancy rates, but did demonstrate that the risk of first pregnancy was decreased (relative risk=, 0.27; 95% CI, 0.09 to 0.82) ($p = 0.03$) among those whose age at first pregnancy was 18 to 21 years and who received prophylactic CRT (18 to 24 Gy) within two years of menarche (28).

Early pregnancy loss, such as could occur in the presence of luteal phase deficiency, can be difficult to diagnose. Wilcox et al. reported that 22% (43/198) of biochemically documented pregnancies were clinically unrecognized (29). Vaginal bleeding following pregnancy loss before six weeks of gestation was 0.4 days longer than a woman's average menstrual bleed, but was associated with less blood loss. These events are unlikely to be recognized by the women as loss of pregnancies (30). The impact of these events could only be demonstrated

if the fertility of a sufficiently large population of women at risk due to lower dose (< 30 Gy) HPT RT, such as the participants in the CCSS, could be studied.

This study has a number of strengths. The CCSS is the largest, most thoroughly characterized cohort of survivors of cancer diagnosed during childhood or adolescence and utilizes a sibling comparison group. Thus, important questions regarding the frequency of outcomes that may be modified by treatment exposures, as well as the relationship of these exposures to significant, though uncommon, late events can be evaluated with substantial statistical power.

There are certain limitations that must be taken into account when interpreting our data. The subjects were ascertained retrospectively, with 15% of the eligible subjects lost to follow-up and 16% declining participation. Participants, however, did not differ from non-participants with regard to demographics or cancer and treatment characteristics (11). The CCSS utilized self-administered questionnaires for ascertainment of pregnancy-related outcomes.

We have demonstrated that fertility is impaired in female CCS who received modest doses (22 to 27 Gy) of HPT RT and no or very low (< 0.1 Gy) doses of ovarian RT. The results suggest that an additional mechanism, luteal phase deficiency, may contribute to infertility. These data may be utilized to counsel patients and their parents prior to initiation of treatment and to guide evaluation of infertility in female CCS who received low-dose HPT irradiation.

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Appendix

The **Childhood Cancer Survivor Study (CCSS)** is a collaborative, multi-institutional project, funded as a resource by the National Cancer Institute, of individuals who survived five or more years after diagnosis of childhood cancer.

CCSS is a retrospectively ascertained cohort of 20,346 childhood cancer survivors diagnosed before age 21 between 1970 and 1986 and approximately 4,000 siblings of survivors, who serve as a control group. The cohort was assembled through the efforts of 26 participating clinical research centers in the United States and Canada. The study is currently funded by a U24 resource grant (NCI grant # U24 CA55727) awarded to St. Jude Children's Research Hospital. Currently, we are in the process of expanding the cohort to include an additional 14,000 childhood cancer survivors diagnosed before age 21 between 1987 and 1999. For information on how to access and utilize the CCSS resource, visit www.stjude.org/ccss

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Table 1

Demographic and Treatment Characteristics of Female Survivors and Siblings

	Survivors (n = 3619)		Siblings (n = 2081)		
	N	%	N	%	p-value
Race/Ethnicity					
Non-Hispanic White	3160	88	1802	89	<0.156
Hispanic	189	5	86	4	
Non-Hispanic Black	145	4	65	3	
Other	113	3	61	3	
Smoking Status					
Never smoked	2739	80	1314	65	< 0.001
Current smoker	417	12	396	20	
Former smoker	276	8	304	15	
Marital Status					
Never married	2226	65	850	42	<0.001
Currently married	977	29	1014	50	
Formerly married	197	6	148	7	
Education Level					
No High School or GED	1345	39	462	23	<0.001
High School or GED	495	15	294	15	
Some college no bachelor’s degree	871	25	588	29	
Bachelor’s degree or higher	703	21	660	33	
Age at Baseline in years					
5–19	1554	43	526	25	<0.001
20–24	778	22	357	17	
25–29	623	17	409	20	
30–34	418	12	343	16	
35–39	193	5	260	12	
40–44	51	1	127	6	
45–49	2	<1	48	2	
50–54	0	0	11	1	
Age at Diagnosis in years					

	Survivors (n = 3619)		Siblings (n = 2081)		
	N	%	N	%	p-value
0–4	1614	45			
5–9	764	21			
10–14	713	20			
15–19	467	13			
20	61	2			
Primary Diagnosis					
Leukemia	1669	46			
CNS	451	12			
HD	167	5			
NHL	169	5			
Wilms	198	5			
Neuroblastoma	266	7			
Soft tissue sarcoma	318	9			
Osteosarcoma	381	11			
Radiation – Hypothalamic/pituitary dose					
0	1960	54			
> 0 to < 1500 cGy	399	11			
≥1500 to < 2200 cGy	526	15			
≥ 2200 to < 2700 cGy	462	13			
≥ 2700 cGy	258	7			
Oophoropexy					
No	3591	99			
Yes	28	1			
Summed AAD **					
0	1851	54			
1	458	13			
2	444	13			
3	452	13			
4	100	3			
5	77	2			

	Survivors (n = 3619)		Siblings (n = 2081)		
	N	%	N	%	p-value
6–11	53	2			
Actinomycin D#					
No	3018	84			
Yes	579	16			
BCNU#					
No	3476	97			
Yes	121	3			
CCNU#					
No	3531	98			
Yes	66	2			
Chlorambucil#					
No	3587	99			
Yes	10	< 1			
Cis-Platinum#					
No	3302	92			
Yes	295	8			
Cyclophosphamide#					
No	1639	46			
Yes	1958	54			
Cytosine arabinoside#					
No	2421	67			
Yes	1176	33			
Daunorubicin#					
No	3058	85			
Yes	539	15			
Doxorubicin#					
No	2518	70			
Yes	1079	30			
DTIC#					

	Survivors (n = 3619)		Siblings (n = 2081)		
	N	%	N	%	p-value
No	3481	97			
Yes	116	3			
Ifosfamide[#]					
No	3572	99			
Yes	25	1			
Melphalan[#]					
No	3563	99			
Yes	34	1			
Nitrogen mustard[#]					
No	3487	97			
Yes	110	3			
Procarbazine[#]					
No	3439	96			
Yes	158	4			
Thiotepa[#]					
No	3582	99			
Yes	15	< 1			
Vinblastine[#]					
No	3527	98			
Yes	70	2			
Vincristine[#]					
No	1012	28			
Yes	2585	72			
VM-26[#]					
No	3391	94			
Yes	206	6			
VP-16[#]					
No	3368	94			
Yes	229	6			

** Alkylating Agent Dose;

Number of missing=22.

Table 2

Univariable Hazard Ratio of Fertility among Female Survivors of Childhood Cancer Who Were Not Surgically Sterile

	HR	95% CI	p-value
Race/Ethnicity			
Non-Hispanic White	1.00		
Hispanic	1.46	1.14, 1.86	0.002
Non-Hispanic Black	1.00	0.79, 1.28	0.974
Other	1.01	0.74, 1.38	0.933
Smoking Status			
Never smoked	1.00		
Current smoker	1.98	1.76, 2.23	<0.001
Former smoker	1.53	1.35, 1.75	<0.001
Marital Status			
Never married	1.00		
Currently married	5.46	4.66, 6.39	<0.001
Formerly married	4.81	3.91, 5.93	<0.001
Education Level			
High School or GED	1.00		
No High School or GED	1.27	1.03, 1.57	0.027
Some college no bachelor's degree	0.83	0.72, 0.95	0.006
Bachelor's degree or higher	0.47	0.41, 0.54	<0.001
Age at Diagnosis in years			
0–4	1.00		
5–9	0.92	0.79, 1.07	0.267
10–14	0.99	0.86, 1.14	0.915
15–19	0.92	0.78, 1.08	0.301
20	0.99	0.70, 1.42	0.975
Oophoropexy			
No	1.00		
Yes	0.80	0.43, 1.51	0.498
Hypothalamic/pituitary Radiation Dose			
0	1.00		
> 0 to < 1500 cGy	0.93	0.76, 1.14	0.481
≥ 1500 to < 2200 cGy	0.81	0.63, 1.03	0.081
≥ 2200 to < 2700 cGy	0.67	0.55, 0.81	<0.001
≥ 2700 cGy	0.49	0.36, 0.67	<0.001
Alkylating Agent Dose summed Score			
0	1.00		
1	0.98	0.77, 1.25	0.855
2	1.07	0.87, 1.31	0.544
3	0.92	0.74, 1.14	0.452

	HR	95% CI	p-value
4	0.67	0.43, 1.02	0.062
5	1.33	0.88, 2.00	0.175
6 – 11	0.75	0.45, 1.26	0.278
Actinomycin D			
No	1.00		
Yes	1.20	1.00, 1.44	0.056
BCNU			
No	1.00		
Yes	0.77	0.53, 1.12	0.172
CCNU			
No	1.00		
Yes	0.48	0.25, 0.94	0.032
Chlorambucil			
No	1.00		
Yes	0.63	0.20, 1.96	0.425
Cis-Platinum			
No	1.00		
Yes	1.15	0.91, 1.46	0.236
Cyclophosphamide			
No	1.00		
Yes	0.99	0.86, 1.13	0.859
Cytosine arabinoside			
No	1.00		
Yes	0.94	0.80, 1.10	0.418
Daunorubicin			
No	1.00		
Yes	0.92	0.74, 1.15	0.486
Doxorubicin			
No	1.00		
Yes	1.07	0.93, 1.23	0.362
DTIC			
No	1.00		
Yes	0.90	0.58, 1.38	0.617
Ifosfamide			
No	1.00		
Yes	1.15	0.46, 2.85	0.762
Melphalan			
No	1.00		
Yes	1.07	0.60, 1.91	0.815
Nitrogen mustard			
No	1.00		
Yes	0.84	0.58, 1.20	0.338

	HR	95% CI	p-value
Procarbazine			
No	1.00		
Yes	0.94	0.71, 1.25	0.660
Thiotepa			
No	1.00		
Yes	0.92	0.30, 2.86	0.885
Vinblastine			
No	1.00		
Yes	1.09	0.72, 1.65	0.682
Vincristine			
No	1.00		
Yes	1.02	0.89, 1.18	0.740
VM-26			
No	1.00		
Yes	0.76	0.49, 1.18	0.219
VP-16			
No	1.00		
Yes	1.13	0.79, 1.60	0.507

Table 3

Multivariable Hazard Ratio of Fertility among Female Survivors of Childhood Cancer Who Were Not Surgically Sterile

	HR*	95% CI	p-value
Race/Ethnicity			
Non-Hispanic White	1.00		
Hispanic	1.00	0.70, 1.43	0.995
Non-Hispanic Black	2.81	2.01, 3.93	<0.001
Other	1.04	0.66, 1.65	0.857
Smoking Status			
Never smoked	1.00		
Current smoker	1.61	1.33, 1.95	<0.001
Former smoker	1.15	0.93, 1.42	0.187
Marital Status			
Never married	1.00		
Currently married	5.98	4.83, 7.41	<0.001
Formerly married	3.70	2.76, 4.97	<0.001
Education			
High school/GED	1.00		
No High school/GED	1.38	1.02, 1.86	0.037
Some college	0.87	0.71, 1.06	0.164
Bachelor or higher	0.48	0.39, 0.60	<0.001
Age at diagnosis (years)			
0 – 4	1.00		
5–9	0.76	0.60, 0.97	0.028
10–14	0.83	0.66, 1.05	0.114
15–19	0.63	0.47, 0.84	0.002
20	0.96	0.55, 1.68	0.896
Hypothalamic/pituitary Radiation Dose			
0	1.00		
> 0 to < 1500 cGy	0.88	0.71, 1.10	0.261
≥ 1500 to < 2200 cGy	1.04	0.79, 1.36	0.793
≥ 2200 to < 2700 cGy	0.67	0.53, 0.84	0.001
≥ 2700 cGy	0.65	0.46, 0.92	0.014
Actinomycin D			
No	1.00		
Yes	1.18	0.96, 1.44	0.112
VP-16			
No	1.00		
Yes	1.54	1.06, 2.24	0.023