RADIATION RISKS

Lack of transgenerational effects of ionizing radiation exposure from the Chernobyl accident

Meredith Yeager[1,2]*†, Mitchell J. Machiela[1]†, Prachi Kothiyal[1,3], Michael Dean[1,2], Clara Bodelon[1], Shalabh Suman[1,2], Mingyi Wang[1,2], Lisa Mirabello[1], Chase W. Nelson[4,5], Weiyin Zhou[1,2], Cameron Palmer[1,2], Bari Ballew[1,2], Leandro M. Colli[1,6], Neal D. Freedman[1], Casey Dagnall[1,2], Amy Hutchinson[1,2], Vibha Vij[1], Yosi Maruvka[7,8], Maureen Hatch[1], Iryna Illienko[9], Yuri Belayev[9], Nori Nakamura[10], Vadim Chumak[9], Elena Bakhanova[9], David Belyi[9], Victor Kryuchkov[11], Ivan Golovanov[11], Natalia Gudzenko[9], Elizabeth K. Cahoon[1], Paul Albert[1], Vladimir Drozdovitch[1], Mark P. Little[1], Kiyohiko Mabuchi[1], Chip Stewart[7], Gad Getz[7,8,12,13], Dimitry Bazyka[9], Amy Berrington de Gonzalez[1], Stephen J. Chanock[1]*

Effects of radiation exposure from the Chernobyl nuclear accident remain a topic of interest. We investigated germline de novo mutations (DNMs) in children born to parents employed as cleanup workers or exposed to occupational and environmental ionizing radiation after the accident. Whole-genome sequencing of 130 children (born 1987–2002) and their parents did not reveal an increase in the rates, distributions, or types of DNMs relative to the results of previous studies. We find no elevation in total DNMs, regardless of cumulative preconception gonadal paternal [mean = 365 milligrays (mGy), range = 0 to 4080 mGy] or maternal (mean = 19 mGy, range = 0 to 550 mGy) exposure to ionizing radiation. Thus, we conclude that, over this exposure range, evidence is lacking for a substantial effect on germline DNMs in humans, suggesting minimal impact from transgenerational genetic effects.

Nearly all inherited genetic variation is present in the germline DNA of at least one parent. However, a small number of transmitted variants are unique, having arisen from random mutations in gametes (sperm and oocytes), and are known as de novo mutations (DNMs). DNMs are critical building blocks of evolution and the only class of genomic variation that has not undergone extensive evolutionary purifying selection (purging of highly deleterious but nonlethal variants), making DNMs a distinctive form of inherited variation that differs from the genetic variation investigated in mapping complex traits and diseases (*1*). DNMs have been a topic of intense interest because of their role in human disease, particularly neurodevelopmental disorders (*2*, *3*).

Only recently has it been feasible to comprehensively investigate DNMs genome-wide at the population level in humans by using whole-genome sequencing (WGS) of mother-father-child trios. Recent reports of human DNMs characterized by WGS of trios estimate that between 50 and 100 new mutations arise per individual per generation (*2*, *4*–*8*), consistent with the population genetic estimate that the human mutation rate for single-nucleotide variants (SNVs) is ~1×10^{-8} per site per generation (*9*, *10*). The strongest predictor of DNMs per individual is paternal age at conception (*2*–*6*, *8*), with an increase of 0.64 to 1.51 mutations per 1-year increase in paternal age (*6*, *8*, *11*), whereas a maternal effect of ~0.35 mutations per 1-year increase in age was observed (*6*, *8*, *12*). Transgenerational studies of radiation exposure have primarily focused on disease (cancer, reproductive, and developmental) outcomes and have reported inconclusive results (*13*, *14*).

Exposure to ionizing radiation is known to increase DNA mutagenesis above background rates (*15*, *16*). Animal and cellular studies suggest that high doses of ionizing radiation can lead to DNMs in offspring, particularly through double-strand breaks (*13*, *17*). Human studies have sought a biomarker of prior radiation injury (*13*, *18*, *19*) but have examined a small number of minisatellites and microsatellites, yielding inconclusive results (*20*–*23*). A WGS study of three trios from survivors of the atomic bomb in Nagasaki, Japan, did not reveal a high load of DNMs (*20*), whereas a single-nucleotide polymorphism (SNP) array study of 12 families exposed to low doses of caesium-137 from the Goiânia accident in Brazil reported an increase in large de novo copy-number variants (*24*). No large-scale, comprehensive effort has explored DNMs genome-wide in children born to parents exposed to moderately high amounts of ionizing radiation, yet possible genetic effects have remained a concern for radiation-exposed populations, such as the Fukushima evacuees (*25*).

Herein, we examine rates of germline DNMs in children born to parents exposed to ionizing radiation from the 1986 Chernobyl (Chornobyl in Ukrainian) disaster, for which levels of exposure have been rigorously reconstructed and well documented (*26*). Our study focused on children born to enlisted cleanup workers ("liquidators") and evacuees from the town of Pripyat or other settlements within the 70-km zone around the Chernobyl Nuclear Power Plant in Ukraine (*27*) after the meltdown, some of whom had extremely high levels of radiation exposure and several of whom experienced acute radiation syndrome. We performed Illumina paired-end WGS (average coverage: 80×), SNP microarray analysis, and relative telomere length assessment on available samples from 130 children from 105 mother-father pairs. The parents had varying combinations of elevated gonadal ionizing radiation exposure from the accident (tables S1 to S3) and included a combination of exposed fathers, exposed mothers, both parents exposed, and neither parent exposed (*27*). The fathers' cumulative gonadal ionizing radiation dose (hereafter, "dose") at conception ranged from 0 to 4080 milligrays (mGy) [mean = 365 mGy, median = 29 mGy, standard deviation (SD) = 685 mGy], with 17 individuals exposed to >1000 mGy, whereas the mothers' dose ranged from 0 to 550 mGy (mean = 19 mGy, median = 2.1 mGy, SD = 72 mGy), with only 2 individuals exposed to >500 mGy (table S3). Paternal age at exposure ranged from 12 to 41 years and maternal from 10 to 33 years. Paternal mean age at conception was 29 (range = 18 to 52, SD = 5.7), whereas maternal mean age was 27 (range = 18 to 39, SD = 5.2). Of the children in our study, 58 (45%) were female and 72 (55%) were male. Children born at least 46 weeks after the Chernobyl accident were included; birth years were between 1987 and 2002 (52% born before 1992). There were 23 families with two or three siblings analyzed, but no twins. Principal component analysis revealed that nearly all parents shared common Eastern European heritage (fig. S1), and pairwise identity-by-descent analysis revealed four first-degree relative sets among the parents.

Two modified Mendelian inconsistency error (MIE) filtering strategies were applied after variant calling and determination of MIE

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD 20892, USA. [2]Cancer Genomics Research Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD 21701, USA. [3]SymbioSeq LLC, Arlington, VA 20148, USA. [4]Biodiversity Research Center, Academia Sinica, Taipei, 11529, Taiwan. [5]Institute for Comparative Genomics, American Museum of Natural History, New York, NY 10024, USA. [6]Department of Medical Imaging, Hematology, and Oncology, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, SP, 14049-900, Brazil. [7]Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA 02142, USA. [8]Center for Cancer Research, Massachusetts General Hospital, Boston, MA 02114, USA. [9]National Research Centre for Radiation Medicine, 53 Yu. Illienka Street, Kyiv, 04050, Ukraine. [10]Department of Molecular Biosciences, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732-0815, Japan. [11]Burnasyan Federal Medical and Biophysical Centre, 46 Zhivopisnaya Street, Moscow, 123182, Russia. [12]Department of Pathology, Massachusetts General Hospital, Boston, MA 02114, USA. [13]Harvard Medical School, Boston, MA 02115, USA.
***Corresponding author. Email: chanocks@mail.nih.gov (S.J.C.); yeagerm@mail.nih.gov (M.Y.)**
†These authors contributed equally to this work.

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(*8*, *28*). All putative DNMs that passed the filtering criteria were examined manually, and the total number of DNMs was tallied for each of the following classes, reflecting distinct mutational mechanisms: (i) SNVs, (ii) small insertions or deletions (indels), (iii) complex variants (variants that arose from a complicated mutational event), and (iv) SNV-indel clusters [two or more variants that, by chance, occur in closer proximity than expected, as defined by Jónsson *et al.* (*6*)] (Table 1). Each instance of a complex variant or cluster was counted once, effectively assuming that clustered changes occurred together during one replication cycle. Length variants at microsatellite loci were examined separately because they have been previously reported as a potentially important class of mutation after radiation exposure (*21*, *22*, *29*–*31*). Although DNMs involving microsatellite loci were analyzed separately, they were tallied with indels overall. All variants are provided in table S1.

There was no evidence of an association between the total number of DNMs and the preconception ionizing radiation dose (cumulative estimated gonadal dose at 38 weeks before birth) for maternal [−0.02 DNM per mGy, 95% confidence interval (CI): −0.04 to 0.007, $P = 0.17$] or paternal (−0.0007 DNM per mGy, 95% CI: −0.003 to 0.002, $P = 0.56$) exposures (Table 2 and fig. S2). In an analysis restricted to DNMs with a known parent of origin (42%; Table 1), no effect of radiation

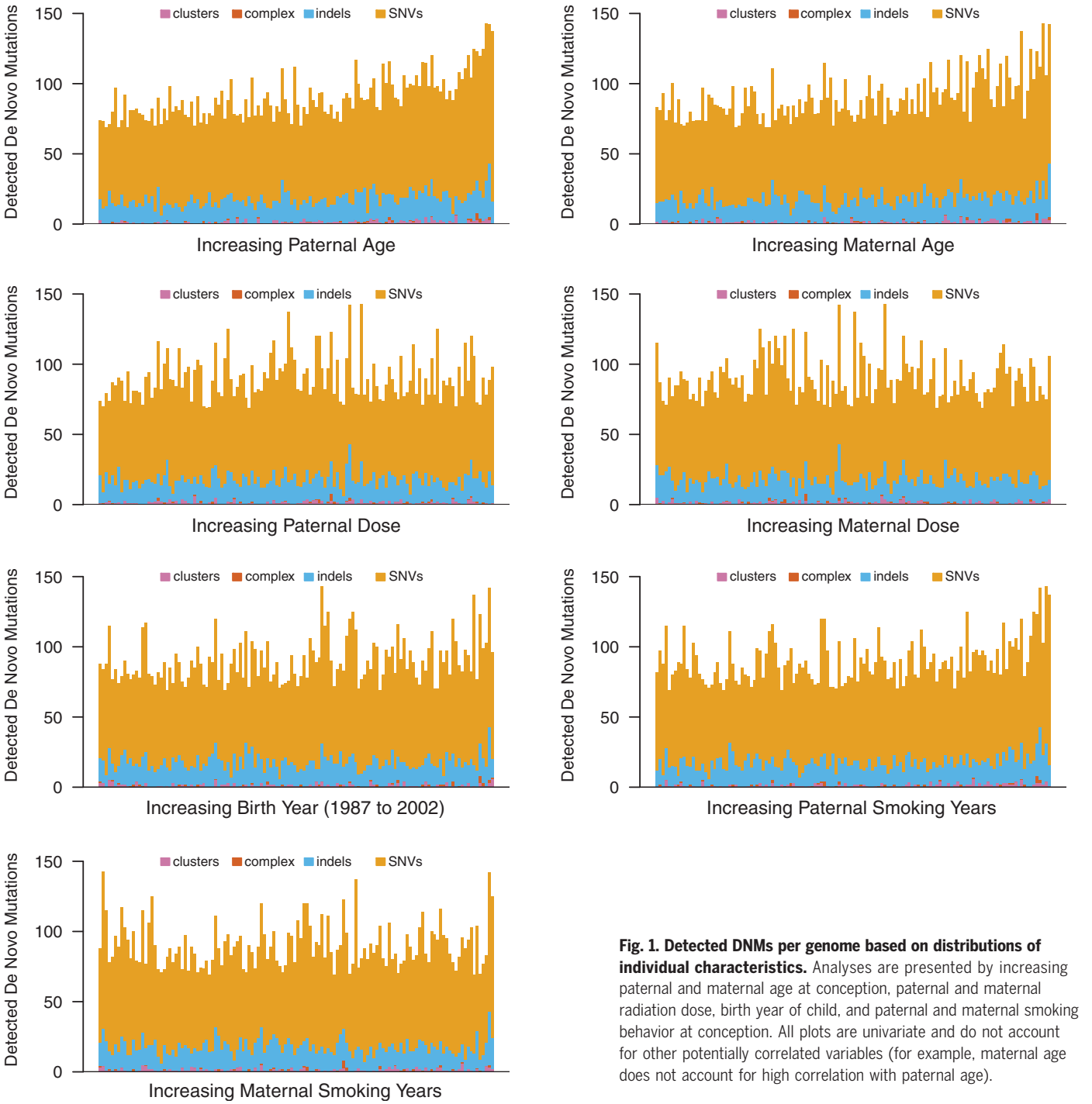

Fig. 1. Detected DNMs per genome based on distributions of individual characteristics. Analyses are presented by increasing paternal and maternal age at conception, paternal and maternal radiation dose, birth year of child, and paternal and maternal smoking behavior at conception. All plots are univariate and do not account for other potentially correlated variables (for example, maternal age does not account for high correlation with paternal age).

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was observed (table S4), whereas the effect of parental age remained robust; the parent-of-origin point estimates for paternal and maternal age effects were 0.71 and 0.28, respectively. Further investigation did not reveal evidence for an effect of preconception dose for any individual class of DNMs evaluated (table S5). Sensitivity analysis conducted with doses truncated at 1000 mGy or log-transformed [ln(1 + dose(mGy))] did not reveal an impact of maternal and paternal dose modeling on association with DNMs (Table 3). We further investigated categorical dose levels and found no increase in DNMs for any dose category, even paternal doses ≥1000 mGy (table S6). No effect of time since exposure was observed between parental preconception ionizing radiation exposure and DNM count for children born in the years immediately after the Chernobyl accident (Fig. 1). Moreover, when restricting our analysis to SNVs, there was no difference in the distribution of nucleotide substitutions based on quartile of maternal and paternal dose (fig. S3). Furthermore, the rates and types (molecular spectra) of DNMs observed in the current study were similar to those observed in prior studies conducted in general populations (Fig. 2 and fig. S4) (*2*–*4*, *6*, *8*).

Because lifestyle exposures such as smoking have been associated with alterations of DNA [for example, mosaic loss of Y chromosome (*32*)], we also investigated possible effects of prenatal parental alcohol consumption and smoking on DNMs. We observed no association between the number of DNMs and either paternal (2.91 DNMs, 95% CI = −0.93 to 6.75, P = 0.14; Table 2 and Fig. 1) or maternal (5.31 DNMs, 95% CI = −0.18 to 10.81, P = 0.06; Table 2 and Fig. 1) tobacco smoking at conception. Similarly, no effect was observed for increasing levels of paternal (P = 0.12) or maternal (P = 0.12) alcohol consumption before conception. In addition, sequencing batch had no impact on the number of DNMs (3.28 DNMs, 95% CI = −0.25 to 6.82, P = 0.07).

Relative telomere length of participants was measured by quantitative polymerase chain reaction (*33*) to investigate the potential transgenerational impact of parental ionizing radiation on leukocyte telomere length in children. As expected, an overall relationship was observed between increasing age (at the time of blood draw) and shorter relative telomere length due to age-related telomere length attrition ($P = 4.49 \times 10^{-19}$; fig. S5). We did not observe an effect of paternal or maternal age at conception on relative telomere length in adult children (P = 0.95 and 0.06, respectively; table S7). Although our analysis did not find evidence for an effect of total paternal preconception ionizing radiation exposure on relative leukocyte telomere length (P = 0.88), we did observe a possible effect of total maternal preconception exposure (-2.75×10^{-4}, 95% CI = -5.20×10^{-4} to -2.90×10^{-5}, P = 0.03; table S7)—this finding will need to be confirmed in subsequent work. There was no evidence for a transgenerational effect of paternal or maternal smoking on telomere length in children (P = 0.91 and 0.22, respectively; table S7).

Although it is reassuring that no transgenerational effects of ionizing radiation were observed in adult children of Chernobyl cleanup workers and evacuees in the current study, additional investigation is needed to address the effects of acute high-dose parental gonadal exposure that occurred closer to conception. The upper 95% confidence bound suggests that the largest effect consistent with our data is <1 DNM per 100 mGy from paternal or maternal exposure (Table 3 and tables S8 and S9). Previously, Dubrova *et al.* (*22*, *29*) reported a twofold increase in minisatellite mutations in children born to parents living in a highly exposed region of Belarus. Weinberg *et al.* (*34*) reported an increase in the mutation rate at microsatellite loci among children born to cleanup workers. Subsequent small studies have not reported increased minisatellite or microsatellite mutation rate in children of cleanup workers, including those with low-dose exposure (0.09 to 0.23 Gy) (*21*, *30*, *35*), or in children of the atomic-bomb survivors of Hiroshima or Nagasaki, Japan (*31*).

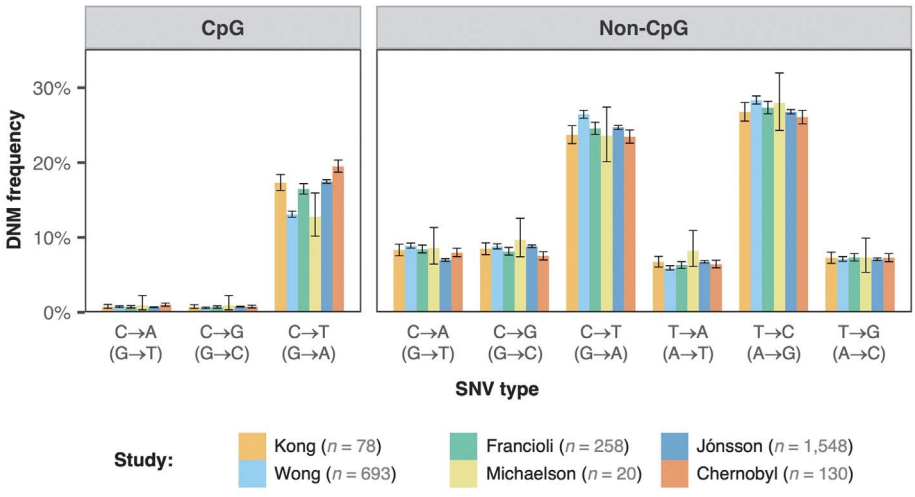

Fig. 2. Distribution of de novo SNVs by type of nucleotide change across six studies. Liftover was used to convert coordinates to hg38 (human reference genome 38) for all studies, and the reference for CpG sites was defined with respect to that reference sequence. Only autosomes were included. Error bars show binomial 95% CIs. Studies included those by Kong *et al.* (*2*), Wong *et al.* (*8*), Francioli *et al.* (*4*), Michaelson *et al.* (*3*), and Jónsson *et al.* (*6*), as well as the present study (Chernobyl). *n*, number of children sequenced. [Image adapted from (*39*).]

Table 1. Distribution of detected DNMs in the Chernobyl trios. Results reported as events per diploid genome per generation and proportion phased to paternal and maternal haplotypes. Microsatellites are a smaller group within indels; the mean microsatellite count (5.62) is part of the total mean indel count (16.18).

Detected DNM category	Mean	Median	Range	SD
Number of clusters	1.39	1	0–6	1.34
Number of complex variants	0.38	0	0–5	0.77
Number of indels	16.18	15	5–38	5.10
Number of microsatellites	5.62	5.5	0–13	2.49
Number of SNVs	72.22	69.5	47–121	13.36
Total number of DNMs	90.17	88	69–143	15.94
Phased to paternal haplotype	29.33	29	12–53	7.08
Phased to maternal haplotype	8.61	8	2–20	4.07
Proportion phased	42.1%	41.5%	27.6–55.8%	6.3%

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Our study evaluated peripheral blood from adult children conceived months or years after the Chernobyl accident, so our ability to assess exposure closer to the time of conception was limited. However, there was no evidence of notable differences in DNMs in children born the year after the accident (1987). Because the families in our study were recruited several decades after the accident, we acknowledge potential survivor bias among sampled children—although this is unlikely because there is no consistent demonstration in humans of sustained clinical effects of preconception ionizing radiation exposure (*36*). The number of parental gonadal radiation-induced double-strand breaks could be lower than anticipated based on animal data, which often assesses acute exposure (as a single burst) at higher doses [2 to 4 Gy (*13*, *37*)]. Doses to which the Chernobyl liquidators were exposed were mostly lower and exposure was fractionated over an extended period of time, which could have decreased the probability of gonadal DNM events. Moreover, it is plausible that the balance between radiation-induced mutations and accurate repair over time favored the latter. Additionally, there could have been a loss of power owing to dose errors. Further human studies are needed to investigate the frequency of radiation-induced mutations and the subsequent response to address both the accuracy and efficiency of DNA repair. In a genomic landscape analysis of 440 cases of papillary thyroid cancer after the Chernobyl accident, increased radiation exposure was associated with a shift in tumor drivers from point mutations to small indels and nonhomologous end-joining events underlying fusions and other structural variants (*38*). Notably, there was no evidence of a radiation-specific single-base substitution signature, gene expression pattern, or methylation profile in cases of thyroid cancer with comparable radiation exposure history; instead, these were strongly associated with the tumor driver.

The rate, class distribution, and SNV type distribution of DNMs in adult children born to parents exposed to ionizing radiation, specifically of the type and amount relevant to Chernobyl cleanup workers and evacuees, are comparable to those reported in the general population. No effect of radiation on the specific classes of DNMs (SNVs, indels, complex variants, or clusters) was observed (table S5). Paternal age remains the strongest contributor to DNMs, although DNMs increase (albeit less so) with maternal age as well (Table 2 and table S4) (*12*). Our study sample did not include mothers with high exposure levels (>1 Gy), but lower maternal dose was not associated with elevated DNMs, consistent with animal studies (*13*). Furthermore, our analysis of 130 adult children from 105 couples, using 80× coverage of short-read technology, suggests that if such effects on human germline DNA occur, they are uncommon or of small magnitude. Our study represents an effort to systematically evaluate alterations in human mutation rates in response to a human-made disaster, such as accidental radiation exposure. Investigation of trios drawn from survivors of the Hiroshima atomic bomb could shed further light on this matter of public health. In summary, children of individuals exposed to either occupational or environmental radiation do not appear to experience elevated rates of DNMs from their parents' exposure. Thus, our study does not provide support for a transgenerational effect of ionizing radiation on germline DNA in humans.

Table 2. Associations of age at conception, cumulative ionizing radiation dose, and smoking history with DNM count. Multiple regression estimates for age and radiation dose are average changes in total DNMs per unit increase in the respective variables. Estimates for smokers are relative to those for individuals who have never smoked. The model was additionally adjusted by sequencing batch.

Variable	Estimate	95% CI	*P* value
Age at conception			
Maternal age	0.46	−0.02–0.93	0.06
Paternal age	1.94	1.51–2.36	3.65×10^{-15}
Cumulative radiation dose (per mGy)			
Maternal dose	−0.02	−0.04–0.007	0.17
Paternal dose	−0.0007	−0.003–0.002	0.56
Smoking history			
Maternal former smoker	−4.13	−10.74–2.49	0.22
Maternal current smoker	5.31	−0.18–10.81	0.06
Paternal former smoker	0.91	−5.16–6.97	0.77
Paternal current smoker	2.91	−0.93–6.75	0.14

Table 3. Sensitivity analyses of the impact of maternal and paternal cumulative radiation dose modeling on association with DNMs. All models are adjusted for sequencing batch, maternal and paternal age, and maternal and paternal smoking status. Additional analyses organized by dose category are in table S6.

Dose measure	Estimate	95% CI	*P* value
Cumulative radiation dose (per mGy)			
Maternal dose	−0.02	−0.04, 0.007	0.17
Paternal dose	−0.0007	−0.003, 0.002	0.56
Cumulative radiation dose truncated at 1000 (per mGy)			
Maternal dose	−0.02	−0.04, 0.009	0.21
Paternal dose	−0.003	−0.008, 0.001	0.17
Cumulative log radiation dose (per ln(1 + mGy))			
Maternal dose	−0.87	−2.12, 0.39	0.18
Paternal dose	−0.37	−1.07, 0.33	0.30

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Competing interests: G.G. receives research funds from IBM and Pharmacyclics and is an inventor on patent applications related to MuTect, ABSOLUTE, MutSig, MSMuTect, MSMutSig, MSIdetect, POLYSOLVER, and TensorQTL. G.G. is a founder and consultant of, and holds privately held equity in, Scorpion Therapeutics. All other authors declare no competing interests. **Data and materials availability:** Molecular data are available from the Genomic Data Commons: https://gdc.cancer.gov/about-data/publications/TRIO-CRU-2021, accessed through the database of Genotypes and Phenotypes (dbGaP, accession phs001163.v1.p1; www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001163.v1.p1). The MIE filtering pipeline code can be found at https://github.com/NCI-CGR/ChernobylDNMCalling.

SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S7
Tables S1 to S10
References (*40*–*47*)
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Meredith YeagerMitchell J. MachielaPrachi KothiyalMichael DeanClara BodelonShalabh SumanMingyi WangLisa MirabelloChase W. NelsonWeiyin ZhouCameron PalmerBari BallewLeandro M. ColliNeal D. FreedmanCasey DagnallAmy HutchinsonVibha VijYosi MaruvkaMaureen HatchIryna IllienkoYuri BelayevNori NakamuraVadim ChumakElena BakhanovaDavid BelyiVictor KryuchkovIvan GolovanovNatalia GudzenkoElizabeth K. CahoonPaul AlbertVladimir DrozdovitchMark P. LittleKiyohiko MabuchiChip StewartGad GetzDimitry BazykaAmy Berrington de GonzalezStephen J. Chanock

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Genomics of radiation-induced damage

The potential adverse effects of exposures to radioactivity from nuclear accidents can include acute consequences such as radiation sickness, as well as long-term sequelae such as increased risk of cancer. There have been a few studies examining transgenerational risks of radiation exposure but the results have been inconclusive. Morton *et al.* analyzed papillary thyroid tumors, normal thyroid tissue, and blood from hundreds of survivors of the Chernobyl nuclear accident and compared them against those of unexposed patients. The findings offer insight into the process of radiation-induced carcinogenesis and characteristic patterns of DNA damage associated with environmental radiation exposure. In a separate study, Yeager *et al.* analyzed the genomes of 130 children and parents from families in which one or both parents had experienced gonadal radiation exposure related to the Chernobyl accident and the children were conceived between 1987 and 2002. Reassuringly, the authors did not find an increase in new germline mutations in this population.

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