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RADIATION SAFETY

Subclinical Carotid Atherosclerosis and Early Vascular Aging From Long-Term Low-Dose Ionizing Radiation Exposure

A Genetic, Telomere, and Vascular Ultrasound Study in Cardiac Catheterization Laboratory Staff

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CME Objective for This Article: At the completion of this article, the learner should be able to: 1) discuss clinical manifestations that may be related to chronic low dose radiation exposure; and 2) understand the connection between radiation exposure and subclinical atherosclerosis.

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Subclinical Carotid Atherosclerosis and Early Vascular Aging From Long-Term Low-Dose Ionizing Radiation Exposure

A Genetic, Telomere, and Vascular Ultrasound Study in Cardiac Catheterization Laboratory Staff

ABSTRACT

OBJECTIVES This study sought to assess the association between long-term radiation exposure in the catheterization laboratory (cath lab) and early signs of subclinical atherosclerosis.

BACKGROUND There is growing evidence of an excess risk of cardiovascular disease at low-dose levels of ionizing radiation exposure.

METHODS Left and right carotid intima-media thickness (CIMT) was measured in 223 cath lab personnel (141 male; age, 45 ± 8 years) and 222 unexposed subjects (113 male; age, 44 ± 10 years). Leukocyte telomere length (LTL) was evaluated by quantitative reverse transcriptase polymerase chain reaction. The DNA repair gene *XRCC3* Thr241Met polymorphism was also analyzed to explore the possible interaction with radiation exposure. The occupational radiological risk score (ORRS) was computed for each subject on the basis of the length of employment, individual caseload, and proximity to the radiation source. A complete lifetime effective dose (mSv) was recorded for 57 workers.

RESULTS Left, right, and averaged CIMTs were significantly increased in high-exposure workers compared with both control subjects and low-exposure workers (all p values <0.04). On the left side, but not on the right, there was a significant correlation between CIMT and ORRS ($p = 0.001$) as well as lifetime dose ($p = 0.006$). LTL was significantly reduced in exposed workers compared with control subjects ($p = 0.008$). There was a significant correlation between LTL and both ORRS ($p = 0.002$) and lifetime dose ($p = 0.03$). The *XRCC3* Met241 allele presented a significant interaction with high exposure for right side ($p_{interaction} = 0.002$), left side ($p_{interaction} < 0.0001$), and averaged ($p_{interaction} < 0.0001$) CIMTs.

CONCLUSIONS Long-term radiation exposure in a cath lab may be associated with increased subclinical CIMT and telomere length shortening, suggesting evidence of accelerated vascular aging and early atherosclerosis.
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Contemporary interventional cardiologists have an annual exposure radiation dose 2 to 3 times higher compared with diagnostic radiologists (1–4). Of special concern, the head organ dose is 10- to 20-fold higher than the whole-body dose recorded below the apron (2–5). Furthermore, the left side of the operator is more exposed than the right side in most cases due to the usual layout of an intervention suite, where the radiologist or cardiologist operates from the right side of the patient so that the scatter radiation comes predominantly from the patient on the radiologist's or cardiologist's left (2,3). The characterization of health risks of accumulated low-dose radiation is incomplete and largely lacking (6,7). The current system of protection against ionizing radiation mainly addresses the risk of cancer from the stochastic effects of prolonged low-dose exposure. At the present time, there is growing evidence of an excess risk of cardiovascular disease at both high- and low-dose levels of ionizing radiation exposure (8–11). However, the association between occupational dose levels (<500 mSv) and late cardiovascular risks is still controversial (8,11,12). There are several mechanisms by which ionizing radiation may

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affect vascular and cardiac function (11). A plausible hypothesis is that DNA damage caused by long-term exposure may accelerate vascular aging leading to atherosclerosis (11,13). We sought to assess the association between long-term radiation exposure in the cath lab and early signs of subclinical atherosclerosis as assessed by carotid intima-media thickness (CIMT) and leukocyte telomere length (LTL). In

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CIMT = carotid intima-media thickness

GISE = Italian Society of Invasive Cardiology

IMT = intima-media thickness

LTL = leukocyte telomere length

ORRS = occupational radiological risk score

PCR = polymerase chain reaction

addition, the contribution of a functional variant (Thr241Met polymorphism) in the x-ray repair cross-complementing group 3 gene (*XRRC3*) in playing a crucial role in the repair pathway of DNA double-strand breaks induced by ionizing radiation was evaluated.

METHODS

STUDY POPULATION. We studied cardiac catheterization laboratory workers who participated in the Healthy Cath Lab study that was organized by the Italian National Research Council with endorsement by the Italian Society of Invasive Cardiology (GISE). The rationale of the study was previously published (3,7,14). The study population comprised 223 cardiac catheterization laboratory workers (141 male; age, 45 ± 8 years) recruited during the 2 consecutive GISE annual meetings. In ad-hoc safety suites, 113 interventional cardiologists (94 male; 47.4 ± 8.8 years) and 110 nurses (46 male; 42.3 ± 7.1 years) received a complete assessment of health status by structured medical questionnaire including health history, lifestyle habits, and medications used. A group of 222 age- and sex-matched unexposed subjects (113 male; age, 44 ± 10 years) was used as a control group. Hypertension was defined as a history of hypertension requiring the use of antihypertensive treatment or as a systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg in untreated individuals. Subjects were deemed hypercholesterolemic if they were receiving lipid-lowering drugs or had a fasting total cholesterol level >5 mmol/l. Diabetes mellitus was defined as the need for oral antidiabetic drug therapy or insulin use. We considered smokers as individuals who smoked at least 3 cigarettes per day at the time of the analysis; ex-smokers were those who stopped smoking at least 6 months before study inclusion, and nonsmokers were those who never smoked. All participants were invited to undergo CIMT assessment and peripheral blood testing for telomere and genetic evaluation. Informed consent was obtained from all subjects before testing, and the study protocol was approved by the institutional ethics committee.

OCCUPATIONAL RADIATION DOSE ASSESSMENT. A reliable reconstruction of the lifetime cumulative professional exposure was obtained only in a limited number of workers (n = 57) from official records of the Health Physics Department, as previously described (5). Therefore, the cumulative occupational radiation dose was also estimated by an occupational radiological risk score (ORRS) in each subject for a first operator (working in proximity to the source of radiation) by multiplying the number of years of cath lab work times the number of procedures per year (>200 = 3, 100 to 200 = 2, <100 = 1). Obtained scores were multiplied by 0.5 (i.e., reduced by 50%) in cases of a second operator, nurse, or technician because they typically stand at a greater distance from the source of radiation and would thus be expected to receive a lower dose (2–4). The ORRS was therefore thought to represent a reasonable surrogate of the cumulative dose by combining the length of employment, individual caseload, and proximity to the radiation source.

CAROTID INTIMA-MEDIA THICKNESS. Common carotid artery scans were obtained by high-resolution ultrasound with a 10-MHz linear array transducer (VIVID I, General Electric, Milwaukee, Wisconsin). Two 10-inch clips were acquired from each common carotid artery and then analyzed offline by means of Carotid Studio (Quipu srl, Pisa, Italy), a software system for the automatic evaluation of the instantaneous carotid diameter and CIMT (15). Left, right, and overall CIMTs (defined as the average of left and right CIMTs) were reported.

LTL ANALYSIS. The LTL was measured quantitatively in genomic DNA from whole blood using the quantitative real-time polymerase chain reaction (PCR) method described previously (16,17). The relative LTL was measured by determining the ratio of the telomere repeat copy number (T) to the single copy gene copy number (T/S ratio) in experimental samples relative to a reference sample (16). All PCRs were performed in triplicate in 384-well plates in a CFX Real-Time PCR System (Bio-Rad, Milan, Italy).

PCR RESTRICTION FRAGMENT LENGTH POLYMORPHISM GENOTYPING ASSAY. The *XRCC3* Thr241Met polymorphism was analyzed by PCR combined with restriction fragment length polymorphism, as described earlier (18). PCR product was digested with specific restriction enzymes that recognized and cut either the wild-type or variant sequence site. The digested PCR products were analyzed on 10% polyacrylamide gels and stained with ethidium bromide.

STATISTICAL ANALYSIS. Statistical analyses of the data were conducted with the Statview statistical package, version 5.0.1 (Abacus Concepts, Berkeley, California). Values are presented as mean ± SD, median (interquartile range), or percent, according to the nature of the data. Characteristics of cases and control subjects were compared by the chi-square test for categorical variables and the 2-sample

TABLE 1 Clinical Characteristics of the Study Population

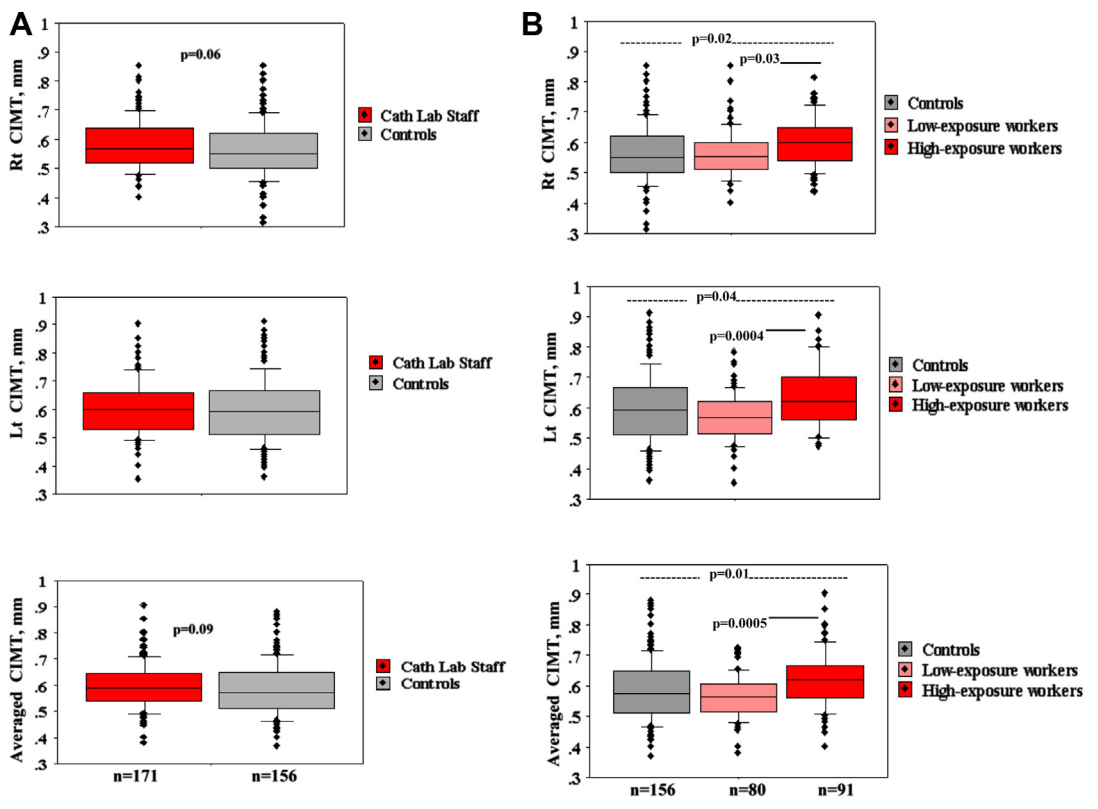
	Cath Lab Workers (n = 223)	Control Subjects (n = 222)	p Value
Age, yrs	44.9 ± 8.4	43.7 ± 9.8	0.2
Male	141 (63)	113 (51)	0.01
BMI, kg/m^2	24.2 ± 3.5	23.5 ± 2.8	0.1
Systolic BP, mm Hg	121 ± 12	119 ± 14	0.1
Diastolic BP, mm Hg	72 ± 10	73 ± 10	0.6
Hypertension	22 (10)	17 (8)	0.4
Hypercholesterolemia	25 (11)	9 (4.0)	0.004
Current smoking	64 (29)	35 (16)	<0.0001
Diabetes mellitus	3 (1.3)	3 (1.3)	0.9
Family history of CAD	83 (37)	92 (41)	0.9

Values are mean ± SD or n (%).
BMI = body mass index; BP = blood pressure; CAD = coronary artery disease.

Student *t* test for quantitative variables. Comparison of 3 means was performed by analysis of variance, followed by Bonferroni post-hoc test for comparison of any 2 groups. Regression or multiple regression analyses were used to characterize relationships between variables. Nonparametric data were analyzed using the Mann-Whitney or Kruskal-Wallis test followed by Dunn's post test, as appropriate. Stratified analyses for low or high exposure were also done. Additionally, the distributions of the T/S ratio of the telomere length were also divided into tertiles among groups, and the cutoff values were ≤0.86 for the lowest tertile, 0.87 to 1.1 for the middle tertile, and >1.1 for the highest tertile. The odds ratios and 95% confidence intervals were estimated for the determinants of tertiles by using conditional logistic regression models. The level of significance set at $p < 0.05$ was used for all statistical analyses.

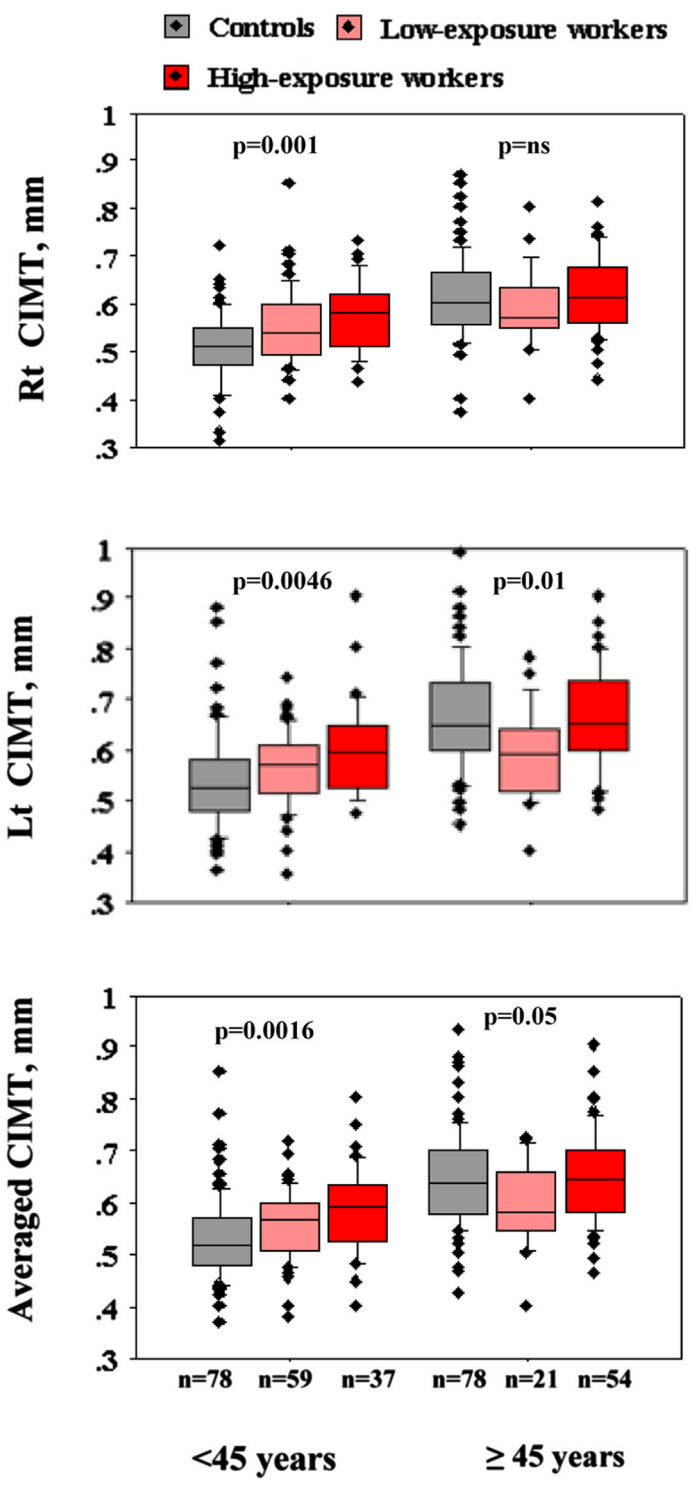
POWER ANALYSIS. A case-control study design was used to assess the difference in CIMT and LTL in exposed health care workers compared with nonexposed ones. Assuming a mean intima-media thickness (IMT) value in middle-aged healthy subjects of 0.58 ± 0.1 mm (19), a study with a sample size of 100

FIGURE 1 Carotid IMT (CIMT) and Cath Lab Exposure



Box-and-whiskers plot of right, left, and averaged CIMT in cath lab staff and control subjects **(A)** and according to low- and high-exposure groups and to median ORSS **(B)**. CIMT = carotid intima-media thickness; Lt = left; Rt = right.

FIGURE 2 Association Between Cath Lab Exposure and Carotid Intima-Media Thickness in Age-Stratified Groups



Right, left, and averaged CIMT in low- and high-exposure groups stratified by age. ns = not significant; other abbreviations as in Figure 1.

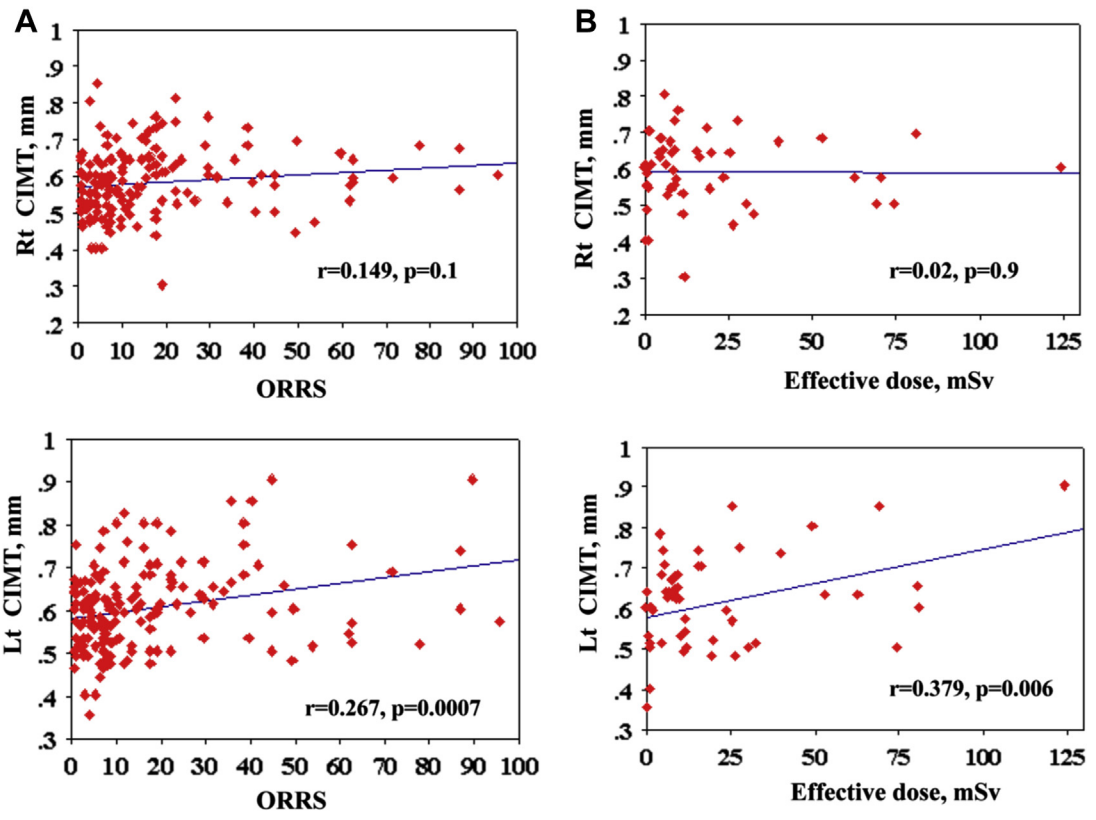
exposed subjects and 100 referent subjects will have a >80% power to detect as statistically significant ($\alpha = 0.05$) a 10% increased IMT in exposed subjects relative to referents. Such an increase in IMT is associated with a 20% increase in myocardial infarction and a 30% increase in stroke at 10 years of follow-up (20). Furthermore, our sample size gives more than 80% power at the 5% level to detect 1-SD difference between group means, which appears to be biologically relevant (21). Finally, we applied a case-only approach to a study gene environment; it achieves greater statistical power than a case-control study of the same size (22).

RESULTS

OCCUPATIONAL RADIATION EXPOSURE. Demographic and clinical characteristics of the study participants are reported in Table 1. None of the subjects had a history of cardiovascular events, defined as ischemic heart disease, transient ischemic attack, or stroke. Exposed personnel were occupationally exposed to ionizing radiation for 12.2 ± 8.3 years (range: 1 to 46 years). The estimated mean ORRS was 18.5 ± 20, ranging from 96 (32 years of work as a first operator, with a yearly caseload of more than 200 per year) to 1 (2 years of work as a nurse, with a yearly caseload <100), with a median value of 11 (interquartile range: 2.5 to 45). For 57 workers (36 male subjects; age, 45 ± 8.3 years; 25 interventional cardiologists and 32 nurses) with a complete lifetime dosimetric reconstruction (12.6 ± 8.6 years of exposure; range: 2 to 33 years), the mean dose was 21.1 ± 26.3 mSv (range: 0.2 to 124 mSv). The median individual effective doses were 19 mSv (interquartile range: 5.1 to 81 mSv) and 7.1 mSv (range: 0.7 to 34 mSv) for interventional cardiologists and nurses, respectively. There was a good correlation ($r = 0.584$; $p < 0.0001$) between estimated ORRS and recorded dosimetry.

CIMT AND CATH RADIATION EXPOSURE. CIMT was measured in 171 cath lab staff and 156 unexposed subjects. Overall, the median CIMT was significantly greater in hypercholesterolemic (0.66 vs. 0.58 mm; $p = 0.0001$) and hypertensive (0.65 vs. 0.57 mm; $p = 0.0002$) subjects with a body mass index (BMI) ≥30 kg/m^2 (0.64 vs. 0.58 mm; $p = 0.01$) and subjects who were smokers (0.59 vs. 0.57 mm; $p = 0.04$). CIMT was higher on the left side than on the right side for both exposed workers (0.60 vs. 0.58 mm; $p = 0.004$) and control subjects (0.59 vs. 0.55 mm; $p < 0.0001$). There was a positive linear relationship between right ($r = 0.523$; $p < 0.0001$), left ($r = 0.537$; $p < 0.0001$), and averaged ($r = 0.576$; $p < 0.0001$) CIMT with age. Overall, borderline

FIGURE 3 Relationship Between Radiation Dose and Carotid Intima-Media Thickness



Scatterplot of left and right CIMT versus occupational radiological risk score (ORSS) **(A)** and lifetime effective dose by recorded dosimetry **(B)**. Abbreviations as in Figure 1.

significant differences in CIMT values were observed in exposed workers compared with control subjects (Figure 1). When cath lab staff were divided into low- (n = 80) or high- (n = 91) exposure workers on the basis of the median of ORSS, CIMT was significantly increased in the high-exposure workers (Figure 1). The association between high radiation exposure and CIMT subjects was consistent in age-stratified groups that had similar prevalence of established traditional cardiovascular risk factors (Figure 2). Furthermore, 2-factor analysis of variance also revealed a significant interaction between cath lab exposure and age older than 45 years ($F = 7.4$; $p = 0.007$), smoking ($F = 3.9$; $p = 0.02$), hypercholesterolemia ($F = 5.3$; $p = 0.02$), and a BMI ≥30 kg/m^2 ($F = 5.6$; $p = 0.02$) on averaged CIMT values. On the left side, but not on the right, there was a significant correlation between estimated ORRS and IMT ($r = 0.267$; $p = 0.001$). Importantly, a significant relationship was also found between lifetime effective dose and left-side CIMT ($r = 0.379$; $p = 0.006$) in the subset of 57 workers (Figure 3). In a multiple regression model, age older than 45 years, a BMI ≥30 kg/m^2, and high exposure (≥median ORSS) correlated independently with both left-side and

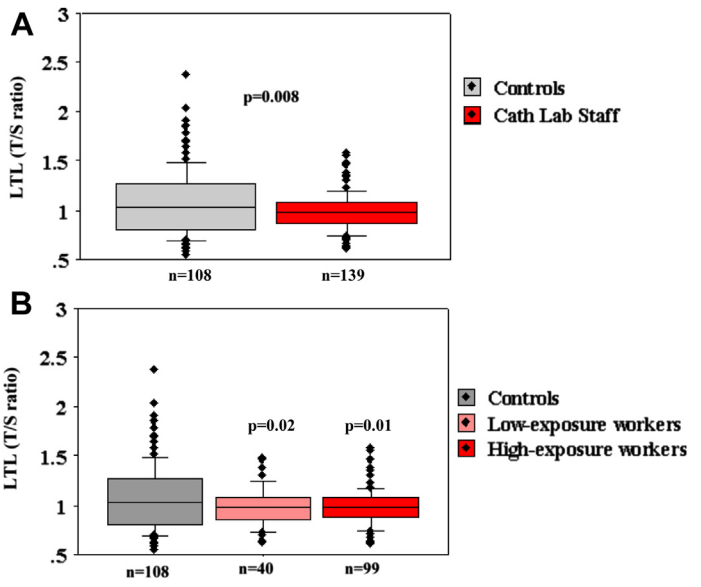
TABLE 2 Risk Factors Affecting CIMT on Multivariate Regression Analysis in the Whole Population

	Right CIMT		Left CIMT		Averaged CIMT	
	β	p Value	β	p Value	β	p Value
Age >45 yrs	0.246	0.005	0.215	0.01	0.246	0.002
Sex	0.05	0.6	0.02	0.8	0.04	0.6
Hypertension	0.07	0.4	0.05	0.5	0.07	0.3
Hypercholesterolemia	0.148	0.07	0.101	0.2	0.105	0.2
Smoking	0.01	0.8	0.01	0.9	0.03	0.6
BMI ≥30 kg/m^2	0.151	0.05	0.181	0.02	0.199	0.01
High exposure (≥median ORSS)	0.136	0.1	0.206	0.01	0.207	0.01

β is the standardized regression coefficient. The magnitude of β allows comparison of the relative contribution of each variable in the prediction of the dependent CIMT.

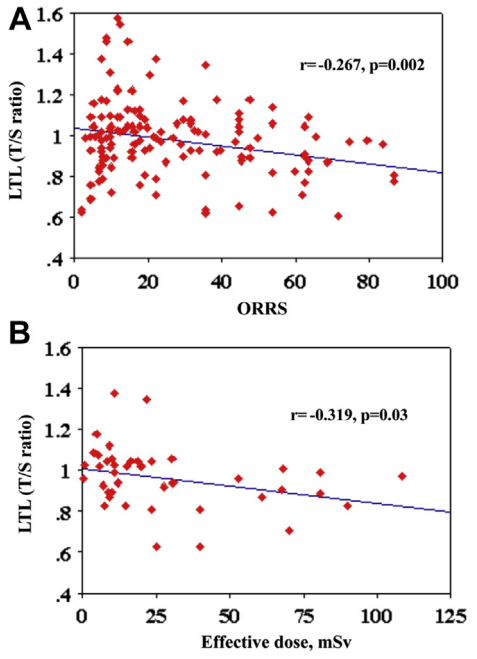
BMI = body mass index; CIMT = carotid intima-media thickness; ORSS = occupational radiological risk score.

FIGURE 4 Leukocyte Telomere Length (LTL) and Cath Lab Exposure



Differences in leukocyte telomere length between cath lab staff and controls in the whole population **(A)** and according to low- or high-exposure groups **(B)**. LTL = leukocyte telomere length; T/S ratio = the ratio of the telomere repeat copy number to the single copy gene copy number.

FIGURE 5 Relationship Between LTL and Radiation Dose



Scatterplot of LTL versus ORSS **(A)** and lifetime radiation dose **(B)**. Abbreviations as in Figures 3 and 4.

averaged CIMTs, but not right-side CIMT. The relative contribution of each variable is shown in Table 2.

TELOMERE AND RADIATION EXPOSURE. Telomere length was measured in a subset of 139 exposed staff and 108 unexposed subjects. In the whole sample, women had longer median LTL compared with men (1.1 vs. 0.98; p = 0.01), and current cigarette smokers had shorter borderline LTL compared with never smokers (0.95 vs. 1.0; p = 0.058). LTL inversely correlated with age for the entire sample (r = −0.218; p = 0.0005) and in separate analyses for both exposed workers (r = −0.182; p = 0.03) and control subjects (r = −0.225; p = 0.02). There was a small but significant association of LTL with CIMT (r = −0.197; p = 0.04). The median LTL was significantly reduced in exposed personnel compared with control subjects (0.97; interquartile range: 0.72 to 1.17 vs. 1.03; interquartile range: 0.68 to 1.48) (p = 0.008) (Figure 4). A significant inverse correlation was found between estimated ORRS and LTL (r = −0.267; p = 0.002) and recorded lifetime dose in the subset of workers (r = −0.319; p = 0.03) (Figure 5). On multiple linear regression analysis, only age (β = −0.188; p = 0.003) and radiation exposure (β = −0.136; p = 0.03) had a significant effect on LTL. In a multivariate-adjusted regression model as well, age (odds ratio: 1.0, 95% confidence interval: 1.0 to 1.1; p = 0.02) and radiation exposure (odds ratio: 2.7, 95% confidence interval: 1.5 to 4.9; p = 0.001) emerged as significant and independent risk predictors of a lower LTL tertile (Table 3).

DNA REPAIR AND VASCULAR AGING. Case-only analyses (n = 139) revealed that exposed workers who are carriers of the Met241 allele had a significantly increased right-side CIMT (0.59 vs. 0.56 mm; p = 0.03), left-side CIMT (0.61 vs. 0.57 mm; p = 0.007), and averaged CIMT (0.60 vs. 0.57 mm; p = 0.006) compared with wild-type homozygotes (Figure 6). Carriers of the *XRCC3* Met241 allele tended also to have

TABLE 3 ORs and 95% CIs per Variable of LTL in the Lowest Tertile Group

	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Age	1.0 (1.0-1.1)	0.006	1.0 (1.0-1.1)	0.02
Male	1.8 (1.0-3.1)	0.04	1.3 (0.7-2.4)	0.3
Cath lab exposure	3.0 (1.6-5.3)	0.0002	2.7 (1.5-4.9)	0.001

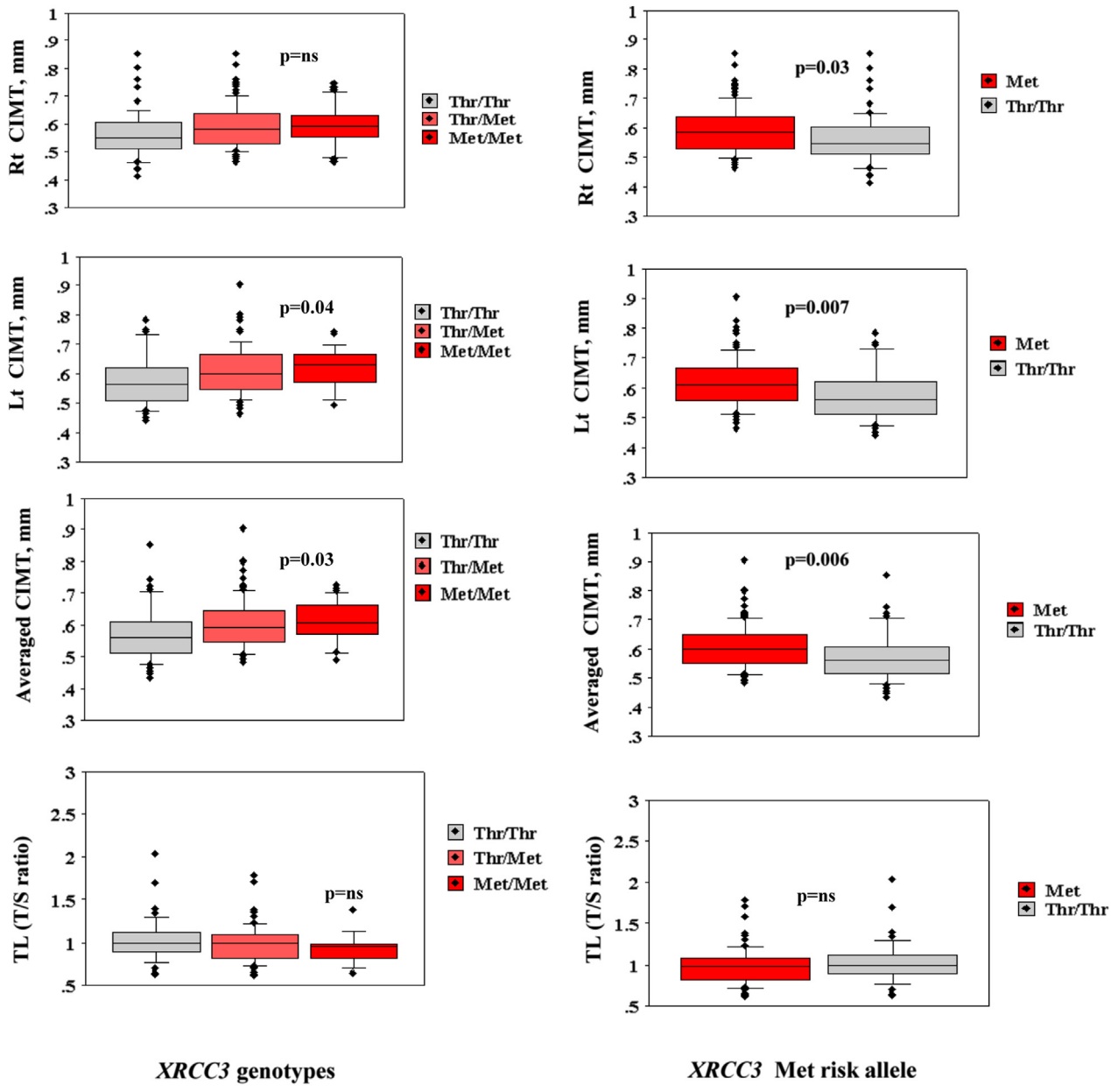
CI = confidence interval; LTL = leukocyte telomere length; OR = odds ratio.

a shorter telomere than wild-type homozygotes, although the difference was not significant (Figure 6). Finally, an interaction between the *XRCC3* Met241 allele and an ORSS higher than 11 on the right-side CIMT ($p_{interaction} = 0.002$), left-side CIMT ($p_{interaction} < 0.0001$), and averaged CIMT ($p_{interaction} < 0.0001$) values was also observed (Figure 7).

DISCUSSION

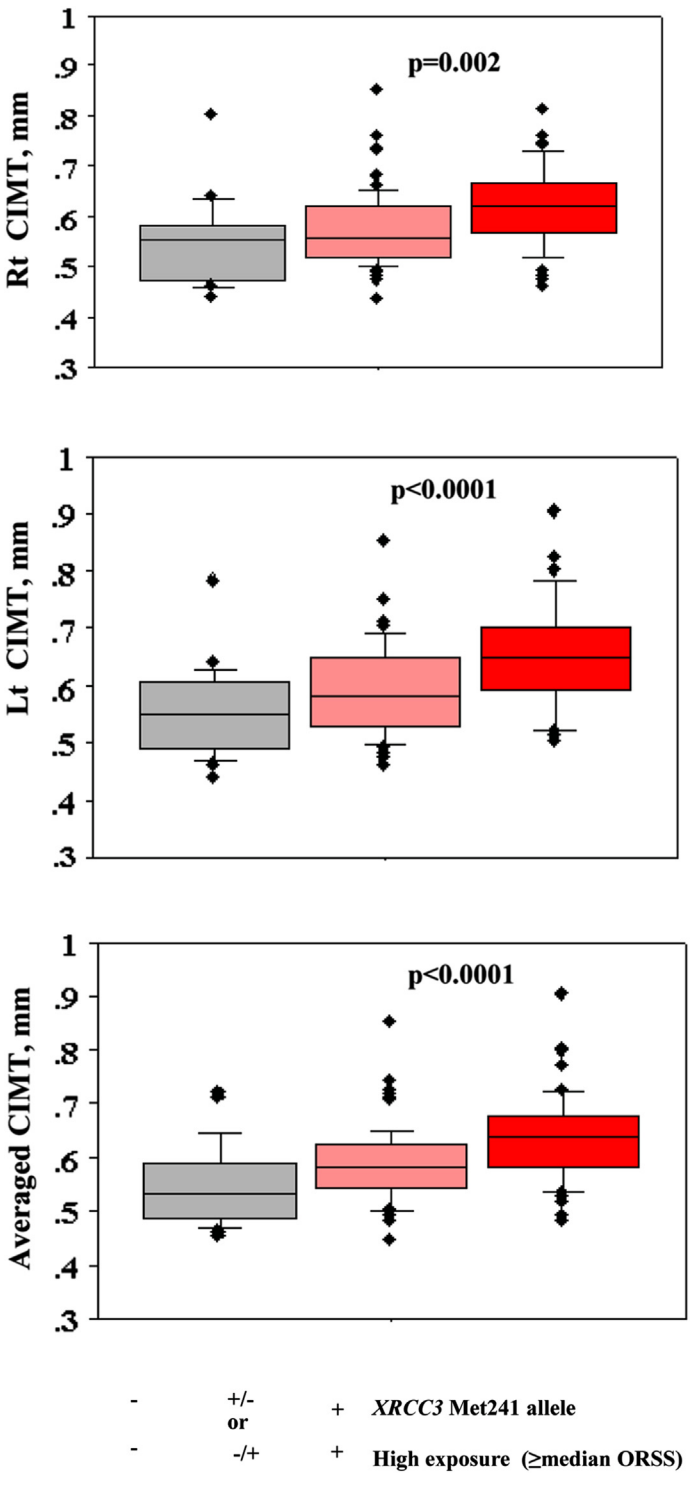
Long-term ionizing radiation exposure in a cardiac catheterization laboratory may be associated with increased subclinical CIMT and with telomere length shortening, suggesting evidence of early and accelerated vascular aging. In particular, it is noteworthy

FIGURE 6 The Modulating Effect of *XRCC3* Thr241Met Polymorphism



Influence of *XRCC3* Thr241Met polymorphisms on the leukocyte telomere length and carotid intima-media thickness in the Cath Lab staff. TL = telomere length; other abbreviations as in Figures 1 and 5.

FIGURE 7 Gene-Radiation Interactions for Carotid Intima-Media in Cath Lab Staff



Interactive effect of *XRCC3* Met241 variant and high exposure (≥median ORSS). Abbreviations as in Figures 1 and 3.

that a significant association with increasing radiation dose was found only on the left side, but not on the right, providing further support for a causal connection between occupational radiation exposure and early signs of subclinical atherosclerosis. A side difference between IMT on the left and right sides was described earlier, and this asymmetry is attributed to different shear stress conditions and various risk factors that have different effects on the left versus the right carotid arteries (23,24). However, our finding may reflect the effects of a differential dose distribution of radiation exposure in operators who typically work with the left side of the head in closest proximity to the primary x-ray beam and scatter, experiencing twice the exposure levels of the right side (2,3). This observation is also consistent with recent updated data on brain cancer location among interventional physicians worldwide working with ionizing radiation (25). In 30 of 35 cases, data were available regarding the side of the brain involved: the malignancy was left sided in 26 (86%) operators, midline in 1, and right sided in 3 (25).

Furthermore, the finding of radiation-associated posterior lens opacities in the eyes of interventional cardiologists and nurses also reflects specific radiation exposure injury and is consistent with a significant cumulative head exposure in operators (7).

Finally, the Thr241Met *XRCC3* polymorphism was significantly associated with carotid CIMT, supporting the hypothesis that altered DNA repair capacity leads to accelerated vascular aging and atherosclerosis.

IONIZING RADIATION AND CARDIOVASCULAR RISK.

It is well known that radiation-induced cardiovascular disease is a major cause of morbidity and mortality in cancer patients undergoing radiotherapy (10). For instance, exposure of the heart during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease, with an increased risk that is proportional to mean dose to the heart and is higher in the presence of pre-existing risk factors (26). The association between low-dose exposures and late-occurring cardiovascular disease has been reported in the Japanese atomic bomb survivors and in various occupationally exposed cohorts (8,9,11,12). With regard to occupational exposure of workers (<500 mSv), there were increased risks of cardiovascular disease and mortality for both stroke and coronary artery disease among U.S. radiologists (27), but no effects were seen in the long-term follow-up of U.K. radiologists (28). Furthermore, a significant relative risk with respect

to cardiovascular mortality was found in a study of workers at 15 nuclear power reactors in the United States (29), but not in Mayak workers (30). More recently, data showed that employees of British Nuclear Fuels in the United Kingdom (31), the Canadian cohort of workers occupationally exposed to ionizing radiation (32), and Chernobyl liquidators (33) have increased incidence or mortality for cardiovascular disease. Furthermore, a recent meta-analysis showed an association between low doses (cumulative mean <500 mSv whole-body exposure) and low-dose rates (10 mSv/day) of ionizing radiation and an excess mortality risk of ischemic heart disease (12). Nonetheless, most of the epidemiological evidence is somewhat variable and lacking information on confounding modification by well-known risk factors (12). To overcome the limitation of an epidemiological approach, the Italian Healthy Cath Lab study is examining surrogates, but robust biomarkers, for health risks to better define the fundamental biochemical, cellular, and molecular mechanisms involved in long-term low-dose exposure (3,7,14). CIMT is an early marker of atherosclerosis and a strong predictor of subsequent risk of death from myocardial infarction and stroke (19,20). Increased CIMT has been described after radiotherapy for Hodgkin lymphoma and head and neck cancer (10,11) and even at relatively lower doses of medical ionizing radiation (34). Telomere shortening is widely considered to be a marker of biological aging as well as an important cause of chromosomal instability, preventing chromosome ends from being recognized as double-strand breaks and processed by DNA damage repair mechanisms (35). Additionally, shorter LTL has been demonstrated to predict cardiovascular disease and mortality (21,35). Interestingly, a recent study showed a significant telomere shortening in peripheral blood samples from Chernobyl clean-up workers in both the early and the late periods (even 20 years) after low-dose radiation, and these changes are related to variation in the apoptosis rates (36).

DNA REPAIR GENETIC SUSCEPTIBILITY AND VASCULAR AGING. The finding that a common polymorphism in the *XRRC3* gene increased IMT supports a causal link between genomic instability and radiation-induced atherosclerosis. Indeed, DNA damage and telomere attrition are believed to play a key role in the development of premature vascular aging and atherosclerosis (37). This line of thought is strengthened by recent data showing that deficient DNA repair capacity is associated with worsened vasodilator function, increased vascular stiffness, and accelerated vascular aging in mice (38). *XRCC3* is an important member of DNA repair genes that belongs to a family of genes responsible for repairing DNA double-strand breaks induced by ionizing radiation exposure (39). The functional single nucleotide polymorphism in codon 241(*Thr* to *Met*, rs861539 C>T) is the most thoroughly investigated polymorphism in the *XRCC3* gene and has been indicated to be involved in the development of some cancers, especially in the presence of environmental factors, such as tobacco smoke and ionizing radiation exposure (39). Furthermore, previous studies reported that the *XRCC3* Thr241Met polymorphism is associated with increased chromosomal DNA damage in workers occupationally exposed to long-term ionizing radiation (18,39).

STUDY LIMITATIONS. The major limitation of the study was the absence of radiation dosimetry based on thermoluminescent dosimeters in the majority of workers. Therefore, information about the individual occupational radiation was also obtained by a radiological score that combined the length of employment, individual caseload, and proximity to the radiation source. However, in a good number of workers, we had reliable dosimetric reconstruction, allowing a direct assessment of a dose-response relationship. With regard to genotyping, we restricted our analysis to a functional *XRCC3* polymorphism, but we cannot exclude the possibility that other genetic factors may have influenced the individual vascular aging response to radiation exposure. Despite these weaknesses, the features of relatively high levels of cumulative exposures make this cohort an ideally suitable research model for investigating the association between radiation exposure and probable, but still imprecisely defined, vascular effects. In addition, we focused on subclinical endpoints, as well as biomarkers because this information is more likely to lead insights as suggested by UNSCEAR 2008 (United Nations Scientific Committee on the Effects of Atomic Radiation): “future epidemiological studies designed to assess clinical and subclinical endpoints, as well as biomarkers, since this information is more likely to lead to insights” (40).

CONCLUSIONS

Results of this study showed that long-term radiation exposure in a cath lab may be related to increased subclinical CIMT values and telomere shortening, which may promote accelerated vascular aging and atherosclerosis. Subjects with a

XRCC3 Thr241Met polymorphism might have a greater susceptibility to radiation-induced vascular effects. Future studies are warranted to better define the relationship between occupational radiation exposure and clinical manifestation of atherosclerotic disease to implement a better health surveillance.

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PERSPECTIVES

WHAT'S KNOWN? Epidemiological and experimental data provide evidence of an increased cardiovascular risk associated with low-dose radiation exposure. However, long-term effects of occupational dose levels (<500 mSv) on the cardiovascular system is still controversial research.

WHAT'S NEW? This study shows that long-term radiation exposure in a cardiac catheterization laboratory is associated with increased subclinical carotid intima-media thickness and with telomere length shortening, suggesting evidence of early atherosclerosis. A functional polymorphism (Thr241Met) in *XRRC3*, the x-ray repair cross-complementing group 3 gene, may alter DNA repair capacity leading to accelerated vascular aging in cath lab personnel.

WHAT'S NEXT? Future studies are warranted to better define the relationship between occupational radiation exposure and clinical manifestation of atherosclerotic disease to implement a better health surveillance.

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