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RESEARCH LETTER

Higher Incidence of Chromosomal Aberrations in Operators Performing a Large Volume of Endovascular Procedures

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Cardiovascular interventions using x-ray guidance are increasing in both volume and complexity. The long-term biological effects of chronic low-dose radiation exposure in operators performing these procedures are, however, largely unknown. Occupational safety limits are based on physical dosimetry only and do not consider individual biological sensitivity to radiation. We previously reported DNA damage in lymphocytes isolated from operators performing endovascular aortic repair (EVAR).[1] Expression of γ-H2AX and pATM (phosphorylated ataxia telangiectasia mutated), which are markers of acute DNA damage/repair, rose immediately after performing EVAR and normalized the following day. These markers, however, do not reflect the effects of chronic exposure, including chromosomal aberrations that may herald genomic instability and predisposition to malignancy. Here we report important findings pertaining to these aberrations in an international group of operators performing a large volume of complex endovascular interventions, including branched and fenestrated EVAR.

Peripheral blood was collected from endovascular operators (n=12; 11 male) and radiation-naïve general surgeons as controls (n=6; 5 male), all of whom gave informed consent. The study was approved by our institutional review committee (reference: 16/LO/1111). The median age of endovascular and control operators (50 [36–55] versus 47 [36–52], respectively; P=0.37) and years in practice (13.5 [3–20] versus 10.5 [5–16], respectively; P=0.19) were comparable. There were no intergroup differences in radiation exposures for personal health reasons, smoking history, or medications. Two endovascular operators had cancer, a squamous skin and renal lesion, both curatively treated at ages 49 and 16 years, respectively. Endovascular operators performed a median of 35 (20–100) standard EVARs and 70 (30–100) branched and fenestrated EVARs annually with a median annual personal radiation dose of 0.96 mSv (0.22–13.64) in the 3 years before blood sampling. All endovascular operators wore lead gowns and thyroid shields. Lead leg shields, headcaps, and goggles were used by 58%, 42%, and 92% of operators, respectively. Two operators used a ceiling-suspended radiation protection suit, and one used scatter radiation–absorbing drapes.

Giemsa-stained metaphase preparations were used to analyze the full complement of chromosomes in at least 3000 lymphocytes per operator (Figure [A]). Semiautomated scoring found a dicentric chromosome frequency of 0.11 (0.03–0.16) per 100 cells in the endovascular operators compared with 0.04 (0–0.06) in controls (P=0.002, Figure [B]). There was no correlation between age of operator and dicentric frequency (Pearson coefficient, r=0.04 [−0.44 to 0.50], P=0.876).

More than 2000 lymphocytes from 9 operators (5 exposed, 4 control) were analyzed by multiplex fluorescence in situ hybridization using fluorescent probes hybridized to metaphase chromosomes. The frequency of unstable, complex exchanges that involve 3 or more breaks in 2 or more chromosomes (0.48 versus 0.24 per 100 cells, Mann-Whitney U test, P=0.32) and stable, reciprocal translocations (0.86 versus 0.59 per 100 cells, Mann-Whitney U test, P=0.38) trended higher in endovascular

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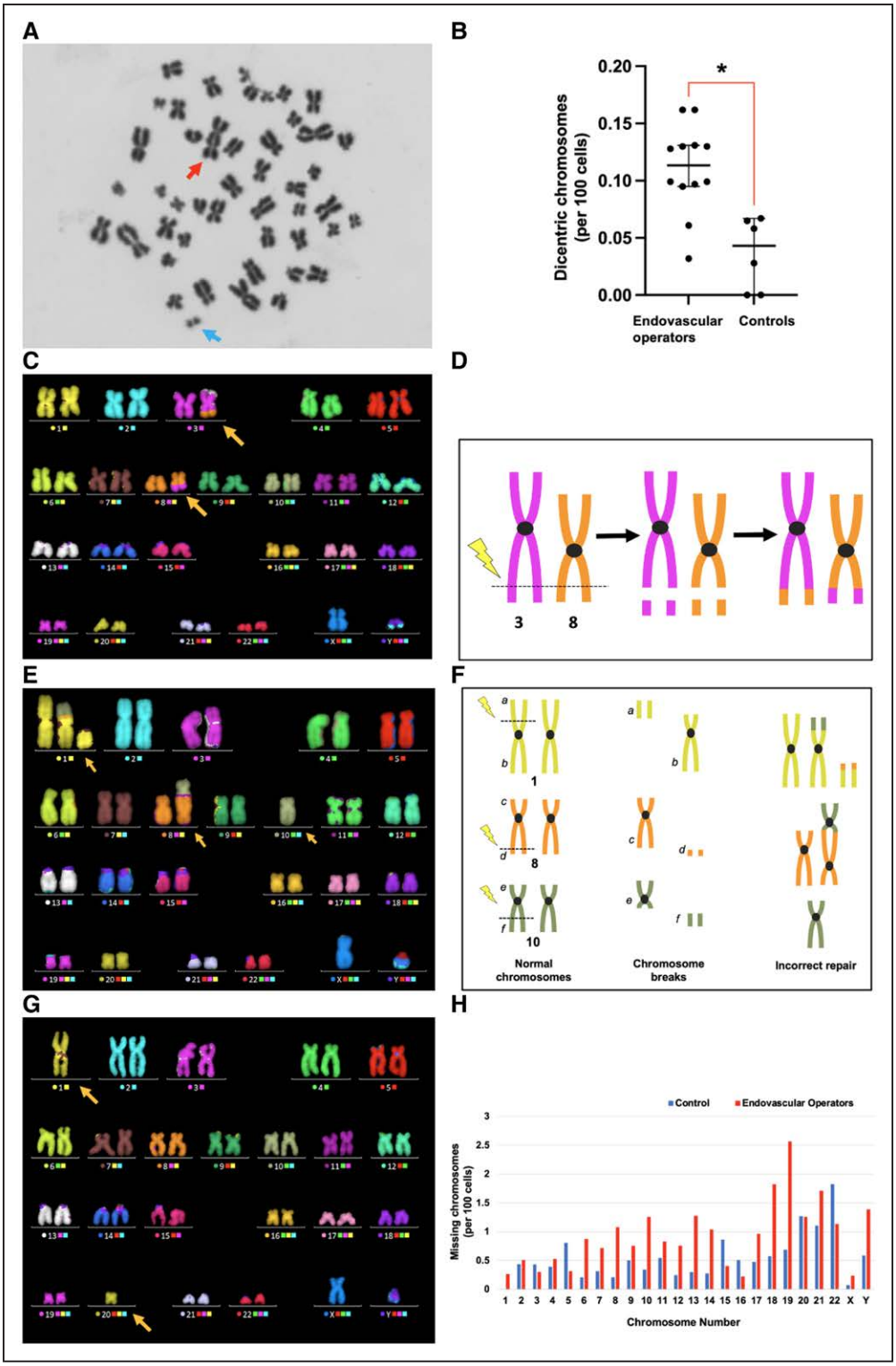

Figure. Chromosomal aberrations in exposed endovascular operators versus controls.
A, Chromosome spread of a lymphocyte in metaphase, visualized by Giemsa staining, showing a dicentric chromosome (red arrow) and an acentric fragment (blue arrow). In this aberration, breaks in 2 chromosomes followed by an incorrect repair have resulted in the formation of a single chromosome containing 2 centromeres and a chromosome fragment containing no centromeres. **B**, Frequency of dicentric chromosomes per 100 cells in endovascular operators compared with radiation-naïve control operators (0.11 versus 0.04, respectively; *Mann-Whitney *U* test; *P*=0.002). **C**, Multiplex fluorescence in situ hybridization (m-FISH) demonstrating a chromosome spread of 22 pairs of autosomes and single X and Y chromosomes. A simple reciprocal translocation between chromosomes 3 and 8 is highlighted by the yellow arrows. **D**, An illustration depicting the formation of the reciprocal translocation seen in **C**, where ionizing radiation has caused breaks in chromosomes 3 and 8, which have then been repaired incorrectly such that a fragment of chromosome 8 is attached to chromosome 3 and vice versa. (*Continued*)

Figure Continued. **E**, A complex, unstable, nontransmissible chromosome rearrangement visualized by m-FISH, with yellow arrows highlighting the chromosomes (1, 8, and 10) affected by breaks and incorrect repair. **F**, Illustration depicting the formation of the complex rearrangement seen in **E**, where ionizing radiation has caused breaks in 3 chromosomes followed by incorrect repair. The centromere-containing portion of chromosome 10 has attached to chromosome 8, and the acentric portion has attached to chromosome 1. Acentric portions of chromosomes 1 and 8 have also attached to form an acentric fragment. Lower case alphabetic labels denote part of chromosomes. **G**, A chromosome spread with aneuploidy visualized by m-FISH. Aneuploidy refers to the abnormal loss or gain of chromosomes within the cell. In this instance, the yellow arrows highlight the missing chromosomes 1 and 20. **H**, Bar chart showing the abnormal loss of each chromosome (aneuploidy) per 100 cells in endovascular operator samples (red) compared with the radiation-naïve controls (blue) after analyzing a total of >2000 cells by m-FISH; median of differences, 0.35; Wilcoxon signed-rank test; P=0.004.

operators (Figure [C through F]). Stable exchanges can be passed on to subsequent cell generations during mitosis and are, therefore, particularly useful for monitoring cytogenetic effects of chronic radiation exposures. Aneuploidy, which refers to abnormal loss of chromosomes, was more frequent in radiation-exposed operators (Wilcoxon signed-rank test, P=0.004, Figure [G and H]), with a median difference of 0.35 per chromosome.

Dicentric chromosomes, formed by cleavage and incorrect repair of double-stranded DNA, indicate genomic instability and reflect radiation exposure during the lymphocyte's lifespan, which is ≈3 years.[2] Their frequency increases proportionally to cumulative radiation exposures (<5Gy), allowing their use for biological assessment of chronic exposures.[2] The dicentric frequencies we observed fall below the threshold that allows reliable inference of effective exposure dose using current nomograms. Nevertheless, we found an almost 3-fold higher incidence of dicentrics in endovascular operators compared with radiation-naïve controls. The dicentric count in the latter group was comparable with that of the general population, which is generally quoted as ≈0.06 per 100 cells.[2] Our findings are corroborated by a recent report of higher dicentric frequency in interventional radiologists.[3] These data highlight the need to investigate whether partial body irradiation to unshielded areas such as the legs may contribute to this level of chromosomal damage over time.[1]

The chromosomal aberrations detected in the present study using multiplex fluorescence in situ hybridization, although not necessarily caused by occupational radiation exposure, are also associated with cancer.[4] These increase the burden of genetic alterations that can cause defects in cell proliferation, induce proteotoxic stress, and promote tumorigenesis, but uncertainties remain around linking these actions to cancer risk. The effect of chronic low-dose occupational radiation exposure on the health of medical workers is uncertain and requires extensive epidemiological and mechanistic studies to inform.[5] Our exploratory findings are hypothesis-generating and strengthen the case for larger-scale prospective studies that accurately record radiation doses to all body parts, capture health events, and relate these to cytogenetic markers of chronic exposure.

Data, materials, and methods will be made available to researchers through direct communication with the corresponding author.

ARTICLE INFORMATION

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