International Journal of Epidemiology, 2020, 448–456
doi: 10.1093/ije/dyz214
Advance Access Publication Date: 19 October 2019
Original article

Occupational Exposures

Female breast cancer risk in Bryansk Oblast, Russia, following prolonged low dose rate exposure to radiation from the Chernobyl power station accident

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Editorial decision 18 September 2019; Accepted 26 September 2019

Abstract

Background: Ionizing radiation is a known cause of female breast cancer, but there have been few studies of the risk after prolonged radiation exposure at low dose rates.

Methods: This population-based case-control study estimated breast cancer risk after $\sim$25 years' exposure to radiation from the Chernobyl accident. Cases ($n = 468$) were women $\leq$55 years old when first diagnosed with invasive breast cancer during October 2008 through February 2013, who lived in Bryansk Oblast, Russia at the time of the accident and their diagnoses. Controls, individually matched to cases on birth year, administrative district of residence and urban vs non-urban settlement during the accident, were women without breast cancer who lived in Bryansk Oblast at the time of the accident and on their cases' diagnosis dates ($n = 468$). Subjects were interviewed regarding residence, dietary and food source histories to support individualized estimation of their radiation doses to the breast, which ranged from 0.04 – 41 centigray (cGy) (mean 1.3 cGy).

Results: In multivariable analyses, the odds ratio for breast cancer risk was 3.0 [95% confidence interval (CI): 1.3, 7.0] and 2.7 (95% CI: 1.0, 7.3) in the seventh and eighth dose octiles, respectively, relative to the lowest octile. Analyses of dose effect modification suggested that radiation-related risk may have been higher in women who were younger at the time of the accident and/or at the time of diagnosis.

Conclusions: This study suggests that prolonged exposure to ionizing radiation at low dose rates can increase risk of breast cancer.

Key words: Breast cancer, ionizing radiation, Chernobyl

Key Messages

- Ionizing radiation is a known cause of female breast cancer, but there have been few studies of the risk after prolonged radiation exposures at low dose rates.
- Residents of areas contaminated by fallout from the Chernobyl accident of 26 April 1986, have received prolonged, low dose rate, mixed internal and external radiation exposures.
- In this case-control study of breast cancer incidence during October 2008 through February 2013 among women living in Bryansk Oblast, Russia, those in the two highest octiles of estimated Chernobyl-related radiation dose to the breast had elevated risk, with odds ratios of 3.0 (95% confidence interval 1.3, 7.0) and 2.7 (1.0, 7.3) relative to the lowest octile.
- This study suggests that prolonged low dose rate radiation exposure may increase risk of female breast cancer.

Introduction

Ionizing radiation is a known cause of female breast cancer, based largely on studies including women exposed to high doses at high dose rates, e.g. Japanese atomic bomb (A-bomb) survivors and cohorts exposed medically.[1,2] The A-bombs caused single acute exposures to a wide range of radiation doses, primarily from γ-rays. Breast dose estimates range up to 600+ centisievert (cSv) in the Life Span Study (LSS) cohort of A-bomb survivors, although an analysis of breast cancer incidence during 1950–1990 found a significant linear dose response when limited to women with DS86 breast doses $\leq$50 cSv.[3] Studies of medical irradiation have addressed scenarios including varying numbers of low- or high-dose γ- or x-ray fractions, usually delivered at high dose rates. Preston *et al.*[4] analysed breast cancer incidence in five cohorts of women who received such exposures to treat benign diseases, along with the LSS. They also included two cohorts in which most patients received $\geq$1 course (mean $\sim$1.5 courses), typically 2 h/course, of low dose rate γ-rays during ^{226}Ra applicator treatment for skin haemangioma in infancy or early childhood. Relative risks associated with medical exposures were generally lower than those following A-bomb exposure, possibly due to the low baseline rate of breast cancer incidence among Japanese women: the seven other cohorts were all US or Swedish. Absolute excess risks were generally more similar, though notably smaller in the haemangioma cohorts when compared with the five other medically irradiated cohorts.

In contrast to the considerable evidence associating breast cancer with high dose or high dose rate ionizing radiation, few studies have investigated the effects of exposure to lower doses protracted over long intervals. Such exposure is of public health concern because it occurs in environmental and occupational settings. The Chernobyl Nuclear Power Station accident of 26 April 1986 contaminated a large area in the former Soviet Union and elsewhere. Residents of that area have been exposed to many radionuclides including ^{131}I and ^{137}Cs among others, through both external exposure and consumption of contaminated milk and other foods. As a result they have accumulated relatively low whole body and breast doses at low dose rates over decades. Pukkala *et al.*[5] examined breast cancer incidence in contaminated areas of Ukraine and Belarus during 1979–2001, in relation to estimated district-average whole-body doses accumulated since the Chernobyl accident from external exposure and ingestion of long-lived radionuclides. Incidence rates increased after the accident, partly due to intensified screening, with larger increases in districts with higher average dose estimates. Although this is consistent with a radiation effect from Chernobyl, an ecological study such as this cannot account for individual women having doses above or below their district's average.

We conducted a population-based case-control study investigating the occurrence and molecular characteristics of breast cancer in women resident in Bryansk Oblast, a 34 900 km^2 region of Russia that was the most heavily contaminated area in the Russian Federation, especially in its western raions (comparable to counties in the USA). Cases were $\leq$55 years old when diagnosed, since studies suggest the radiation effect may be greatest for diagnoses at younger ages. Here we explore the dose–response relationship between radiation dose from the Chernobyl accident and subsequent breast cancer; analyses of molecular characteristics will be reported separately.

Methods

Identification of subjects

Eligible cases were women $\leq$55 years old when first diagnosed with invasive breast cancer between 20 October 2008 and 28 February 2013, who were residents of Bryansk Oblast at the time of the accident (ATA) on 26 April 1986 and at their breast cancer diagnosis. Cases were identified by the Bryansk Oncology Registry, a population-based registry of all newly diagnosed cancer cases among residents of Bryansk Oblast. Controls were living women with no diagnosis of breast cancer (no other disease criteria applied). Menopausal status did not affect eligibility, although women currently receiving hormonal therapy for postmenopausal symptoms were ineligible. One control, individually matched to her case on calendar year of birth, raion of residence and type of settlement (urban vs non-urban) ATA, was randomly selected from the essentially complete raion population roster maintained by the case's local polyclinic.

Data collection

In-person interviews were conducted with each subject, in her home whenever possible. Eight participants born after 1968 were assisted by an older person(s) with direct knowledge of her life from the Chernobyl accident until age 18. Information collected included known or possible risk factors for breast cancer (e.g. age at menarche, pregnancy history, body mass index, radiation exposures other than Chernobyl, and family history of cancer), as well as residence and dietary history. For the case and her matched control, this information was collected for the interval from the Chernobyl accident until the reference date, i.e. the case's breast cancer diagnosis date. Medical records of cases were reviewed and selected clinical and diagnostic information abstracted; slides and paraffin-embedded tissue blocks were sought; and all available pathology specimens and the original pathology reports were collected. When existing slides were inadequate for review, new slides were prepared from tissue blocks if available.

All procedures and data collection instruments were approved by Institutional Review Boards at the Fred Hutchinson Cancer Research Center and the Russian National Center for Hematology in Moscow. All study participants provided written informed consent to participate in the study prior to data collection.

Dose estimation

The sum of each participant's external and internal radiation doses to the breast from the Chernobyl accident, accumulated through her diagnosis/reference date, was estimated from the following: her self-reported histories of residence location(s), of quantities and sources of milk and selected foods, and of pregnancy/lactation; soil contamination measurements or estimates for her residence and food source locations; and standard coefficients for external dose rates from soil contamination, and for soil-to-food transfer and ingestion-to-internal-dose conversion for selected radionuclides (see the Supplementary data, available at *IJE* online).

Statistical methods

Conditional logistic regression was used to estimate odds ratios (ORs) for breast cancer risk in relation to estimated radiation dose and other factors while accounting for the individual matching of cases and controls. For analyses treating radiation dose as a continuous variable, the linear model $\mathrm{OR}(d) = 1+ \beta d$ was used, where d denotes the estimated Chernobyl-derived radiation dose and β is the excess odds ratio (EOR). Generalizations of this model were used to test for confounding or effect modification, as described in the Supplementary data, available at *IJE* online. Parameter estimation was based on maximum likelihood methods.

Results

The Bryansk Oncology Registry identified 707 potential cases, of whom 476 were eligible for this study (Supplementary Table 1, available as Supplementary data at *IJE* online). Of these, eight were excluded: the diagnosis of breast cancer was not confirmed by study pathologists for three women, and interviews were not completed for five. Of the 468 included cases, 388 (83%) had ductal carcinoma and 54 (12%) had lobular or mixed ductal/lobular carcinoma. One eligible control was selected and interviewed for each case, for a total of 936 participants.

The average age of the cases at diagnosis was 46.7 years (range 25–55 years), and 60% lived in urban areas ATA (Table 1). The mean age at menarche was 13.7 years (range 9–18 years). Most women had at least one live birth (94%; Table 2). Among parous women the mean age at first live birth was slightly higher for cases than controls (22.9 vs 22.4 years). Cases were less likely than controls to be premenopausal at the diagnosis/reference date (43% vs 53%), due to a higher frequency with menopause related to medical interventions or diseases (21% vs 11%). Breast cancer

Table 1. Age and matching factors of breast cancer cases ($n = 468$) and matched controls ($n = 468$) from Bryansk Oblast, October 2008 to February 2013

	n	%
Age at diagnosis/reference date, years		
25–29	12	1
30–39	131	14
40–49	424	45
50–55	369	39
Birth year		
1954–59	294	31
1960–64	278	30
1965–69	182	19
1970–79	160	17
1980–85	22	2
Settlement type ATA		
Urban	560	60
Non-urban	376	40

ATA, at the time of the Chernobyl accident (April 26, 1986).

in first degree relatives was more frequent in cases (9%) than controls (5%; $P = 0.02$).

Most participants (95%) had prior medical radiation exposures to the chest, heart or lungs, due largely to tuberculosis screening. Breast diagnostic imaging procedures, primarily mammography, were more common among cases (16%) than controls (11%), likely reflecting procedures related to the breast cancer diagnosis.

Cases were less likely than controls to have received secondary education (technical school, college or university; 86% vs 91%), and were also less likely to have a parent who received secondary education (39% vs 49%). Employment in chemical/petrochemical and metallurgy/mining industries, although infrequent, was somewhat more common among cases.

Mean age of cases ATA was 21.5 years (range 0–31 years). Estimated radiation doses ranged from 0.04 to 41 centigray (cGy) (mean 1.3 cGy; Table 3, Figure 1). These generally included significant contributions from both internal exposure (0.004–19 cGy, mean 0.73 cGy) and external exposure (0.01–23 cGy, mean 0.59 cGy). Total doses of the cases averaged 0.16 cGy larger than those of their matched controls.

The ORs for breast cancer risk, estimated without adjustment for any covariates, were elevated in the upper dose octiles (Table 4, 'Unadjusted'). As described in the Supplementary data, available at *IJE* online, investigation of possible confounding led to adjustment for six covariates: menopausal status at diagnosis/reference date (premenopausal vs natural menopause vs other menopause); breast cancer in any first degree relative (yes vs no); nulliparity (yes vs no); age at first live birth; subject's education level (≤grade 11 vs technical school vs college/university); and history of employment in metallurgy/mining (yes vs no). The unadjusted and adjusted ORs in Table 4 are similar, suggesting that the apparent association with radiation dose did not arise from confounding by any of the available covariates. In analyses treating dose as a continuous variable, however, the EOR was quite sensitive to the inclusion of the covariates, with an unadjusted $\text{EOR} = 0.18\,\text{cGy}^{-1}$ [95% confidence interval (CI): –0.00, 1.78] and adjusted $\text{EOR} = 0.57\,\text{cGy}^{-1}$ (95% CI: –0.00, 15.5, see Figure 2).

Analyses of radiation dose effect modification are described in detail in the Supplementary data, available at *IJE* online. When the radiation dose response was allowed to vary between subgroups defined by covariates, the resulting ORs or EORs had quite wide CIs for some or all subgroups, often due to small subgroup sizes. Only two covariates were identified as likely effect modifiers: age ATA and age at diagnosis/reference date. These two ages are very highly correlated in these data (Pearson correlation = 0.98), since all diagnoses occurred 22.5–26.8 years after the Chernobyl accident. The EOR for the women of age ATA <13 years was markedly higher than for older women, although the CIs for the two EORs are wide and overlapping (Table 5; similar analyses by dose octile are in Table D of the Supplementary data, available at *IJE* online). Allowing the EOR to vary as a continuous function of age ATA, it decreased by a multiplicative factor of 0.26 (95% CI: 0.09, 0.74) per 1-year increase in age ATA, suggesting that the radiogenic risk may be inversely associated with age ATA and/or at diagnosis.

Discussion

This study is the first to investigate breast cancer risk in relation to individual estimates of radiation dose to the breast from the Chernobyl accident. More generally, this is one of the few analytical epidemiological studies of breast cancer in women exposed to internal and external irradiation over a very prolonged period: most study participants accumulated their doses over more than two decades (much of the dose was accrued during the early years when exposure rates were highest). Our results suggest that risk was indeed elevated in women who accumulated the highest radiation doses (Table 4).

This is one of the few studies to investigate the association between breast cancer risk and exposure to radiation through environmental pathways. As described above, results of the ecological study of Pukkala *et al.*[5] were consistent with a radiation-related increase in breast cancer incidence in areas of Ukraine and Belarus contaminated by Chernobyl fallout. Ostroumova *et al.*[6] reported a dose

Table 2. Potential breast cancer risk factors of cases and controls from Bryansk Oblast, October 2008 to February 2013

	Cases ($n = 468$)		Controls ($n = 468$)			
Potential risk factor	*n*	%	*n*	%	OR[a]	95% CI
Age at menarche, years						
9–12	77	16	86	18	1.00	Ref
13–14	262	56	264	56	1.09	(0.78, 1.53)
15–18	127	27	117	25	1.18	(0.80, 1.74)
Unknown	2	0.4	1	0.2	–	–
Nulliparous[b]	30	6	30	6	1.00	(0.59, 1.69)
Age at 1st live birth[c], years						
<20	69	16	75	17	1.00	Ref
20–24	254	58	276	63	1.01	(0.69, 1.50)
25–29	89	20	62	14	1.73	(1.04, 2.89)
≥30	26	6	25	6	0.98	(0.51, 1.88)
Number of live births						
0	30	6	30	6	1.00	Ref
1	162	35	151	32	1.08	(0.62, 1.89)
2	239	51	244	52	0.97	(0.57, 1.67)
≥3	37	8	43	9	0.84	(0.42, 1.68)
Total number of pregnancies						
0	24	5	18	4	1.00	Ref
1–2	137	29	150	32	0.66	(0.34, 1.31)
3–4	181	39	179	38	0.75	(0.38, 1.46)
5–7	100	21	95	20	0.78	(0.39, 1.55)
≥8	26	6	26	6	0.74	(0.32, 1.72)
BMI 1 year before diagnosis/ref. date, kg/m^2						
<25	134	29	134	29	1.00	Ref
25–29	154	33	166	35	0.93	(0.65, 1.32)
≥30	180	38	168	36	1.08	(0.76, 1.54)
Menopausal status at diagnosis/ref. date						
Premenopausal	200	43	246	53	1.00	Ref
Natural menopause	167	36	170	36	1.40	(0.97, 2.02)
Other menopause[d]	99	21	51	11	2.48	(1.65, 3.73)
Unknown	2	0.4	1	0.2	–	–
Breast cancer in 1st degree relative[b]	41	9	22	5	1.90	(1.12, 3.23)
Diagnostic radiological procedure[b]	448	96	447	96	1.50	(0.25, 8.98)
Breast[b]	73	16	50	11	2.35	(1.33, 4.15)
Chest/lung/heart[b]	446	95	445	95	1.25	(0.34, 4.65)
Cigarette smoking						
Never smoked	380	81	380	81	1.00	Ref
Former smoker	29	6	21	4	0.88	(0.59, 1.30)
Current smoker	59	13	67	14	1.39	(0.77, 2.51)
Alcohol consumption						
Never	61	13	41	9	1.00	Ref
≤Monthly	266	57	268	57	0.68	(0.44, 1.04)
2–4/Month	130	28	146	31	0.62	(0.39, 0.97)
≥Weekly	11	2	13	3	0.59	(0.23, 1.47)
Subject's education level						
Grade 5–8	7	1	4	1	2.22	(0.62, 7.87)
Grade 9–11	58	12	39	8	2.03	(1.19, 3.45)
Technical school	266	57	265	57	1.27	(0.93, 1.73)
College/university	137	29	160	34	1.00	Ref
Parent's education level[e]						
Grade ≤4	99	21	76	16	1.89	(1.13, 3.15)
Grade 5–8	112	24	109	23	1.41	(0.89, 2.24)

(Continued)

Table 2. Continued

	Cases ($n = 468$)		Controls ($n = 468$)			
Potential risk factor	*n*	%	*n*	%	OR[a]	95% CI
Grade 9–11	65	14	45	10	1.95	(1.14, 3.36)
Technical school	129	28	162	35	1.01	(0.65, 1.56)
College/university	52	11	66	14	1.00	Ref
Unknown	11	2	10	2	1.40	(0.52, 3.78)
Occupational history[b]						
Chemistry, petrochemistry	12	3	5	1	2.75	(0.88, 8.64)
Agriculture	23	5	21	4	1.14	(0.56, 2.34)
Metallurgy, mining	14	3	6	1	2.60	(0.93, 7.29)
Health care or research with exposure to radiation	28	6	32	7	0.87	(0.51, 1.47)
Any of the above[f]	75	16	63	13	1.27	(0.86, 1.89)

ATA, at the time of the Chernobyl accident (April 26, 1986); BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] OR for each factor was estimated by conditional logistic regression, to account for matching on birth year, raion and type of settlement ATA; no other covariates were included.

[b] OR is reported for Yes, relative to No, for the following variables: nulliparous, breast cancer in 1st degree relative, diagnostic radiological procedures (any, breast, chest/lung/heart) and each category of occupational history.

[c] Nulliparous women excluded.

[d] Other menopause includes menopause related to medical or surgical intervention, or resulting from any disease.

[e] Highest level of mother's and/or father's education level.

[f] Three women reported multiple occupational exposure categories.

Table 3. Distributions of estimated total radiation doses to the breast from the Chernobyl accident, accumulated since April 26, 1986 by breast cancer cases and controls from Bryansk Oblast, October 2008 to February 2013

	Estimated total dose, cGy		
	All women	Cases	Controls
No. of women	936	468	468
Minimum	0.04	0.04	0.05
Median	0.25	0.26	0.93
Mean	1.3	1.4	1.2
Maximum	41	41	21

cGy, centigray.

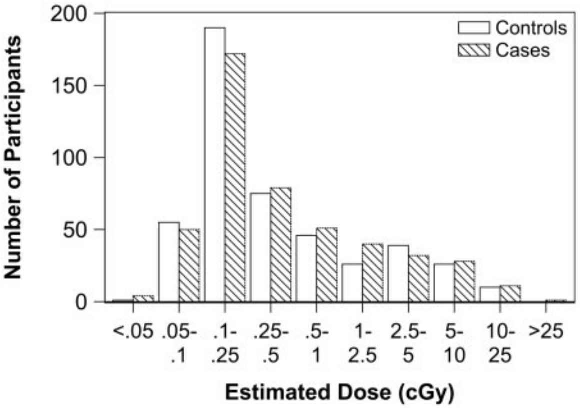

Figure 1. Distributions of estimated total radiation dose to the breast from the Chernobyl accident among breast cancer cases and controls from Bryansk Oblast, October 2008 to February 2013.

response during 1956–2004 among women with chronic low dose rate exposures to external γ irradiation and internal ^{137}Cs from waste discharged into the Techa-Iset River System from the Mayak nuclear weapons facility. In that study the estimated linear excess relative risk (ERR) was 0.05 cGy^{-1} (95% CI: 0.008, 0.13). However, in an updated analysis that extended the follow-up through 2007 and used an improved radiation dosimetry system, the dose response was smaller (ERR = 0.02 cGy^{-1}; 95% CI: −0.01, 0.06).[7] Bauer *et al.*[8] reported a dose response for female breast cancer mortality during 1960–1999 in the Semipalatinsk historical cohort, with ERR = 0.01 cSv^{-1} (95% CI: 0.00, 0.16; $P = 0.0047$). Hwang *et al.*[9] investigated breast cancer among Taiwanese women exposed to γ irradiation while living for prolonged periods in cobalt-contaminated buildings. With a loglinear model, the estimated ERR was 0.01 cGy^{-1} (90% CI: 0.00, 0.02), however the study's limitations prevent a definitive conclusion.[10]

Most studies of radiogenic breast cancer risk have investigated A-bomb survivors or women exposed to radiation in occupational or medical settings. The risk of breast cancer was elevated by radiation exposure in studies of incidence and mortality among A-bomb survivors.[11,12] The average ERR of breast cancer mortality during 1950–2003 in the LSS was 0.015 cGy^{-1} (95% CI: 0.009, 0.023).[12] ERR was inversely associated with age at exposure: the average ERR for those exposed under age 20 was 0.033 cSv^{-1} (95% CI: 0.023, 0.044), compared with 0.010 (95%

CI: 0.004, 0.016) for older women.[13] Further analyses of A-bomb survivor data have suggested that this apparent effect of age at exposure may be due largely to age at diagnosis.[3,11] In particular, for diagnoses at age <35 years the background breast cancer incidence rates (i.e. rates in the absence of A-bomb radiation exposure) were estimated to be lower than in previous analyses, which increased the apparent radiation-related excess risk.[11] The most recent updated analysis of breast cancer incidence in A-bomb survivors suggests that ERR is higher for diagnoses at early ages and for young women with early menarche around the time of exposure.[14] The results of our study are consistent with radiogenic risk being higher with younger age at exposure (Table 5) or at diagnosis/reference date, but cannot distinguish between effects of these two highly correlated age variables. Also, few women in our study were premenarchal ATA, so meaningful analysis of the timing of menarche and radiation exposure was not possible. Estimates of the EORs from our data (Table 5) are substantially larger that the ERRs seen in A-bomb survivors, however the EOR confidence intervals are very wide, indicating those estimates should be viewed cautiously.

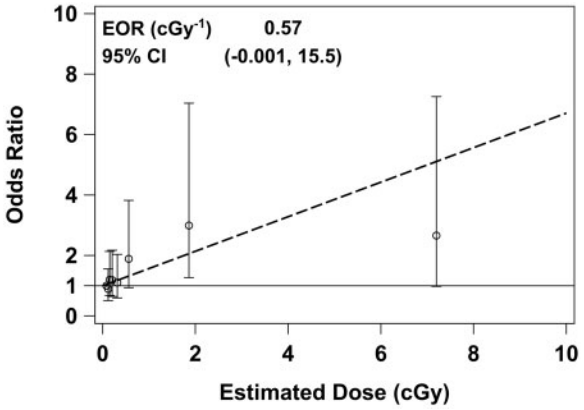

Figure 2. Odds ratios for breast cancer among breast cancer cases and controls from Bryansk Oblast, October 2008 to February 2013, in relation to estimated total radiation dose to the breast from the Chernobyl accident. Point estimates and 95% CIs are shown for dose octiles 2–8, relative to the lowest octile (octiles are based on all $n = 936$ cases and controls combined). The dashed line shows the fitted linear odds ratio obtained by treating dose as a continuous variable. For both the categorical and continuous treatment of dose, multivariable conditional regression methods were used to account for the individual matching of cases and controls and for the following covariates: menopausal status (premenopausal vs natural menopause vs other menopause), breast cancer in any first degree relative (yes vs no), nulliparity (yes vs no), age at first live birth, subject's education level (≤grade 11 vs technical school vs college/university) and history of employment in metallurgy or mining (yes vs no).

The exposures addressed in the A-bomb, occupational or medical studies were primarily from external γ- or x-ray radiation, usually delivered over one or more very short periods of time, several seconds in the case of A-bombs, and in various modes for occupational and medical exposures. As a result, many women in those studies received relatively high doses delivered at high dose rates. In contrast, the radiation exposures from Chernobyl in this study were from a mix of external γ sources (primarily ^{137}Cs) and internal β and γ sources from ingesting contaminated food and milk (primarily ^{131}I and ^{137}Cs), resulting in low doses for most women, delivered at lower dose rates over prolonged periods. Howe and McLaughlin[15] found that effects of fractionated moderate-dose-rate exposures on breast cancer mortality in the Canadian Fluoroscopy Cohort were similar to those reported for A-bomb survivors. Preston *et al.*[4] in a pooled analysis of breast cancer incidence in A-bomb survivors and seven medically exposed cohorts, found similar radiation effects from acute and

Table 4. Odds ratios for breast cancer risk, by estimated total radiation dose to the breast from the Chernobyl accident, among female residents of Bryansk Oblast, October 2008 to February 2013

Dose octile[a]	Mean (min – max) dose, cGy	No. (%) of cases ($n = 468$)	No. (%) of controls ($n = 468$)	Odds Ratio[b] (95% CI)	
				Unadjusted	Adjusted
1	0.08 (0.04–0.10)	57 (12)	60 (13)	1.0	1.0
2	0.12 (0.10–0.13)	54 (12)	63 (13)	0.9 (0.5, 1.5)	0.9 (0.5, 1.6)
3	0.15 (0.13–0.17)	59 (13)	58 (12)	1.1 (0.6, 1.9)	1.2 (0.7, 2.1)
4	0.20 (0.17–0.25)	56 (12)	61 (13)	1.0 (0.6, 1.8)	1.2 (0.6, 2.2)
5	0.32 (0.25–0.41)	58 (12)	59 (13)	1.2 (0.7, 2.2)	1.1 (0.6, 2.0)
6	0.56 (0.41–0.76)	61 (13)	56 (12)	1.6 (0.8, 3.3)	1.9 (0.9, 3.8)
7	1.86 (0.79–3.57)	64 (14)	53 (11)	2.4 (1.1, 5.6)	3.0 (1.3, 7.0)
8	7.28 (3.61–41.5)	59 (13)	58 (12)	2.3 (0.9, 5.8)	2.7 (1.0, 7.3)

[a] Octiles of estimated breast dose were calculated for all 936 cases and controls combined.

[b] Odds ratios were estimated by conditional logistic regression, to account for individual matching on birth year and raion and type of settlement ATA, in a univariable model ('Unadjusted'), or in a multivariable model ('Adjusted') that included the following covariates: menopausal status at diagnosis/reference date (premenopausal vs natural menopause vs other menopause), history of breast cancer in first degree relative (yes vs no), nulliparity (yes vs no), age at first live birth, subject's education level (≤grade 11 vs technical school vs college/university) and history of employment in metallurgy or mining (yes vs no). The 'Adjusted' model excluded three case–control pairs in which menopausal status was unknown for one case or control.

ATA, at the time of the Chernobyl accident (April 26, 1986); cGy, centigray; CI, confidence interval.

Table 5. Radiation dose effect modification of breast cancer risk by age ATA[a], among female residents of Bryansk Oblast, October 2008 to February 2013

		Without radiation effect modification	With radiation effect modification
	Nos. of cases, controls	EOR[b] (95% CI), cGy^{-1}	
All Ages ATA[a]	465, 465	0.57 (−0.00, 15.5)	–
Age ATA[a] <13	51, 51	–	9.59 (0.90, 99.8)
Age ATA[a] ≥13	414, 414	–	0.38 (−0.01, 11.5)
Covariates		OR[b] (95% CI)	
Menopausal status	Premenopausal	1.00	1.00
	Natural menopause	1.43 (0.97, 2.10)	1.45 (0.98, 2.14)
	Other menopause	2.55 (1.65, 3.94)	2.59 (1.68, 4.00)
Breast cancer in 1st degree relative	Yes vs no	2.24 (1.27, 3.95)	2.24 (1.27, 3.96)
Participant's education level	College/university	1.00	1.00
	Grade ≤11	2.39 (1.37, 4.16)	2.33 (1.34, 4.08)
	Technical school	1.38 (0.99, 1.94)	1.41 (1.01, 1.97)
Nulliparous	Yes vs no	0.93 (0.52, 1.66)	0.91 (0.50, 1.64)
Age at 1st live birth	Per year	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)
Occupation in mining/metallurgy	Yes vs no	2.43 (0.83, 7.07)	2.34 (0.80, 6.83)

[a] Each matched pair's age ATA was based on the breast cancer case.

[b] EORs and ORs were estimated by conditional logistic regression, to account for matching on birth year, raion and type of settlement ATA, in a multivariable model including the covariates.

ATA, at the time of the Chernobyl accident (April 26, 1986); cGy, centigray; CI, confidence interval; EOR, excess odds ratio; OR, odds ratio.

fractionated high dose rate exposures, but possibly smaller effects from low dose rate exposures.

This study had several strengths. It was population-based, including essentially all eligible cases from Bryansk Oblast over a 52-month period. Breast cancer diagnoses were confirmed by study pathologists. Controls were individually matched to cases with respect to year of birth, raion of residence and type of settlement ATA, preventing confounding by age or factors that might be related to place and type of residence (about 45% of the oblast population lived in the city of Bryansk ATA). Each participant was extensively interviewed for information about known or possible breast cancer risk factors as well as factors that determined her radiation dose from Chernobyl. Each woman's radiation dose to the breast due to Chernobyl was estimated, based on her residence and dietary histories. The impacts of pregnancy and lactation on dose from ^{131}I during the first months after the accident were also accounted for. This study had adequate statistical power to detect associations similar to or smaller than those reported in other populations. The study protocol projected a total of 500 cases, and although only 468 were available, this caused very little loss of power: the dose-response coefficient detectable with a given level of power with $n = 500$ cases increases by only $(500/468)^{1/2} = 1.033$ or 3.3% compared with the actual accrual.

Potential limitations of the study include the following. Matching of cases and controls on raion of residence and settlement type may have forced their doses to be more similar than is typical for the population (overmatching). In particular, the largely rural raions in western or central Bryansk Oblast had few urban settlements, increasing the chance that a case from one of those urban settlements has a control from the same settlement. However, a woman's radiation dose is influenced by her histories of residence locations and of the types, quantities and sources of the milk and foods she consumed. Therefore, women from the same settlement ATA can accumulate quite different doses. Data concerning dose-determining factors and other risk factors were obtained from interviews in which neither the participant nor the interviewer was blind to case–control status. Thus, the results may have been influenced by recall or reporting bias. There is no evidence that study participants were particularly knowledgeable about radiation exposure pathways or breast cancer risk factors, however this possibility cannot be excluded. This study included only cases diagnosed during a relatively short period of time 22.5–26.8 years after the Chernobyl accident. Consequently, ages ATA and at diagnosis/reference date were highly correlated and their effects on the radiation dose response could not be distinguished.

Further analyses will address whether and how molecular and other characteristics of the breast cancers are related to radiation dose. Additional development of the dose estimation system may enable analyses of risk in relation to features of dose accumulation, such as latency or maximum dose rate.

Supplementary data

Supplementary data are available at *IJE* online.

Funding

This work was funded by the National Cancer Institute at the U.S. National Institutes of Health [R01 CA118914].

Acknowledgements

The authors want to thank the following for their efforts in the conduct of this study: Theresa Taggart, Laurie Shields, Teri Kopp and Robert Day (Fred Hutchinson Cancer Research Center, Seattle, USA); Galina Pochtennaya (Bryansk Oncology Dispensary, Bryansk, Russian Federation); Galina Romanova (Bryansk Diagnostic Center, Bryansk, Russian Federation); Elena Iaskova, Tymofey Kolyzhenkov and Alexey Tyshkin (Medical Radiation Research Center, Obninsk, Russian Federation); Elena Maslova (Synovate Comcon, Moscow, Russia); and especially Andrey Vorobiev (Russian National Research Center for Hematology, Moscow, Russian Federation) and Anatoly Tsyb (Medical Radiation Research Center, Obninsk, Russian Federation). They also gratefully acknowledge the women of Bryansk Oblast who contributed their time and recollections as cases and controls.

Conflict of interest: None declared.

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International Journal of Epidemiology, 2020, 456–458
doi: 10.1093/ije/dyaa038
Advance Access Publication Date: 26 March 2020

Commentary: Breast cancer risk among women exposed to fallout after the Chernobyl accident

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Received 19 February 2020; Accepted 27 February 2020

In their study in the *IJE*, Rivkind and colleagues investigate the risk of breast cancer among women residing in Bryansk, Russia, who were exposed to prolonged internal and external radiation from the 1986 Chernobyl accident.[1] Although more than 30 years have passed since the accident, this is the first study to evaluate breast cancer risk in relation to individual radiation dose estimates among residents of areas contaminated by Chernobyl fallout. The