Occupational Radiation, Neighborhoods and Circulatory Disease Incidence and Mortality

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Gabriela Bustamante Callejas

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Advisor: Bruce H. Alexander, Ph.D.

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Dedication

This is dedicated to all those who have believed and supported me through this challenge. To my husband, Tiago, who has been dad, mom and housekeeper during these last few months, and an incredible friend and partner always. To my son Rafael, who has been the most wonderful blessing during the PhD program and continues to brighten my days with his energy and smiles. To my parents, my sisters, and my mother-in-law who have never stopped praying for me. And to my wonderful friends around me, especially Shannon, who did save me from drowning in more than one occasion.

Abstract

Background: Exposure to ionizing radiation has been primarily linked with the development of cancer, but in recent decades it has also been recognized to be a risk factor for circulatory diseases (CDs). High doses of ionizing radiation above 500mGy are associated with damage of the circulatory system and increased mortality from circulatory diseases (CD). The biological mechanism is hypothesized to include inflammation, oxidative stress, changes in platelet activity, DNA damage, endothelial dysfunction and cell death. However, the risks of occupational exposure to low protracted doses of medical ionizing radiation on CD mortality are not well understood. The risk of CD is also influenced by an individual's social environment, and this may modify the effect of occupational exposures like ionizing radiation. Most studies on the association between neighborhood context and coronary heart disease found increased risk of this disease among residents of neighborhoods of lower socioeconomic status. The socio-biological mechanism of this relationship is multifactorial, and it includes the physical environment, availability of services, neighborhood social interactions, experiential perceptions, spread of disease, stress levels, health behaviors and other shared factors.

To understand the effect of cumulative ionizing radiation and the neighborhood context on CD, we used longitudinal data from the US Radiologic Technologists (USRT) study and the US Census Bureau. The USRT is a large national historical cohort of 146,022 radiation technologists that has followed participants since 1982 through four comprehensive study waves. It is known that the average participation rate across these four questionnaires was 68%, but the characteristics of participants and non-participants have not been compared to date. If non-participation and attrition are not a random process, this could introduce bias to any effect estimates calculated with this data, including estimates of CD incidence and mortality.

Objective: The overall aim of the current thesis was to investigate the effect of protracted exposure to low doses of occupational radiation on CD incidence and mortality and assess if these associations are influenced by the residential neighborhood socioeconomic status (nSES) or by sequential participation bias.

Manuscript 1: ***Aim:*** Examine the dose-response relationship between low chronic doses of occupational radiation exposure and CD mortality in a large cohort of radiologic technologists. ***Methods:*** 109,300 radiologic technologists in the US were followed for mortality from completion of baseline surveys during 1983-89 or 1994-98 through 2012. Using discrete time hazard models, HR and 95%CI were estimated for the association between cumulative ionizing radiation (as badge and organ doses) and mortality from any CD, ischemic heart disease (IHD) and cerebrovascular disease (CeVD). Calendar year was included as a time scale and adjusted for age as a time-varying covariate, sex, race, ethnicity, BMI and smoking. ***Results:*** We found evidence of increased risk of CD mortality with increased cumulative exposure to occupational radiation. For every 100mSv increase in cumulative badge dose, the risk of mortality from any CD increased in 3% (95% CI 2-4%) adjusted for age, sex, race, ethnicity, BMI and smoking. For every 100mGy increase in heart dose, the HR for IHD mortality was 1.07 (95% CI 1.02 – 1.13) and the hazard ratio per 100mGy increase in brain dose was 1.39 (95%CI 1.14 – 1.64) for CeVD. Categorical analyses supported this linear trend for all outcomes. There was evidence of effect modification by gender for CD and IHD mortality (p-value for interaction < 0.001 for both), but not by BMI or certification year.

Manuscript 2: ***Aim:*** Determine whether the association between cumulative occupational radiation exposure on CD incidence and mortality is confounded or modified by residential nSES. ***Methods:*** Tertiles of nSES were created from an nSES index calculated for each block-group in the U.S. using 6 components from the 1990 Census and assigned it to participants by geocoding their 1990 mailing address. The confounding role of nSES tertiles was assessed by including it in

discrete time hazard models along radiation exposure and adjusting for educational attainment. To determine the presence of effect modification by nSES tertiles, we tested a two-way multiplicative interaction between nSES tertiles and radiation, and assessed an additive interaction using the relative excess risk due to interaction (RERI). ***Results:*** Compared to residents from the top tertile of nSES, technologists from low-nSES areas had an elevated risk of overall CD mortality, IHD mortality and incidence, and CeVD incidence with (HRs ranging from 1.21 to 1.31), but not for CeVD mortality (HR: 0.97, 95%CI: 0.80-1.18). We found no evidence of confounding by nSES on the association between radiation and any CD outcomes. There was evidence of a multiplicative interaction between nSES tertiles and radiation exposure for all mortality outcomes (p-value for interaction: <0.001 for overall CD, 0.003 for IHD and 0.004 for CeVD), but not for incidence. People from high nSES had higher HRs for mortality than low-nSES residents for the same radiation dose.

Manuscript 3: ***Aim:*** Compare the characteristics of participants and non-participants of each survey and estimate the impact of low chronic exposure to radiation on incidence and mortality from ischemic heart disease (IHD) and cerebrovascular disease (CeVD) adjusting for possible selection bias. ***Methods:*** Our main exposure was cumulative radiation exposure estimated for 110,374 technologists. After identifying predictors of participation from baseline and survey information, we created inverse probability weights (IPW) of participation to account for selection bias and included them in discrete time hazard models of the association of radiation and circulatory outcomes. ***Results:*** Being younger, female, white, married, non-smoker, having a normal BMI, reporting good health status, and living in a rural area was associated higher probability of participating in any survey. The difference between our estimates with or without IPWs ranged between 1-4%-points for IHD incidence, IHD mortality and CeVD mortality and supported evidence of increased risk of disease with higher chronic radiation exposure. For CeVD

incidence, the weighted estimate was 15%-points lower than the unweighted estimate, but it still suggested an increased risk of CeVD incidence from chronic exposure to ionizing radiation.

Conclusion: This study of medical radiation technologists who were chronically exposed to low-doses of radiation found consistent evidence of radiation-induced circulatory effects below the current 0.5Gy threshold. In addition, we found that nSES was independently associated with CD mortality and incidence in a group of US technologists occupationally exposed to low-doses of radiation, but there was no consistent evidence that it confounded the association between radiation and CD outcomes. We found a multiplicative two-way interaction between radiation and nSES, where residents of high nSES areas had higher risk of CD mortality than residents of low nSES exposed to the same radiation dose. In terms of our selection bias analysis, we found only a small impact of selection bias on our estimates of the association of cumulative radiation exposure and CD outcomes despite consistent differences in the characteristics of participants and non-participants.

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Organization

This dissertation is organized in five chapters. The first chapter provides background information followed by three chapters containing independent manuscripts and a last chapter with concluding remarks. Because the three manuscripts in chapters 2-4 are in preparation for peer-review, there may be some redundancy in the content.

Chapter 1

Introduction

Ionizing radiation and circulatory disease

Since the discovery of the X-ray by Roetgen in 1895, the use of radiation in medical applications has increased exponentially, particularly in the last few decades (1). Indeed, exposure to medical radiation increased 7-fold between 1980 and 2006 (2). A recent study analyzed Medicare data between 2009 and 2015 reported that, per 1,000 beneficiaries, the use of chest radiography nearly doubled in this period and the use of CT in 2015 was almost 60 times larger than in 2009 across the US (3). While these radiation-based technologies have improved diagnosis and treatment for patients, the risks from radiation exposure to patients and workers continue to be explored to date. Radiologic technologists are healthcare professionals that perform diagnostic or therapeutic procedures including X-ray, MRI, computed tomography (CT), fluoroscopy, or sonography equipment(4). It is estimated that 75% of the 9.8 million workers around the world who are exposed to man-made sources of radiation are medical workers (1,5). Despite this, most of the current knowledge about occupational exposure to radiation comes from studies on nuclear workers.

Cancer risks have dominated the landscape of radiation-related health effects and in most recent years, the dose at which these effects can directly be seen has been gradually lowered to reach about around 10–50 mSv for acute exposures and 50–100 mSv for chronic exposures (6). The mechanism through which radiation leads to cancer is generally well-understood, and it is centered on targeted and non-targeted mutational effects on DNA structures (7). Current evidence shows that exposure to ionizing radiation from occupational and environmental sources may also lead to other chronic diseases beyond cancer, including circulatory diseases (CD). Indeed, CDs

account for more than a third of deaths among groups exposed to radiation including patients, nuclear workers and atomic bomb survivors (8–10). Studies of patients with Hodgkin's lymphoma who had received high doses of radiotherapy reported an increased risk of cardiovascular disease outcomes (including myocardial infarction and heart disease mortality) at doses ranging between 42 and 45 Gy. Similarly, among irradiated breast cancer female patients, incidence of circulatory disease was elevated including all heart disease (8%), higher ischemic heart disease (ERR/Gy 0.10, 95%CI=0.05, 0.15) and cerebrovascular disease (ERR/Gy 0.20, 95%CI=0.14, 0.25), but not for other circulatory diseases (11).

However, as radiation doses decrease, the relationship between circulatory endpoints and exposure to ionizing radiation becomes less clear and consistent across studies. For example, in a cohort from UK Atomic workers, there was a marginally significant trend between increased cumulative badge dose and circulatory mortality but not so in a cohort of German uranium miners. The 15-country study of nuclear workers, a multinational retrospective cohort, combined data from multiple occupational cohorts and found an elevated risk of radiation on circulatory disease mortality (ERR/Sievert of 0.09, 95%CI: -0.43, 0.70) and for cerebrovascular diseases 0.88 (95%CI= -0.67, 3.16) with no evidence of a dose-response (8).

Shimizu *et al* evaluated whether there was a dose-response association between radiation exposure and the risk of heart disease and stroke among Japanese atomic bomb survivors after 53 years of follow up (12). They found an estimated excess relative risk (ERR) per gray of 9% (95%CI= 1%-17%) but this was not statistically significant below 1Gy. In terms of heart disease, the ERR/gray was 14% (95%CI= 6%-23%) and the dose-response relationship followed a linear trend even at doses below 1Gy. Specifically, the ERR/gray under 1Gy was 18% (95%CI= 3%-33%)(12). A meta-analysis summarized data from various epidemiological studies with low-to-moderate radiation doses (≤0.2Gy) and found evidence of a statistically significant excess relative

risk (ERR) for ischemic heart disease (ERR/Sv 0.10, 95%CI=0.05, 0.15) and cerebrovascular disease (ERR/Sv 0.20, 95%CI=0.14, 0.25), but not for other circulatory diseases. However, the considerable variability among these studies has made it challenging to reach a consensus on the non-cancer effects of radiation exposure. After reviewing existing data until 2013, the International Commission on Radiological Protection (ICRP) considered that there was strong evidence that radiation is associated with CD mortality at doses above 0.5mGy, but at levels below that, evidence was weak and inconsistent (13).

The biological mechanism of ionizing radiation on CD is not entirely understood, but it has been hypothesized that radiation may promote atherosclerosis which in turn may lead to heart and vascular disease. Evidence from *in vivo* and *in vitro* studies indicated that radiation doses above 1-2 Sv lead to cardiovascular damage including inflammation, oxidative stress, changes in platelet activity, DNA damage, endothelial dysfunction and cell death(14). Overall, the mechanism of radiation-induced vascular damage includes a combination of inflammatory alterations(7,14) (high levels of cytokine interleukin 6 (IL6), C-reactive protein (CRP), and cell adhesion molecules including ICAM1, VCAM1 and ELAM1), procoagulant alterations(14) (Von Willebrand expression, tissue factor levels, thrombomodulin downregulation), oxidative stress(7,14) (reactive oxygen species, eNOS downregulation, NFkB activation, mitochondria dysregulation) and genetic instability(7,14) (DNA damage, vascular senescence, apoptosis). Studies on the Japanese atomic bomb survivors have reported high levels of pro-inflammatory cytokines IL6, CRP, TNF-α, and INF-γ, IgG, IgA, and total immunoglobin levels (but also high levels of anti-inflammatory cytokine IL10 (15).

While it is possible that these multipronged mechanisms through which ionizing radiation can lead to circulatory damage are also relevant at low doses, there is limited and inconsistent evidence on this issue. In 2010, the Advisory Group in Ionising Radiation (AGIR) evaluated

evidence of radiation-induced biological damage on the circulatory system and concluded that many the inflammatory biomarkers found at high levels of ionizing radiation may have a different dose-response relations below 0.5Gy (16). Other studies observed markers of cardiovascular damage and other biological changes at an average dose of 93mGy (45-495mGy) including increased wall thickness and stenosis of the carotid arteries, increased arterial stiffness, and reductions in ejection fractions (14). More recently, a pilot study reported that the total microparticle content, a marker of cellular damage, was approximately 5 times higher in the blood of healthy medical workers occupationally exposed to low doses of radiation than in healthy controls(17). These results suggest that radiation may induce systemic inflammation and vascular damage which may in turn be prospectively associated with circulatory disease, but this remains particularly unclear at low doses.

Due to this uncertainty regarding CD effects from low protracted doses of ionizing radiation and the exponential increase in the use of medical radiation, it is particularly relevant to investigate this association among radiologic technologists who are chronically exposed to low-doses of ionizing radiation. The U.S. Radiologic Technologist (USRT) study is the largest longitudinal study of medical occupational radiation exposure to date (18). The cohort was enumerated in 1982 from the lists of the American Registry of Radiologic Technologists (ARRT) and was initially comprised of 146,022 radiologic technologists who resided in any US state or territory (19). Since then, more than 110,000 technologists have completed at least one of the four comprehensive questionnaire surveys regarding demographic characteristics, health status, employment history and exposure information (20). Current analyses from this cohort are consistent with a positive trend between increased chronic exposure to ionizing radiation and circulatory diseases, but results are unclear at low doses. Hauptmann *et al.* reported that technologists who were first employed before 1950 (who had higher cumulative radiation doses) had increased risk of mortality from circulatory diseases compared to post-1960(21). A more

recent study found a 34% increase in stroke incidence in technologists who worked with fluoroscopically guided interventional procedures compared to those who did not (22). These studies also explored incidence and mortality of other circulatory diseases, but they did not find clear associations. In ***manuscript 1***, we examine the dose-response relationship between low chronic doses of occupational radiation exposure and CD mortality in a large cohort of radiologic technologists.

Neighborhood context and circulatory disease

As with any multifactorial chronic diseases, individual risk factors of CD have been insufficient to explain the entire burden of disease. Among ecologic (or group-level) determinants of disease, the neighborhood context has been previously recognized as an important contributor to health and wellbeing. Neighborhoods have physical and social attributes that may impact human health, including environmental exposures such as air pollution, food and recreational services, the characteristics of the built environment, quality of housing, perceptions of safety and violence, social cohesion and network connections. All of these may impact health directly or indirectly through behavioral, physical and stress-related mediation(23). In addition, neighborhood structure is strongly patterned by race, ethnicity and social position which are recognized determinants of disease themselves.

Oftentimes, studies have bundled these neighborhood attributes into a single proxy variable: neighborhood socioeconomic status, or socioeconomic position (nSES). No single standard definition of nSES exists but it is commonly defined as a composite index from several census-level variables. Evidence suggests that this composite index is associated with specific neighborhood attributes. For example, Roblin found that nSES was associated with presence of sidewalks, street lights available at night, presence of walking/cycling paths nearby, and perception of safety from crime, or whether dogs are a problem(24). In turn, nSES has been

associated with health outcomes including mortality(25,26), cardiovascular risk factors(27), hypertension(28), and coronary heart disease(29). Winkleby *et al* combined the National Health Interview Survey, the 1990 census data and the National Death Index to determine if nSES was related to mortality. With approximately 60,000 participants from around the US, they found that living in a neighborhood with low nSES increases the risk of mortality beyond individual (25) socioeconomic status (iSES). A later study of 8,000 participants from 4 Californian cities further examined whether the influence of nSES on mortality differed by iSES. The study reported the highest mortality rates among individuals of low iSES living in neighborhoods of high nSES which suggests that income inequality is a key health determinant.

Circulatory diseases (CDs), which include all diseases of the heart and circulatory system, have been the main cause of death around the world for the past three decades (30). Like other chronic diseases, CDs are multifactorial in nature and are influenced by various biological, lifestyle and contextual factors, including the neighborhood environment (23). Indeed, there is extensive evidence that supports the association of increased CD morbidity and mortality among residents of neighborhoods of low nSES versus neighborhoods of high nSES (31). By 2009, over 40 studies had evaluated the association between neighborhood deprivation and coronary heart disease (CHD) (32). Most of the studies found increased risk of heart disease among individuals residing in low nSES areas compared to those living in more affluent areas(32). Using data from the Atherosclerosis Risk in Communities Study and the U.S. Census, the Diez-Roux and colleagues examined the association between nSES and incidence of CHD in communities in North Carolina, Mississippi, Minnesota and Maryland (29). They found that hazard ratios for CHD among low-income people living in disadvantaged neighborhoods were 3 times higher than high-income people in neighborhoods of high nSES even after controlling for personal income, education and occupation.

Similarly, Dragano and colleagues examined the association between risk factors of CD and neighborhood characteristics in a cross-national design with data from 9 industrial towns in Germany and Czech Republic(27). They found that smoking, obesity, and low physical activity, were significantly more common in deprived neighborhoods even after adjusting for individual characteristics. Morenoff *et al* estimated the effect of nSES disparities in the prevalence, awareness, treatment and control of hypertension using the Chicago Community Adult Health Study(28). The authors reported that hypertension was significantly negatively associated with neighborhood affluence and gentrification even after adjusting for individual risk factors. Although most studies of neighborhood influence on health come from observational studies, a major example of an experimental study is the Moving to Opportunity Study. This is a randomized housing mobility experiment that explored the effects of a voucher system to enable families from disadvantaged neighborhoods to move into more affluent communities(33). After 10-15 years of follow up, the study found that obesity and diabetes were, respectively, 4.61% and 4.31% lower among the voucher group than in the control(34).

Physical characteristics of the environment and health

Given the complexity of the neighborhood context and the distal nature of its relation to health it is difficult to ascertain a single sociobiological mechanism through which neighborhoods are related to CD morbidity and mortality. Therefore, multifactorial mechanisms have been proposed which include a variety of physical, social, biological determinants, and their interaction. Diez Roux and Mair argued that the physical environment and health are related through land use patterns, density, access to destinations, street connectivity and transportation systems, features of urban design, access to healthy food and recreational resources, neighborhood physical decay(23). The Multiethnic Study of Atherosclerosis (MESA) Neighborhood Study provided further evidence that: 1) density of recreational resources around participant's home was associated with greater probability of being physically active, 2) greater

neighborhood availability of healthy foods was consistently associated with better quality diet, and 3) better physical activity and food environments were associated with significantly lower BMI, insulin resistance and diabetes after adjustment for multiple measures of socioeconomic position and race/ethnicity (reviewed in Diez Roux & Mair, 2010). Roblin examined the association between nSES and neighborhood residential characteristics and found that nSES was statistically significantly associated with presence of sidewalks, street lights available at night, presence of walking/cycling paths nearby, and perception of safety from crime, or whether dogs are a problem. Taken together, these observations indicate that nSES is associated to specific physical neighborhood attributes, which have been individually linked to CD and/or their risk factors(24).

Social characteristics of the environment and health

In addition to physical attributes of neighborhoods, social characteristics have also been seen to influence development of CD. In a 2009 review, Chaix discusses several components of social environments that may impact development of coronary heart disease and include social cohesion, social fragmentation, social disorder; neighborhood identities as sources of reward or stigma; neighborhood norms and capital of knowledge; and neighborhood affective, cognitive, and relational experiences(32). Similarly, Diez Roux and Mair argue that elements of social cohesion and related elements may impact health through the transmission of health behaviors and norms, and by increasing or buffering stress levels among neighbors(23). These constructs have been more commonly associated with mental outcomes, but can also impact BMI, self-rated health and several circulatory outcomes. Specifically, greater levels of neighborhood social cohesion and social capital were significantly associated with lower cardiovascular disease incidence and mortality in two out of three studies. Finally, social and physical attributes of neighborhoods are likely to interact with each other (and with individual characteristics) to further impact development of CD. For example, stress may induce smoking and overeating,

potentiated by easily available unhealthy food sources; or urban design/street connectivity impacting on walkability and perceived safety from crime, which in turn may affect walkability.

Studies in occupational epidemiology, like the USRT study, have focused mostly on those exposures found in the workplace, and have only more recently considered the social, demographic and economic context surrounding the worker (35). Currently, there is little research on the influence of the neighborhood of residence on the effect of occupational exposures on disease, including medical radiation. Within the USRT and other occupational cohorts of ionizing radiation, the influence of the socioeconomic context of the workers has not been explored with respect to CD incidence and mortality. In addition, it is not yet known whether the effect of protracted low-doses of ionizing radiation may be confounded or modified by the nSES of residence. In ***manuscript 2*** we assess: 1) the effect of residential nSES on CD morbidity and mortality within the cohort, and 2) whether the previously described association between protracted low-dose occupational radiation exposure is either confounded or modified by neighborhood socio-economic status.

Potential connection of nSES with the association of occupational ionizing radiation and CD

No previous studies have assessed the impact of the residential neighborhood context on the link between ionizing radiation and CD. Thus, the mechanism for this potential confounding or moderating effect of nSES, is indirectly derived from parallel literature. Daniel *et al* proposed a *direct-contextual path* and an *indirect-cognitive path* connecting neighborhood context and cardiometabolic disease(36). The first component includes many of the physical attributes of neighborhoods previously described such as presence of green spaces, safe walking paths, availability of healthy food stores and density of fast-food establishments. These attributes have been linked to more direct risk factors of CD including physical activity, BMI, cholesterol and blood pressure. The second path accounts for behavioral and social attributes of neighborhoods

like social networks, group norms and behaviors. Through both paths, an area of low nSES may result in increased levels of chronic stress among residents which results in chronic activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and dysregulation of sympathetic-adrenal-medullary (SAM) system (36). Among other functions, these systems regulate levels of inflammation and other stress-related biomarkers such as fibrinogen, interleukin-6, C-reactive protein, and cell-adhesion molecule which are also involved in the mechanism of radiation-induced circulatory disease. Indeed, Clark *et al.* examined the association between state-level socioeconomic conditions and inflammatory biomarkers in a nation-wide cohort of 26,000 women(37). They found an association between affluent socioeconomic conditions and lower C-reactive protein, after adjustment for individual income. Because both exposures, occupational ionizing radiation and nSES are mediated by stress and inflammation, it is likely that we will see higher levels of CD morbidity and mortality among USRT participants that reside in neighborhoods of low nSES for similar cumulative exposures of radiation.

Impact of nSES and other subject characteristics on selection bias

Selection bias is a common phenomenon in epidemiology that occurs when methods of subject recruitment and follow-up result in selection of a sample that is not representative of the target population. When the exposure and the outcome, or factors affecting either one, have causal effects on study participation, restricting analysis to subjects who participate in the study can create, weaken, or strengthen an association between the exposure and outcome. In longitudinal cohort studies, non-participation is the proportion of people who refuse to participate at baseline (nonresponse) and the proportion of people who enter the study initially, but do not complete one or more of the follow-up steps(38–40). Thus, the resulting sample may not accurately represent the source population and, if attrition continues at each wave, the final sample might not even represent the original cohort.

This issue has been extensively studied and most studies report that non-participants are more likely to be younger, male, and non-white compared to subjects who participate at baseline and/or at follow-up waves(41–43). In addition, there are several health factors associated with increased participation including never smoking(44–47), having a normal BMI(44,47), and being generally healthier(41). According to these studies, the most important determinant of participation is a higher socioeconomic status and higher educational level. For example, a large nation-wide occupational study found that subjects in managerial positions (a proxy for high SES) were 3.15 times more likely to participate in the study than blue-collar workers(41). A smaller study in the U.S. also reported that subjects from low socioeconomic households were 1.33 and 1.74 times more likely to be lost-to-follow-up at 12 and 24 months, respectively(42). Fewer studies have explored the influence of neighborhood context on study participation. Namely, Chaix *et al.* found that the rate of study participation is higher among neighborhoods with higher levels of educational attainment, high median income, and high mean property value after controlling for individual education(48). These results suggest that the neighborhood context, the rate of participation and the onset of chronic diseases may be associated but have not been sufficiently explored.

The historical USRT cohort has not been immune to attrition and other selection processes. Over the three decades of the USRT study, participation among living eligible cohort members across study waves was 68% on average(49). If the characteristics of the radiologic technologists who decided to participate and remain in the study are systematically different from those who did not participate or were lost-to-follow-up, this might introduce bias to risk estimates. This might be problematic in this cohort because, although mortality outcomes are obtained through linkage with federal sources, exposure estimation and incidence of disease are dependent on questionnaire completion. Thus, conditioning on participation might be introducing selection bias to this historical cohort. The pattern of participation in the USRT cohort since its conception in

1982 and the potential impact of selection bias on risk estimates have not yet been explored. In response to this concern, ***manuscript 3*** has two main objectives: 1) describe the characteristics of participants and non-participants as they relate to completing the questionnaires at each of the four study waves of the USRT cohort, and 2) estimate the association between occupational radiation and circulatory disease (CD) morbidity and mortality, adjusting for possible selection bias using marginal structural models.

Chapter 2

Manuscript 1. Effects of low-to-moderate chronic radiation exposure on circulatory disease mortality in a large cohort of radiologic technologists

Introduction

It is well recognized that acute high doses of ionizing radiation, such as those received by the atomic bomb survivors, can lead to cancer and other fatal diseases (12,50). These risk estimates coming from radiation doses above 1000mGy have been extrapolated to low doses to set occupational limits of radiation exposure around the world (51). In the US, for example, the Occupational Safety and Health Administration (OSHA) limits occupational radiation doses to 5rems (50mSv) in any given year (52). However, since most occupational radiation exposures today are low-to-moderate protracted doses accumulated over time (53), limits based on acute exposures may not appropriately protect workers considering current working conditions. Existing studies on radiation health effects have not consistently identified the dose-response relationship between radiation exposure and disease at low protracted doses.

While cancer is a well-recognized outcome of radiation exposure, circulatory diseases (CD) account for more than a third of deaths among groups occupationally exposed to radiation (8,9). The International Commission on Radiological Protection (ICRP) considered that there was strong evidence to show that radiation is associated with CD mortality at doses above 500mGy of weighted colon dose (12), but evidence from low levels of radiation was weak and inconsistent (13). A meta-analysis summarized data from various studies with low-to-moderate radiation doses (≤500mSv) and found evidence of excess risk for ischemic heart disease (excess relative risk per sievert [ERR/Sv]=0.10, 95%CI=0.05, 0.15) and cerebrovascular disease (ERR/Sv= 0.20,

95%CI=0.14, 0.25), but not for other circulatory diseases (11). However, there was considerable variation between the included studies which highlighted the need for additional research.

Similarly, data from *in vivo* and *in vitro* studies have also shown that radiation doses above 1000mSv may lead to cardiovascular damage including inflammation, oxidative stress, changes in platelet activity, DNA damage, endothelial dysfunction and cell death (14). Altered levels of various biomarkers have been observed in populations exposed to radiation including cytokine interleukin 6 (IL6), C-reactive protein (CRP), Von Willebrand factor, reactive oxygen species, mitochondria dysregulation and genetic instability (7,14,15). Together, these studies suggest that radiation-induced systemic inflammation is a potential biological mechanism for circulatory disease but this remains unclear at low chronic doses (14,16).

The majority of occupational epidemiologic studies investigating the impact of radiation on CD are focused on nuclear workers. However, it is estimated that 75% of the 9.8 million workers around the world who are exposed to man-made sources of radiation are medical workers (1,5). Thus, it is particularly relevant to investigate the effect of radiation exposure on CD mortality among a population occupationally exposed to medical radiation. The U.S. Radiologic Technologist (USRT) study is the largest longitudinal study of medical occupational radiation exposure to date (18). Previous analyses from the USRT are consistent with a positive trend between increased chronic exposure to ionizing radiation and CD, but dose estimations have not been used in connection with CD mortality in this cohort (21,22). In this paper, we examine the dose-response relationship between low chronic doses of occupational radiation exposure and CD mortality in a large cohort of radiologic technologists.

Methods

Study design, setting and population

The USRT study is a longitudinal cohort study that started in 1982 with the enumeration of 146,022 radiation technologists who were certified for at least two years between 1926 and 1982 by the American Registry of Radiologic Technologists (ARRT). Data was collected through four extensive mail surveys. The first questionnaire (Q1) was completed between 1983 and 1989, the second questionnaire (Q2) between 1994 and 1998. Respondents to at least one of the first two questionnaires were mailed a third questionnaire (Q3) between 2003 and 2005, and a fourth questionnaire (Q4) between 2012 and 2013. For the purpose of this analysis, technologists were included if they completed Q1 and/or Q2 (110,374 participants). A total of 73,793 technologists (66.9% of participants) completed both questionnaires; 19,234 (17.4%) completed Q1 only and 17,347 (15.7%) completed Q2 only. The remaining 35,648 technologists registered with ARRT in 1982 (24.4%) did not complete either questionnaire so they were excluded from the analysis because estimates of occupational radiation exposure were not available. Additionally, 1,074 certified radiologic technologists who reported that they never worked and therefore were excluded from the analysis.

Circulatory disease (CD) mortality

The outcomes tested in this study include mortality from all circulatory diseases combined and the more specific conditions of, ischemic heart disease, and cerebrovascular disease. Vital status for all participants was determined from baseline until December 31st, 2012. For decedents, underlying causes of death were obtained from NDI-*Plus* using ICD 8, 9 and 10 codes (22). Specific outcomes evaluated were mortality from: all circulatory diseases (ICD-8 390–458; ICD-9 390–459; ICD-10 I00–I99), ischemic heart disease (ICD-8 410–414; ICD-9 410–414; ICD-10 I20–I25), and cerebrovascular diseases (ICD-8 430-438; ICD-9 430-438; ICD-10 I60-I69). Other CD subtypes were also considered but are not presented in this paper. Decedents from other underlying causes of death were classified as non-CD mortality cases.

Cumulative ionizing radiation exposure

Cumulative exposure to ionizing radiation has been estimated for 110,374 participants as previously described (54,55). Briefly, personal annual exposure and organ specific absorbed doses estimated for the years 1916-1997 using information from personnel monitoring badge records, years working as radiation technologists, individual employment practices based on the first three surveys (e.g. frequency of performing certain procedures, shielding, holding patients), individual apron usage from the second and third surveys (Q2 and Q3), and literature-reported measurements for years when badge doses were not available. In this study, two main metrics of cumulative radiation exposure were used in the analysis: 1) the estimated effective badge dose to the whole body (mSv) which is used in occupational health monitoring, and 2) cumulative absorbed radiation doses to the heart, brain and thyroid (mGy) to characterize the biological relation between radiation and CD.

Covariates

Potential confounders of the association between ionizing radiation and circulatory disease development were specified based on directed acyclic graphs (DAGs) (Figure 2 [Supplemental Figure S1]). The following variables were self-reported at baseline (Q1, or Q2 if Q1 was not completed): age, sex, race, Hispanic ethnicity, education level, smoking habits, and BMI. In addition, diagnoses of hypertension, diabetes and high cholesterol were included as covariates; they were self-reported in Q2 and considered to be baseline conditions since they had not been previously inquired in Q1.

Data Analysis

Circulatory disease mortality risks were estimated using discrete time hazard models with calendar year as a time scale and age as a time-varying covariate. Follow-up started in 1983 and ended at the earliest of the following events: year of death, year of loss-to-follow-up (censored) or

2012 when the latest mortality data were ascertained (censored). Cumulative annual badge dose and organ doses were treated as time- varying variables. At each time point, a person's exposure was the sum of all yearly doses up to and including that year. Additionally, several exposure lag periods were considered in sensitivity analyses: 0, 5, 10 and 15 years. For instance, a lag time of 10 years meant that the cumulative radiation exposure in 1990 was the sum of all the yearly doses up to and including 1980.

Radiation dose was included in the model as continuous variables and also divided into four categories (cumulative badge dose: >0-49.9, 50-149.9, 150-399.9, and 400+ mSv; cumulative thyroid dose: >0-24.9, 25-99.9, 100-199.9, and 200+ mGy; cumulative heart dose: >0-9.9, 10-99.9, 100-199.9, and 200+ mGy; and cumulative brain dose: >0-9.9, 19-24.9, 25-99.9, and 100+ mGy). The cut points were selected considering the skewed distribution of the data and after modeling the crude association between radiation exposure and CD-mortality with quadratic splines. A test for linearity was conducted by modeling these categories ordinally.

Three models were tested to account for confounding and selection bias. Specifically, model 1 adjusted only for age, model 2 added sex, race, ethnicity, smoking habits and BMI as collected in either Q1 or Q2 to model 1, and model 3 added diagnoses of hypertension, diabetes and high cholesterol to model 2 which were only available for respondents of Q2. To assess the presence of effect modification by gender, BMI and year of certification, an interaction term was included in the model and stratified analysis was presented separately. Hazard ratios and 95% confidence intervals adjusted for age and cohort effects are presented as measures for the impact of radiation exposure on CD mortality. Missing data were not imputed in this analysis.

Results

A total of 109,300 technologists who responded to the baseline questionnaire, reported working for at least one year between 1926 and 1997 and had annual dose estimates were

included in this study. The median follow-up time was for this sample was 27 years. At the end of follow-up in 2012, there were a total of 14,896 deaths among this group (13.6%). From these, 4,458 (30.0%) had circulatory disease as the underlying cause of death. Table 1 describes demographic, occupational and health characteristics of the sample. In general, the cohort was predominately female, white, non-Hispanic, and the average birth year was 1946 (range: 1890-1966). In terms of occupational characteristics, 32% of CD cases had worked as radiation technologists for more than 30 years compared to 25.7% of decedents from non-CD causes and 11.1% of those who were alive in 2012. The distribution of cumulative radiation exposure was highly skewed in this cohort with a median of 46.0 mSv (range: 0 – 2972 mSv). Technologists who died from CD causes had a median cumulative badge dose of 154 mSv, those who died of other causes 102mSv, and technologists alive in 2012 had a median dose of 43mSv. Finally, participants who died of CD causes had a worse health profile at baseline than participants who were alive at the end of follow-up (including a higher proportion of obese or overweight people, current heavy smokers, and those with a diagnosis of hypertension, diabetes or high cholesterol).

[Table 1]

Out of 4,581 CD deaths, 2,328 (50.8%) were classified as ischemic heart disease (IHD) and 754 (16.5%) were classified as cerebrovascular disease (CeVD) (Table 2). Other CD subtypes are detailed in this table but were not examined separately.

[Table 2]

Treating cumulative radiation doses as continuous, we found evidence of increased risk of CD mortality with increased exposure to occupational radiation (Table 3). Although the specific magnitude of the effect estimates varied depending on whether badge dose or organ dose was

used as a measure of exposure, and which covariates were included in the model, all hazard ratio point estimates had a consistent harmful direction. For instance, for every 100mSv increase in cumulative badge dose, the risk of mortality from any CD increased in 3% (95% CI 2-4%) after adjusting for age, sex, race, ethnicity, BMI and smoking. In terms of CD subtype, the hazard ratio per 100mGy increase in heart dose for IHD was 1.07 (95% CI 1.02 – 1.13), adjusting for age, sex, race, ethnicity, BMI and smoking. Adjusting for the same covariates, the hazard ratio per 100mGy increase in brain dose was 1.39 (95%CI 1.14 – 1.64) for CeVD. Different lag periods were considered during sensitivity analyses to model the delayed effect of radiation exposure on the circulatory system. Considering a 5-, 10- and 15-year lag period, we did not find differences in effect estimates between the four lag periods (Table 6 [Supplemental Table S1]). This was also the case for models using organ doses and subclassifications of disease (not shown).

[Table 3]

Categorical analysis suggested a linear dose-response trend between cumulative exposure to occupational medical radiation and CD mortality. Figure 1 shows the estimated hazard ratios of CD mortality for categories of radiation exposure using badge and organ doses using calendar year as a time scale and adjusted for age, sex, race, ethnicity, BMI and smoking at baseline. Compared to technologists who accumulated less than 50mSv of radiation exposure, technologists who accumulated over 400mSv of radiation had a HR of 1.60 (95%CI 1.39, 1.84, p trend <0.001). For IHD mortality, the HR among technologists with more than 200mGy of radiation to the heart was 1.67 times larger than the risk for those with a cumulative heart dose less than 10mGy (95%CI 1.30, 2.15, p trend <0.001). Similarly, the HR for CeVD mortality was 1.62 times larger among technologists with more than 100mGy of radiation to the brain than those with less than 10mGy (95%CI 1.23, 2.12, p trend=0.003).

[Figure 1]

To better understand the risk of CD mortality at low doses of cumulative radiation exposure, we restricted the analysis by excluding participants below and above a range of radiation badge doses (Table 4). Exclusively including observations above 500mSv of cumulative badge doses (N=1,167) in the model, the HR and 95%CI for a 100mSv increase in cumulative dose was close to the null for all mortality outcomes (HR: 1.01, 95%CI: 0.99 - 1.04 for overall CD mortality, HR: 1.01, 95%CI: 0.98 - 1.04 for IHD mortality, and HR: 1.01, 95%CI: 0.97-1.07 for CeVD mortality). In contrast, the risk estimates for a 100mSv increase in cumulative badge dose were consistently elevated for all CD mortality even when restricting the dose range below 500mSv. For instance, for cumulative doses between >0 and 300mSv, the HR of mortality for a 100mSv increase in cumulative badge dose was 1.18 (95%CI: 1.11, 1.24) for overall CD mortality, 1.19 (95%CI: 1.10, 1.28) for IHD mortality and 1.15 (95%CI: 1.00, 1.31) for CeVD mortality.

[Table 4]

Analysis of effect modification by gender, BMI and certification year is summarized in Table 5. There was only evidence of a multiplicative interaction between gender and cumulative badge dose for CD and IHD mortality ($p<0.001$ for both), but not for CeVD mortality ($p=0.66$). Specifically, the risk estimates for CD mortality for a 100mSv increase in exposure were slightly higher for women (HR=1.03, 95%CI 1.02, 1.05) than men (HR=1.02, 95%CI 1.00, 1.05). In terms of BMI at baseline, people with normal weight had the lowest hazard ratio estimates for all CD combined and for IHD mortality, but there was no statistical evidence of effect modification by BMI. Similarly, we did not find statistical evidence to support a multiplicative interaction between certification year and cumulative badge dose.

[Table 5]

Discussion

We observed a dose-response relationship between cumulative occupational medical radiation exposure and circulatory disease mortality in radiologic technologists. Independent of whether badge dose or organ doses were considered, there was consistent evidence that higher doses of cumulative radiation increased the risk of death from all types of CD combined and from IHD and CeVD alone. Categorical analysis of radiation doses on CD outcomes was consistent with the continuous models suggesting that higher levels of cumulative medical radiation increase the risk of CD, IHD and CeVD mortality. Analyses with different lengths of lag time did not change the direction or magnitude of the effect of radiation on CD mortality. Finally, analysis of effect modification showed that there was evidence of an interaction between gender and cumulative badge dose in which women had slightly higher estimates than men. We did not find evidence that risk estimates of radiation on CD mortality varied by BMI or certification year.

The findings of this study must be interpreted in light of some limitations. First, the exact dose of radiation that participating technologists received each year was not directly measured, but estimated through dosimetry reconstruction (54). While some uncertainty remains around the specific exposure estimates, the comprehensive nature of the dose reconstruction was effective at ranking cumulative dose within the cohort. These dosimetry estimates were validated by analyzing the rate of chromosomal translocations in bone marrow for a subset of samples which showed a correlation between dose estimates and chromosomal changes (56). It is possible that our results are impacted by the healthy worker effect because technologists who were sick may have worked less and accrued less cumulative exposure than their healthier counterparts. To avoid introducing further healthy worker bias, we excluded technologists who did not work between 1926 to 1982 (and therefore accrued no occupational radiation) from our analysis.

Second, it is possible that the underlying cause of death obtained from NDI-Plus may have not been appropriately coded. Studies have reported that CD diagnoses tend to be overreported as the underlying cause of death in death certificates which may result in overestimating the number of CD cases (57,58). There is no evidence that this misclassification bias of the outcome is related to radiation exposure, so the impact on these results may be negligible, but undetermined. The measurement of co-morbid conditions was limited to what was available from the second survey. Consequently, a large proportion of the cohort had missing data for these potentially important confounding factors. Although the magnitude of the effect was higher when including all covariates in the model, it did not change the direction of the effect. Finally, for many technologists, exposure began many years before the cohort started in 1982 so all participants were survivors to this date. Thus, our results may suffer from some degree of survival-related selection bias that should be further investigated in future studies.

Previous analyses from this cohort are consistent with a positive trend between increased chronic exposure to ionizing radiation and CD, but dose estimations have not been used in connection with CD mortality in this cohort. Hauptmann *et al.* reported that technologists who were first employed before 1950 (who had higher cumulative radiation doses) had increased risk of mortality from circulatory diseases compared to technologists starting post-1960 (21). A more recent study found a 34% increase in stroke incidence in technologists who worked with fluoroscopically guided interventional procedures compared to those who did not (22). The current study incorporated radiation dose estimates for 109,300 technologists and found evidence of a linear increase in CD mortality risk of 3% (95% CI 1-4%) for every 100mSv increase in cumulative badge dose.

Our results contribute to the growing body of evidence supporting an elevated risk of CD mortality even at low protracted doses of ionizing radiation. Two meta-analyses have summarized the existing evidence of low-dose radiation-induced circulatory disease including occupationally, therapeutically and environmentally exposed samples (11,59). Taken together, results from these analyses provide evidence to support a linear-no-threshold relationship between radiation and circulatory disease at cumulative doses under 0.5Gy. Restricting the analysis to studies of low-dose rate of radiation exposure, this meta-analysis found an excess relative risk per Gy (ERR/Gy) of 0.114 (95%CI=-0.003, 0.232) for IHC mortality and an ERR/Gy of 0.175 (95%CI=-0.058, 0.408) for CeVD mortality(59).

Among the studies included in these reviews, the Life Span Study (LSS) evaluated the relation between radiation exposure and the risk of stroke and heart disease (HD) mortality among Japanese atomic bomb survivors after 53 years of follow up (12). For all HD mortality, the ERR/Gy was 0.14 (95%CI= 0.06, 0.23) with evidence of a linear dose-response relationship below 1 Gy. However, this increased risk was not evident when restricting the analysis to doses below 0.5 Gy. A more recent publication from this cohort reported an elevated risk of HD mortality even when restricting the analysis to doses below 0.7Gy without an evident threshold (ERR/Gy= 0.25, 95%CI=0.08, 0.43) (60). The direction of our estimates is consistent with LSS results but may not be directly compared due to differences in the mode and length of radiation exposure. While atomic bomb survivors experienced high acute doses of ionizing radiation, medical radiation technologists in the USRT were exposed to low protracted doses across their life.

The pattern of exposure to radiation experienced by medical technologists more closely resembles the pattern of other groups occupationally exposed to radiation, such as nuclear

workers (61–63). A recent analysis of non-cancer outcomes among 308,297 nuclear workers from France, the United Kingdom, and the US (INWORKS cohort) reported an elevated mortality risk for all CD mortality, IHD and CeVD (62). At cumulative doses below 0.7 Sv, the ERR/Sv was 0.22 (90%CI 0.08, 0.37) for all CD mortality combined, 0.18 (90%CI 0.004, 0.36) for IHD mortality and 0.50 (90%CI 0.12, 0.94) for CeVD. The categorical model supported a linear dose-response association between radiation and CD mortality, but this was not entirely consistent when analyzing IHD or CeVD separately. Our estimated risk of CD mortality per 1 Sv increase in cumulative radiation dose was 30% (95%CI: 10, 40%) which is similar in size and direction to the INWORKS results. However, the exact magnitude of the effect estimate cannot be directly compared due to differences in model choice and measure of effect.

We found evidence of a dose-response relationship between cumulative radiation exposure and CD mortality even when restricting the analysis to doses below 0.5Sv. Indeed, the risk for each additional 100mSv in cumulative badge dose was steeper for doses below 500mSv than doses above this level. This plateauing effect of cumulative radiation on CD mortality is likely due to survival bias; early workers accumulated the highest levels of radiation but if they survived long enough to participate in the study, they were likely more resistant to the effects of radiation than the average radiation worker.

Other studies of cumulative occupational exposure to radiation reported similar results when restricting dose ranges. Gillies *et al* reported excess relative risks estimates for CD mortality that excluded zero down to a restricted maximum dose of 300mSv (ERR/Sv=0.28, 90%CI 0.03, 0.53) (62). For IHD mortality, the linear ERR/Sv among these nuclear workers was only consistently above 0 when limiting the analysis to doses below 500mSv but was not clear when limiting to

400mSv (62). In our analysis of medical radiation technologists, we found evidence of a consistently elevated risk of CD mortality even when we restricted the analysis to doses below 200mSv of cumulative radiation exposure. A sub-analysis focused on UK radiation workers restricted the analysis to different doses and showed that risk of HD mortality was consistently elevated for cumulative doses up 200mSv but not if the analysis was restricted to doses below 100mSv (63). For CeVD mortality, we did not find evidence of a linear dose-response below 300mSv while Gillies *et al* reported an elevated risk of death even when restricting to doses below 100mSv (ERR/Sv of 2.07, 90%CI: 0.43, 3.80) (62). A study of tuberculosis fluoroscopy patients in Canada and Massachusetts found evidence of a positive dose-response association between radiation levels below 0.5Gy and CD mortality (64). For all CD mortality, the ERR/Gy was 0.246 (95%CI=0.036, 0.469) at doses between 0 and 0.5Gy. This effect was consistent when restricting the analysis to doses below 0.4Gy and 0.3Gy with some loss of statistical power at lower doses. Similarly, there was an elevated risk of IHD mortality (ERR/Gy = 0.268, 95%CI= 0.003, 0.552) at doses below 0.5 Gy but not for CeVD (ERR/Gy = 0.441, 95%CI= -0.119, 1.090).

In this study, our results did not change when considering the lag period between cumulative occupational exposure and CD mortality outcomes which is both consistent (61,65) and discrepant (8) with existing research. Some studies have found that linear effect estimates tend to moderately increase with longer lag periods, but this is not entirely consistent across CD subclassification (62,63). In contrast, other studies have reported a decreasing trend in mortality risk for longer lag periods (64).

We found evidence of an interaction between gender and exposure to radiation in relation to CD and IHD mortality which aligns with some studies (62,66), but not others (8,60). Consistent

with our findings, the INWORKS study of nuclear workers reported higher risk estimates for both IHD and CeVD among women than men (62). When we stratified by certification year, we only observed an elevated mortality risk that excluded the null among radiation technologists who were certified before 1950. However, there was no statistical evidence to support the interaction between certification year and radiation. Other studies of radiation-related CD effects have reported some cohort effects, but the direction was not entirely consistent among them (8,61–63).

This study of medical radiation technologists in the US contributes evidence to support a dose-response between cumulative radiation exposure and CD mortality at doses below 0.5Sv. Our results are consistent with many other studies of long-term exposure to low-doses of ionizing radiation such as those with nuclear workers. In addition, this study uniquely focuses on occupational exposure to radiation in a medical setting as opposed to nuclear power plants. Although medical radiation use has steeply increased around the world in the recent decades (67), this particular worker population has been underrepresented among radiation-related studies. Our results indicate an association between CD mortality and occupational ionizing radiation exposures below the current radiation protection standards. (52).

Conclusions

There is an ongoing debate regarding the non-cancer effects of ionizing radiation exposure at low doses. This study of medical radiation technologists who were chronically exposed to low-doses of radiation provides evidence of radiation-induced circulatory effects below the current annual 0.5Sv threshold. Further follow-up of this cohort will help clarify the potential effect extending to persons certified after 1950.

Tables and figures

Table 1. Demographic, occupational and health characteristics of 109,300 radiation technologists

	Circulatory disease		Other cause of death		Alive in 2012	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Total	4,458	100.0	10,438	100.0	94,404	100.0
Demographic						
Birth year						
<1930	2,439	54.7	3,735	35.8	2,766	2.9
1930-39	973	21.8	2,728	26.1	11,019	11.7
1940-49	740	16.6	2,569	24.6	32,597	34.5
1950+	306	6.9	1,406	13.5	48,022	50.9
missing	0	0.0	0	0.0	0	0.0
Sex						
male	1,934	43.4	3,651	35.0	20,812	22.0
female	2,524	56.6	6,787	65.0	73,592	78.0
missing	0	0.0	0	0.0	0	0.0
Race						
white	4,141	92.9	9,768	93.6	89,019	94.3
black	170	3.8	403	3.9	2,934	3.1
other	135	3.0	244	2.3	2,374	2.5
missing	12	0.3	23	0.2	77	0.1
Ethnicity						
non-Hispanic	4,327	97.1	10,172	97.5	91,662	97.1
Hispanic	92	2.1	193	1.8	2,408	2.6
missing	39	0.9	73	0.7	334	0.4
Educational attainment						
Vocational, Highschool or less	583	13.1	930	8.9	3,837	4.1
Radiation Technology	1,565	35.1	3,976	38.1	41,791	44.3
Some college	1,535	34.4	3,545	34.0	30,958	32.8
missing	775	17.4	1,987	19.0	17,818	18.9
Occupational						
Certification year						
<1950	1,034	23.2	1,369	13.1	679	0.7
1950-59	1,572	35.3	3,364	32.2	8,176	8.7
1960-69	1,170	26.2	3,305	31.7	26,809	28.4
1970-79	651	14.6	2,261	21.7	52,911	56.0
1980+	31	0.7	139	1.3	5,829	6.2
missing	0	0.0	0	0.0	0	0.0
Years working as Rad-tech						
>0-10yrs	876	19.7	2,366	22.7	18,272	19.4
11-20yrs	982	22.0	2,474	23.7	26,144	27.7
21-30yrs	1,132	25.4	2,856	27.4	39,450	41.8
>30yrs	1,468	32.9	2,742	26.3	10,538	11.2
missing	0	0.0	0	0.0	0	0.0
Cumulative radiation dose (mSv)						
Median (range)	154	(0.5 - 2972)	102	(0.5 - 2777)	43	(0.5 - 1912)
>0-49.9mSv	718	16.1	2,687	25.7	55,053	58.3
50-149.9mSv	1,456	32.7	4,075	39.0	34,378	36.4
150-399.9mSv	1,496	33.6	2,743	26.3	4,754	5.0
400+ mSv	788	17.7	933	8.9	219	0.2
missing	0	0.0	0	0.0	0	0.0

Table 1. *(continued)*

Characteristic	Circulatory disease n	Circulatory disease %	Other cause of death n	Other cause of death %	Alive in 2012 n	Alive in 2012 %
Health at baseline						
BMI						
underweight	141	3.2	357	3.4	2,906	3.1
normal weight	1,955	43.9	5,473	52.4	60,213	63.8
overweight	1,532	34.4	3,006	28.8	21,948	23.2
obese	830	18.6	1,602	15.3	9,337	9.9
missing	0	0.0	0	0.0	0	0.0
Smoking status						
never	1,437	32.2	3,335	32.0	46,675	49.4
ex-smoker, <=20p-yr	726	16.3	1,639	15.7	22,166	23.5
ex-smoker, >20p-yr	1,210	27.1	2,575	24.7	11,563	12.2
current, <=20p-yr	231	5.2	620	5.9	7,299	7.7
current, >20p-yr	828	18.6	2,233	21.4	6,501	6.9
missing	26	0.6	36	0.3	200	0.2
Hypertension						
no	1,631	36.6	4,719	45.2	67,767	71.8
yes	1,127	25.3	1,920	18.4	10,541	11.2
missing	1,700	38.1	3,799	36.4	16,096	17.1
Diabetes						
no	2,411	54.1	5,985	57.3	76,478	81.0
yes	347	7.8	654	6.3	1,830	1.9
missing	1,700	38.1	3,799	36.4	16,096	17.1
High cholesterol						
no	2,205	49.5	5,601	53.7	70,568	74.8
yes	553	12.4	1,038	9.9	7,740	8.2
missing	1,700	38.1	3,799	36.4	16,096	17.1

Table 2. Classification of circulatory disease (CD) mortality among 109,300 radiation technologists who responded to questionnaire 1 (Q1) or questionnaire 2 (Q2) and reported working for at least one year

Outcome classification	N	% of CD
Circulatory disease mortality	4,458	
All heart disease	3,520	79.0
Rheumatic diseases	33	0.7
Hypertensive diseases	236	5.3
Ischemic heart diseases (IHD)	2,265	50.8
Acute myocardial infarction (AMI)	876	19.6
Other IHD	1,389	31.3
Pulmonary heart disease	99	2.2
Other heart disease	887	19.9
Cerebrovascular disease (CeVD)	735	16.5
Stroke	638	14.3
Other CeVD	97	2.2
Other circulatory disease	203	4.6

Table 3. Estimated hazard ratios⁋ of circulatory disease (CD) mortality using different continuous metrics of cumulative exposure to occupational radiation and covariate adjustment

Radiation metric	Model 1 n=109,300		Model 2 n=108,583		Model 3 n=68,037	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
All circulatory disease (CD)						
Cumulative badge dose (100mSv)	1.03	(1.01, 1.04)	1.03	(1.02, 1.04)	1.06	(1.03, 1.09)
Cumulative thyroid dose (100mGy)	1.04	(1.02, 1.06)	1.04	(1.02, 1.06)	1.08	(1.04, 1.11)
Ischemic heart disease (IHD)						
Cumulative badge dose (100mSv)	1.02	(1.01, 1.04)	1.03	(1.01, 1.04)	1.07	(1.03, 1.11)
Cumulative heart dose (100mGy)	1.06	(1.02, 1.11)	1.07	(1.02, 1.13)	1.20	(1.08, 1.34)
Cerebrovascular disease (CeVD)						
Cumulative badge dose (100mSv)	1.04	(1.01, 1.06)	1.04	(1.01, 1.07)	1.05	(0.99, 1.10)
Cumulative brain dose (100mGy)	1.40	(1.15, 1.65)	1.39	(1.14, 1.64)	1.47	(0.99, 1.99)

⁋ HR and 95% CI are estimated using discrete time hazard models with calendar year as a time scale and age as a time-varying covariate for an increase of 100mSv in badge dose, 100mGy increase in thyroid and heart doses, and 100mGy increase in brain dose. Follow-up started in 1983 and ended in 2012.

Model 1 adjusted only for age and calendar year

Model 2 added sex, race, ethnicity, smoking habits and BMI as collected in either Q1 or Q2 to model 1

Model 3 added diagnoses of hypertension, diabetes and high cholesterol to model 2 which were only available for respondents of Q2.

CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease

Table 4. Effect of restricting dose ranges on linear mortality estimates for all circulatory disease, ischemic heart disease and cerebrovascular diseases (HR/100mSv increase in badge dose)

Dose range	Total	All CD mortality		IHD mortality		CeVD mortality	
	N	HR*	95% CI	HR*	95% CI	HR*	95% CI
Overall (>0-2972 mSv)	108,583	1.03	(1.02, 1.04)	1.03	(1.01, 1.04)	1.04	(1.01, 1.07)
Restricting dose range							
≥500 - 2972mSv	1,167	1.01	(0.99, 1.04)	1.01	(0.98, 1.04)	1.01	(0.97, 1.07)
<500mSv	107,416	1.13	(1.09, 1.16)	1.12	(1.07, 1.18)	1.10	(1.02, 1.20)
<400mSv	106,704	1.15	(1.10, 1.20)	1.15	(1.08, 1.22)	1.15	(1.04, 1.28)
<300mSv	105,472	1.18	(1.11, 1.24)	1.19	(1.10, 1.28)	1.15	(1.00, 1.31)
<250mSv	104,411	1.17	(1.10, 1.25)	1.18	(1.07, 1.29)	1.13	(0.97, 1.32)
<200mSv	102,538	1.19	(1.09, 1.29)	1.18	(1.05, 1.33)	1.19	(0.97, 1.46)
<150mSv	98,934	1.17	(1.04, 1.32)	1.20	(1.01, 1.42)	1.11	(0.84, 1.48)
<100mSv	90,892	1.26	(1.03, 1.53)	1.21	(0.92, 1.60)	1.68	(1.02, 2.77)

*****HR and 95% CI estimated using discrete time hazard models with calendar year as a time scale and age as a time-varying covariate for an increase of 100mSv in badge dose adjusted by sex, race, ethnicity, BMI and smoking at baseline.
CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease

Table 5. Stratified risk of cumulative radiation badge dose (per 100mSv increase) for circulatory disease (CD) mortality among 109,300 radiation technologists

	All CD combined		IHD		CeVD	
Badge dose (100mSv)	**HR***	**95% CI**	**HR***	**95% CI**	**HR***	**95% CI**
Sex						
Male	1.02	(1.00, 1.05)	1.02	(0.99, 1.05)	1.04	(0.99, 1.10)
Female	1.03	(1.02, 1.05)	1.03	(1.01, 1.05)	1.04	(1.01, 1.07)
p-value interaction		*<0.001*		*<0.001*		*0.66*
BMI						
Underweight	1.08	(1.02, 1.13)	1.10	(1.01, 1.19)	1.07	(0.96, 1.18)
Normal weight	1.02	(1.00, 1,04)	1.01	(0.99, 1.04)	1.04	(1.01, 1.07)
Overweight	1.04	(1.01, 1.07)	1.04	(1.00, 1.07)	1.05	(1.00, 1.11)
Obese	1.03	(0.98, 1.08)	1.05	(0.98, 1.11)	0.97	(0.88, 1.08)
p-value interaction		*0.07*		*0.37*		*0.69*
Year certified						
<1950	1.04	(1.02, 1.06)	1.04	(1.02, 1.07)	1.05	(1.01, 1.09)
1950-59	1.02	(0.99, 1.05)	1.02	(0.98, 1.06)	0.99	(0.93, 1.06)
1960-69	1.00	(0.93. 106)	0.98	(0.91, 1.05)	1.03	(0.95, 1.12)
1970-79	1.09	(0.93, 1.28)	0.98	(0.80, 1.20)	1.41	(0.90, 2.20)
1980+	1.75	(0.77, 3.97)	2.32	(0.87, 6.20)	0.09	(0.01, 1.36)
p-value interaction		*0.84*		*0.67*		*0.49*

*****HR and 95% CI estimated using discrete time hazard models with calendar year as a time scale and age as a time-varying covariate for an increase of 100mSv in badge dose adjusted by sex, race, ethnicity, BMI and smoking at baseline.
CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease

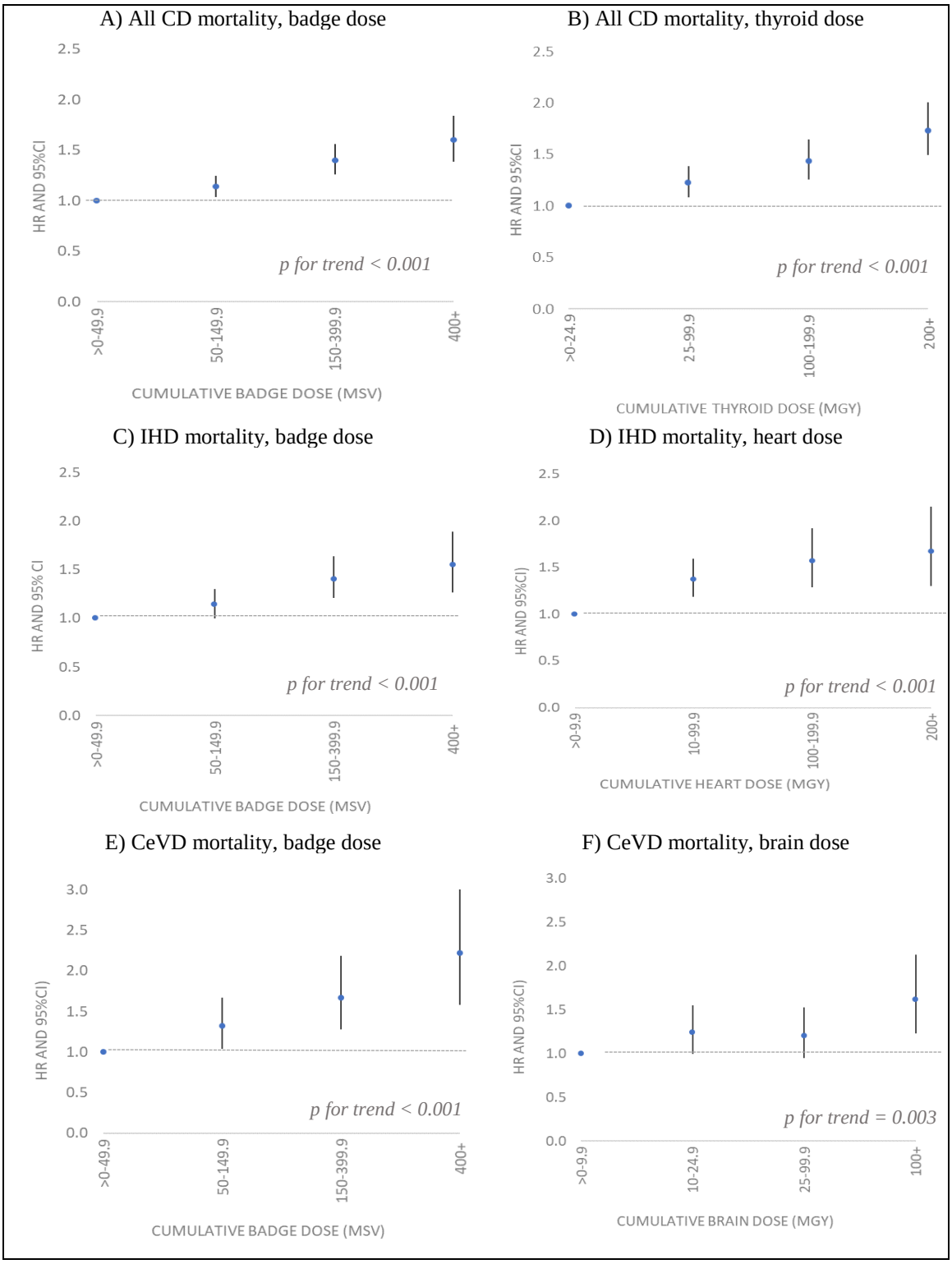

Figure 1. Estimated hazard ratios of circulatory disease (CD) mortality for categories of radiation exposure using badge and organ doses.

HRs and 95% CI estimated using discrete time hazard models with calendar year as a time scale and adjusted for age, sex, race, ethnicity, BMI and smoking. Left panels use cumulative badge doses (mSv) as the exposure metric, right panels use specific organ doses. The first row shows HR for all

circulatory (CD) mortality combined, the second row for ischemic heart disease (IHD) and the third for cerebrovascular disease (CeVD).

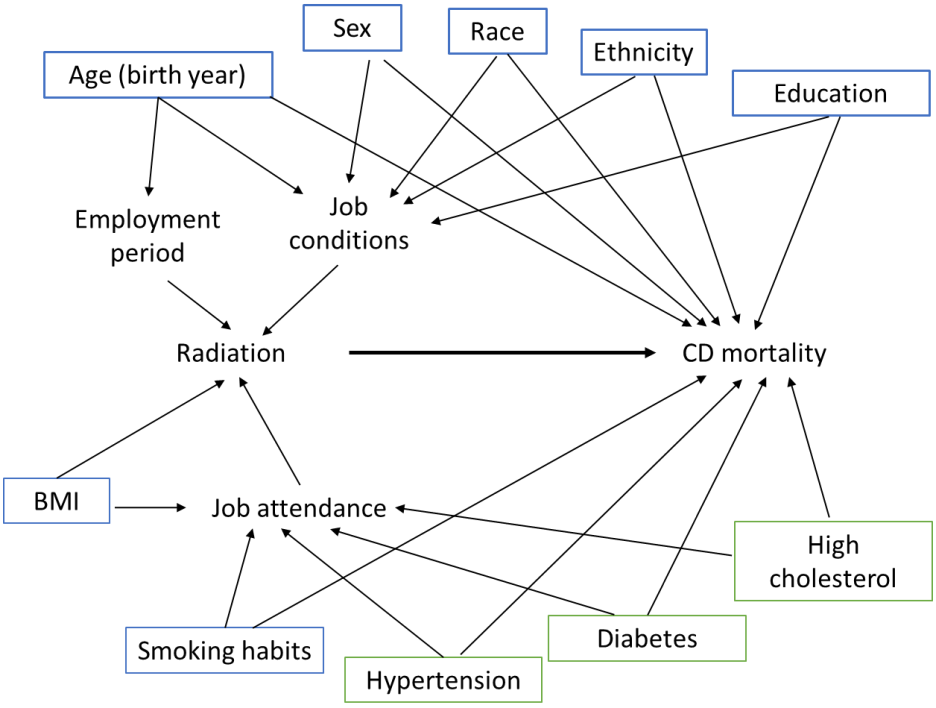

Figure 2. [Supplemental Figure S1] Directed Acyclic Graph (DAG) of confounders of the association between cumulative exposure to occupational radiation on circulatory disease (CD) mortality among radiologic technologists

Table 6. [Supplemental Table S1] Estimated hazard ratios of circulatory disease (CD) mortality by different lag periods of cumulative radiation exposure (per 100mSv of badge dose)

All CD mortality	HR*	95%CI LL
Cumulative badge dose (100mSv)		
0-yr lag	1.0298	(1.0162, 1.0435)
5-yr lag	1.0299	(1.0162, 1.0436)
10-yr lag	1.0300	(1.0163, 1.0437)
15-yr lag	1.0297	(1.0160, 1.0435)

*****HR and 95% CI estimated using discrete time hazard models with calendar year as a time scale and adjusted by age, sex, race, ethnicity, BMI at baseline and smoking at baseline

Chapter 3

Manuscript 2. Influence of the neighborhood socioeconomic status on the association between ionizing radiation and circulatory disease morbidity and mortality

Introduction

Studies in occupational epidemiology have focused mostly on exposures found in the workplace, and have only more recently considered the social, demographic and economic context surrounding the worker (35). Currently, there is little research on the influence of the neighborhood of residence on the effect of occupational exposures on disease. Neighborhoods have physical and social attributes that may impact human health, including environmental exposures such as air pollution, food and recreational services, characteristics of the built environment, quality of housing, perceptions of safety and violence, and social cohesion and network connections (23). These attributes of the neighborhood context may impact health directly or indirectly through behavioral, physical and stress-related mediators, or they may act as effect modified of the associations between workplace exposures and health outcome.

These neighborhood attributes are closely related with the socioeconomic status of the area, where lower income neighborhoods tend to have higher concentration of damaging exposures (68). Neighborhood socioeconomic status (nSES) has been commonly defined as a composite index from several census-level variables such as percent of population employed, median housing value or percent poverty. This composite factor may capture processes that run with the socioeconomic composition of household in the area, may reflect individual income of the residents and may also serve as proxy for other more specific neighborhood attributes such as financial and health resources, green spaces, air pollution, and social networks (68,69). For example, Roblin found that nSES was associated with presence of sidewalks, street lights

available at night, presence of walking/cycling paths nearby, and perception of safety from crime (24). In turn, nSES has been associated with a wide range of health outcomes as previously reviewed (70). More recently, studies have found that nSES is associated with mortality (25,26), cardiovascular risk factors (27), hypertension (28), and coronary heart disease (29). Winkleby *et al.* combined data from the National Health Interview Survey, the 1990 Decennial US Census and National Death Index (NDI) and found that living in a neighborhood with low nSES increased the risk of mortality beyond individual socioeconomic status (25).

Circulatory diseases (CDs), which include all diseases of the heart and circulatory system, have been the main cause of death around the world for the past three decades (30). Like other chronic diseases, CDs are multifactorial in nature and are influenced by various biological, lifestyle and contextual factors, including the neighborhood environment (23). Indeed, there is extensive evidence that supports the association of increased CD morbidity and mortality among residents of neighborhoods of low nSES versus neighborhoods of high nSES (31). By 2009, over 40 studies had evaluated the association between neighborhood deprivation and coronary heart disease(32). Most of the studies found increased risk of heart disease among individuals residing in low nSES areas compared to those living in more affluent areas(32). A study conducted by Diez Roux and colleagues found that hazard ratios for coronary heart disease among people living in disadvantaged neighborhoods were 3 times higher than people in neighborhoods of high nSES, even after controlling for individual income, education and occupation (29). Similarly, Morenoff *et al.* estimated that hypertension was negatively associated with neighborhood affluence even after adjusting for individual risk factors (28).

At the same time, there is evidence increasingly showing that exposure to ionizing radiation can damage heart and vascular tissue and lead to development of CDs (11,59). Studies of radiologic technologists, professionals who perform medical diagnostic and therapeutic

procedures with radiation, have found that increased exposure to ionizing radiation is associated with CD mortality (21,22). A recent analysis of the US Radiologic Technologist (USRT) study found that radiation technologists who were chronically exposed to low-doses of radiation have elevated risks of CD mortality even at low doses below 0.5Gy (71). Within this and other occupational cohorts of ionizing radiation, the influence of the socioeconomic context of the workers has not been explored with respect to CD incidence and mortality. In addition, it is not known whether the attendant associations with ionizing radiation exposure may be confounded or modified by residential nSES. In this paper we assess: 1) the effect of residential nSES on CD incidence and mortality within the cohort, and 2) whether the previously described association between protracted low-dose occupational radiation exposure is either confounded or modified by nSES. To address this objective, the study combined neighborhood socioeconomic characteristics from the US Census Bureau with data from the USRT study, the largest longitudinal study of medical occupational radiation exposure to date.

Methods

Study design, setting and population

The US Radiologic Technologist (USRT) study is a longitudinal study of radiologic technologists living across the US that were certified for at least two years between 1926 and 1982 by the American Registry of Radiologic Technologists (ARRT). A total of 146,022 technologists were eligible to participate and were sent the first questionnaire (Q1) between 1983 and 1989, and the second questionnaire (Q2) between 1994 and 1998. A total of 70,851 technologists (48.5%) completed both questionnaires; 19,417 (13.3%) completed Q1 only, 17,347 (13.8%) completed Q2 only. 110,374 participants who completed either Q1 or Q2 were subsequently sent the third and fourth surveys (Q3 between 2003 and 2005, and Q4 between 2012 and 2013). These four comprehensive surveys inquired about demographic information, exposure to ionizing radiation and other risk factors, incidence of disease and general health status.

Neighborhood socioeconomic status (nSES)

To better understand the contextual socioeconomic environment of participants, we relied on the contact addresses that were used to send Q2 in 1994 since addresses used to send Q1 were no longer available at time of geocoding. As a result, 1994 was the earliest start of follow-up in this analysis. Participants who completed Q1 and not Q2 were still included in the analysis if they were alive in 1994 and had a valid address used to send Q2 (regardless of Q2 completion). We geocoded participants' mailing addresses using ESRI's USA Composite Geocoding service in ArcGIS® to a 1990 block-group within the US. We used census block-groups as proxies for neighborhoods because they are the smallest administrative unit from which socioeconomic tabular information is available from the US Census. A total of 145,006 contact addresses were available in 1994 for Q2 distribution. From these, 76.4% were geocoded to a specific street address and 22.8% were mapped to the centroid of a zip-code because low address quality prevented ArcGIS® from precisely locating the street address. The remaining 0.8% of addresses were could not be geocoded due to poor address quality and were excluded from analysis.

Similar to other studies testing the effect of nSES on health, we constructed a composite nSES index for all block-groups in the US using 1990 decennial census data which most closely corresponded to the date when Q2 was sent (24–26,29). We downloaded tabular sociodemographic data from the 1990 US Census at the block-group level from the Minnesota Population Center: National Historical Geographic Information System (72). We created an nSES index using 6 components previously identified by Diez Roux *et al*. via principal component analysis: 1) regionally-adjusted median household income, 2) regionally-adjusted median housing value, 3) percent of households with interest/income, 4) percent of adults who completed high school, 5) percent of adults who completed college, and 6) percent of employed persons in managerial occupations (29). To adjust median household income and median housing value, we

used the average measures for the corresponding metropolitan statistical area (MSA) in 1990. If a block-group did not have a corresponding MSA (e.g. for rural areas), we used the state average to regionally adjust income and housing value. To combine the 6 components into an overall nSES index score, an individual z score was calculated for each component within each block group and then summed for an overall nSES index score as detailed below.

Z scores for each component *j* were calculated using the mean and standard deviation among all block-groups in the US:

$$z_{ij} = (x_{ij} - \bar{x_j})/sd_j \text{ for each block-group } i \text{ and component } j.$$

The nSES index for all 1990 US block-groups ($nSES_{ij}$) was constructed by summing the z scores of each of the six components:

$$nSES_i = \sum_{j=1}^{6} z_j \text{ for each block-group } i$$

In general, USRT participants lived in areas of higher nSES compared to the average US block-group. Considering all US block-groups in 1990, only 9% of USRT participants lived in the lowest nSES quintile and 31% lived in the most affluent quintile. Finally, we standardized the nSES index using the mean $nSES_{USRT}$ calculated using only the neighborhoods in the US where USRT participants lived, *m*:

$$nSES_{sm} = {nSES_m}\Big/{\overline{nSES_{USRT}}} \text{ for each USRT block-group } m$$

Higher $nSES_{sm}$ scores denote higher neighborhood socioeconomic advantage within the cohort. For this paper, $nSES_{sm}$ was divided into tertiles (cut at -0.43 and at +0.40 of $nSES_{sm}$).

Individual socioeconomic status

To account for confounding of the effect of nSES on CD outcomes, we used educational attainment at baseline as a measure of individual socioeconomic status. Educational attainment at baseline was inquired in Q1 (but not in Q2) and was divided into 3 categories: 1) vocational, high school or less, 2) radiation technology, and 3) some college. A total of 89,638 people provided

this information (84% of eligible participants). During sensitivity analyses, we also considered annual household income as a measure of individual socioeconomic status, but this was only available in 2003 from a limited subset of Q3 respondents. Household annual income was inquired only in Q3 (<$50,000, $50,000-74,999, $75,000-99,999, and ≥$100,000) and a total 54,303 people provided this information (51% of eligible participants).

Circulatory disease (CD) outcomes

CD mortality

Vital status for all USRT participants was determined through December 31st, 2012. For decedents, the underlying cause of death was obtained from the National Death Index (NDI-*Plus*) and coded using the ICD version in effect at the time of death (22). Specific mortality outcomes evaluated in this study were: all circulatory diseases (ICD-8 390–458; ICD-9 390–459; ICD-10 I00–I99), ischemic heart disease (ICD-8 410–414; ICD-9 410–414; ICD-10 I20–I25) and cerebrovascular diseases (ICD-8 430-438; ICD-9 430-438; ICD-10 I60-I69).

CD incidence

Self-reported incidence of ischemic heart disease, myocardial infarction, and stroke were obtained from responses in Q3 and Q4. In each of these surveys, participants were asked to select any medical conditions that they had been diagnosed with by a doctor and report the first year (or age) of diagnosis. To unify conditions across questionnaires, we included myocardial infarction as part of ischemic heart disease (IHD) and stroke as part of cerebrovascular diseases (CeVD). People who reported multiple CD comorbidities were included in the analysis for each condition.

Cumulative ionizing radiation

Personal annual doses of ionizing radiation were estimated for 110,374 technologists for the years 1916-1997 as previously described (54,55). Briefly, individual annual doses were derived

for each year worked using several sources of information including recorded badge doses from monitoring devices, length and type of work as a radiation technologist, usage of personal protective equipment, other individual employment practices reported in the second and third questionnaires (Q2, and Q3) and literature-reported exposure measurements for years when badge doses were not available. Badge doses (in mSv) were converted to organ absorbed doses (in mGy) using dosimetry factors that accounted for engineering changes in radiologic technology, reported use of protective equipment and body mass index. To best capture the biological impact of radiation on each CD outcome, we used cumulative thyroid dose for all CD mortality combined, cumulative heart dose for IHD, and cumulative brain dose for CeVD as measures of radiation exposure.

Data analysis

Inclusion and exclusion criteria

Participants were included in the mortality analyses if they were alive in 1994, had information on educational attainment in Q1, reported working as radiologic technologists for at least one year between 1916 and 1997, and had an address on record (n=86,147). During sensitivity analysis, we excluded individual educational attainment from the model and evaluated the effect of nSES and radiation on the full eligible cohort (n=105,802). Participants were included in the incidence analyses if they were alive and CD-free in 1994, had information on educational attainment in Q1, reported working as radiologic technologists for at least one year between 1916 and 1997, had an address on record, and completed a follow-up questionnaire (Q3 and/or Q4). We excluded participants if: 1) they reported having any of the following conditions in either Q1 or Q2: myocardial infarction (Q1 & Q2), stroke (Q2), angina pectoris (Q2), or a coronary bypass (Q2), or 2) they reported a year of diagnosis earlier than 1994 (earliest availability of nSES) or did not report a year. A total of 76,055 participants were included in the

main analysis but as part of sensitivity analysis we excluded education from the model and evaluated the effect of nSES and radiation on the full eligible cohort (n=88,989).

Follow-up

For mortality outcomes, follow-up started when Q2 was completed (or 1994 if Q1 was completed instead of Q2) and ended at the earliest of the following events: year of death, year of lost-to-follow-up (censored) or 2012 when the latest mortality data were ascertained (censored).

For CD incidence, start of follow-up was the year when Q2 was completed (or 1994 if Q1 was completed instead of Q2) and follow-up ended at the earliest of the following events: year of first diagnosis or year when the latest questionnaire was completed (Q4, or Q3 if Q4 was missing). Cumulative organ doses of radiation were treated as continuous time-varying factors such that, at each time point, a person's exposure was the sum of all yearly doses up to and including that year.

Model specification

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated as effect estimates of the association between radiation, nSES tertiles and CD incidence and mortality. HR and 95%CI were estimated using discrete time hazard models with calendar year as the time scale adjusted for age as a time-varying factor, sex (M/F), self-reported race (white, black, other), ethnicity (Hispanic/non-Hispanic), smoking habits and body mass index (BMI) at baseline. Smoking habits at baseline were categorized as: never smoker, light ex-smoker (≤20 pack years), heavy ex-smoker (>20 pack years), light current smoker (≤20 pack years) and heavy current smoker (>20 pack years). Baseline BMI was categorized using standard definition: underweight (<18kg/m^2), normal weight (18 to <25 kg/m^2), overweight (25 to <30 kg/m^2) and obese(≥30 kg/m^2)(73).

Five models were evaluated to assess the impact of confounding and effect modification by nSES. All the discrete time hazard models detailed below used calendar year as a time scale, adjusted by baseline covariates (age as a time-varying covariate, sex, race, ethnicity, BMI and smoking).

1. Model 1: baseline covariates + cumulative radiation organ dose
2. Model 2: baseline covariates + nSES tertiles
3. Model 3: baseline covariates + cumulative radiation organ dose + nSES tertiles
4. Model 4: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment
5. Model 5: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + (cumulative radiation organ dose * nSES tertiles)

Based on our study objectives, Models 1 and 2 evaluate the independent effect of radiation and nSES on CD outcomes, respectively; Models 3 and 4 evaluate the joint effect of radiation and nSES on CD outcomes (with and without adjusting for individual education); and Model 5 evaluates a multiplicative interaction between radiation and nSES. To facilitate interpretation of the potential modifying effect of nSES on radiation-CD estimates, we present the HR and 95% for a 100mGy increase in cumulative organ dose on each CD outcome stratified by nSES.

To evaluate the presence of an additive interaction between nSES and radiation on CD outcomes, we calculated a relative excess risk due to interaction (RERI) (74). To estimate the RERI between nSES tertiles and radiation on all CD outcomes, we dichotomized radiation exposure using the median cumulative organ dose among participants (cumulative thyroid dose was cut at 40mGy, heart dose at 11mGy and brain dose at 8mGy). We estimated the RERI by comparing high (≥median) and low (<median) cumulative radiation exposure between the highest and lowest tertile of nSES. Because discrete time hazard models did not allow bootstrapping analyses to calculate the 95% CI for the RERI, we approximated the RERI and its 95% CI using

Cox proportional hazard models with year as a time scale, and adjusted for birth year, sex, race, ethnicity, smoking habits and BMI at baseline. 95% CI were estimated using bootstrapping with 400 repetitions.

Additional sensitivity analysis was conducted to determine the effect of individual household income on CD mortality and incidence. To gage the confounding impact of this variable beyond selective inclusion of respondents with available information, we first re-ran the models without income on a subset of participants with this information (Models 4† and 5‡). All analyses were performed using Stata/IC v.14.2.

- Model 4†: same as Model 4, but restricted to 45,506 participants with information on household income in Q3
- Model 5‡: same as Model 5, but restricted to 45,506 participants with information on household income in Q3

6. Model 6: cumulative radiation organ dose and nSES tertiles together, adjusted for educational attainment and household income
7. Model 7: cumulative radiation organ dose, nSES tertiles, educational attainment and a multiplicative two-way interaction between radiation and nSES tertiles, adjusted for household income

Results

Characteristics of the sample

The average birth year among participants was 1946. Around 76% were female and 94% were white. The sample had a mean baseline BMI of 24.1 kg/m^2 and an average cumulative thyroid dose of 60.2mGy. Table 7 presents the characteristics of these participants across tertiles of nSES. 62.6% of black participants of this cohort lived in neighborhoods of low nSES while only 31.5% of whites resided in these neighborhoods. Among participants with some college

education, 29.8% lived in low nSES and 36.5 lived in high nSES areas. A higher proportion of current heavy smokers lived in neighborhoods of low nSES than in high nSES (37.0% versus 29.5%, respectively).

There was a total of 3,743 deaths with CD as an underlying cause of death among 105,802 eligible participants; 1,873 (50.0%) were ischemic heart disease (IHD) and 625 (16.7%) were cerebrovascular disease (CeVD) cases (Table 7). A higher proportion of IHD cases occurred among people in low nSES areas compared to high nSES neighborhoods (40.8% versus 28.9%, respectively). Meanwhile, CeVD deaths were evenly distributed across tertiles of nSES. In terms of CD incidence, there was a total of 3,634 non-fatal cases of IHD and 1,796 cases of CeVD among 88,989 eligible participants. A higher proportion of incidence of IHD and CeVD were reported among low nSES residents than high nSES residents (36.8% vs. 29.9% for IHD, and 35.4% vs. 32.6% for CeVD).

[Table 7]

Independent Effects of Radiation and nSES on CD mortality

Table 8 presents the HR and 95% CI for the estimated effect of cumulative radiation exposure and nSES on CD mortality. The effect of nSES and radiation was considered separately, jointly, and adjusted by educational attainment at baseline. Considering a 100mGy increase in cumulative organ dose, we found a 6% increase in the hazard ratio of all CD mortality combined (95% CI 3-9%); a 13% increase in the HR of IHD mortality (95% CI 5-22%) and a 48% increase in the HR of CeVD mortality (95% CI 6-107%) without including nSES in the models. There was an elevated risk of all CD mortality combined for people living in neighborhoods of low nSES compared to those living in high nSES places (HR: 1.19, 95%CI: 1.08-1.30). This was also the case for IHD mortality (HR: 1.26, 95%CI: 1.12-1.43) but not for CeVD mortality (HR: 0.95,

95%CI: 0.77-1.18). These estimates did not change when both variables, radiation and nSES, were included in the models simultaneously (Model 3) or when educational attainment was included as a confounder (Model 4). Education itself was not associated with any of the mortality outcomes. The effect estimates for nSES and radiation did not substantially change when the full eligible cohort was included in the analysis (n=105,802) and educational attainment was not included as a confounder during sensitivity analysis (Table 11 [Supplemental Table S2]).

[Table 8]

Interaction between radiation and nSES on CD mortality

While there was no evidence that educational attainment influenced the association of nSES and radiation in a confounding model, we observed a consistent two-way interaction between radiation and nSES when adjusting for education (Table 8, Model 5). Adjusting for educational attainment, the p-value for the two-way interaction between radiation and nSES for all CD mortality combined was <0.001, for IHD mortality 0.003, and for CeVD mortality 0.004). For all these mortality outcomes, we found a more harmful effect of radiation among people living in high nSES areas compared to low and middle nSES when adjusting for education. For all CD mortality combined, residents of high nSES areas had a HR of 1.13 (95%CI: 1.09, 1.17) per 100mGy of thyroid dose while residents of low nSES areas had a HR of 1.03 (95%CI: 0.99, 1.06) for the same increase in exposure. For IHD mortality, residents of high nSES areas had a HR of 1.31 (95%CI: 1.17, 1.46) per 100mGy of heart dose while residents of low nSES areas had a HR of 1.05 (95%CI: 0.97, 1.14) for the same increase in exposure. Finally, for CeVD mortality, residents of high nSES areas had a HR of 2.71 (95%CI: 1.75, 4.18) per 100mGy of brain dose while residents of low nSES areas had a HR of 1.08 (95%CI: 0.68, 1.73) for the same increase in radiation exposure.

Independent Effects of Radiation and nSES on CD incidence

Similar analyses were conducted for incidence of IHD and CeVD (Table 9). Without considering the neighborhood of residence or education, we found a HR of 1.27 (95% CI: 1.12, 1.44) in incidence of non-fatal for a 100mGy increase in cumulative heart dose, after adjusting for calendar year, age, sex, race, ethnicity, BMI and smoking. Adjusting for the same covariates, the HR for a 100mGy increase in cumulative brain dose was 1.51 (95%CI: 0.95, 2.38) for CeVD incidence. When nSES was included in the model without radiation, the hazard ratio of IHD incidence was 1.22 (95%CI: 1.11, 1.34) for the lowest nSES compared with people in the highest nSES. For CeVD incidence, the HR in the lowest nSES tertile was 1.23 (95%CI: 1.07, 1.41) times larger than the estimate for the highest nSES tertile. The estimates for both, radiation and nSES tertiles, remained consistent when both variables were included together in the model as confounders of each other. Education itself was not associated with incidence of CD, and it did not confound the association between nSES and radiation and CD incidence. The effect estimates for nSES and radiation did not substantially change when the full eligible cohort was included in the analysis (n=88,989) and educational attainment was not included as a confounder (Table 12 [Supplemental Table S3]).

Interaction between radiation and nSES on CD incidence

We did not find any statistical evidence to suggest a multiplicative interaction between radiation and nSES tertiles on their relationship with incidence of IHD and CeVD, adjusting for educational attainment (p-value for interaction: 0.73 and 0.48, respectively) (Table 9).

[Table 9]

Additive interactions between radiation and nSES for CD mortality and incidence

The relative excess risk due to interaction (RERI) estimates are summarized in Table 10 for all CD outcomes. Most RERIs were positive, suggesting that people in high nSES neighborhoods have a higher risk of all CD outcomes evaluated compared to people in low nSES areas, assuming similar cumulative radiation doses and baseline characteristics. However, all the confidence intervals included the null so this possible interaction should be interpreted with caution.

[Table 10]

Sensitivity analysis: Individual household income as a potential confounder of these associations

Information about individual household income was only inquired on Q3 and completed by 45,506 participants eligible for mortality analysis (Table 13 [Supplemental Table S4]) and 45,102 eligible for incidence analysis (Table 14 [Supplemental Table S5]). In this subset of Q3 respondents, we observed moderate changes in the HRs of radiation or nSES and CD mortality and loss of precision of the confidence intervals (Models 4† and 5‡). Once we included income in the model (Models 6 and 7), we did not observe substantial changes in the point estimates or confidence intervals for radiation, nSES or the two-way interaction between them. Finally, we found an inverse association between reported household income and all CD mortality combined and IHD mortality, after adjusting for radiation, nSES, education and other risk factors (Table 13 [Supplemental Table S4]).

In terms of incidence of CD (Table 14 [Supplemental Table S5]), we found that the effect of nSES in the sub-cohort with income information (Model 4†) was similar to that reported in Table 9 with some loss in precision (Model 4). However, the estimates of cumulative radiation were larger in the subset of participants with income data than those without this information. Once we included income in the model (Models 6 and 7), we did not observe substantial changes in the

point estimates or confidence intervals for radiation, nSES or the two-way interaction between them. We also found an inverse association between household income and incidence of IHD after adjusting for radiation, nSES, education and other risk factors.

Discussion

In this longitudinal study of occupational exposure to low protracted doses of medical radiation, we found that a lower socioeconomic status of the neighborhood of residence was associated with increased risk of CD incidence and mortality independently of radiation. Specifically, radiation technologists from low nSES neighborhoods had between 20 and 30% increased risk of all CD mortality combined, IHD mortality and incidence, and CeVD incidence (but not mortality) compared to their counterparts living in high nSES areas across the US. At the same time, we showed that increased levels of cumulative radiation exposure were associated with CD incidence and mortality, even after accounting for nSES.

We observed a multiplicative interaction between cumulative exposure to radiation and nSES, particularly when education was included in the model, but this was not consistent for all outcomes and the pattern of interaction across tertiles was not clear. In the cases where we found statistical evidence of a multiplicative interaction (all CD mortality combined, IHD mortality and CeVD mortality), stratified analysis showed that the harmful effect of radiation on these outcomes was slightly higher among people from high nSES neighborhoods compared to other areas. In terms of additive interactions, our results indicated that people in high nSES neighborhoods have higher risks of radiation compared to people from low nSES areas exposed to similar cumulative organ doses. Among a subset of participants who provided income information in questionnaire 3, technologists from low income household had a higher risk of all CD outcomes compared to more affluent people. However, individual income generally did not confound or modify the association between nSES, radiation and CD outcomes.

These results must be interpreted considering some limitations in our study. First, our definition of neighborhood boundaries and use of a standardized nSES index as proxies for the true neighborhood construct might have introduced misclassification bias to our study. In general, neighborhoods can be defined at different scales. Defining neighborhoods along administrative boundaries such as census block-groups is a useful tool for large studies, but it may not accurately capture the spaces that individuals consider their neighborhoods. Future studies should consider alternative approaches to define neighborhood boundaries such as using a circular buffer around the individual's address and calculating a weighted nSES average from all census block-groups surrounding the individual(75). In addition, we did not model more specific neighborhood attributes that could be more causally related to CD incidence and mortality such as food outlets(76), air pollution(68,77,78), and availability of green space(79), among others. Given that the USRT is a historical and national cohort, it would have been difficult to gather comparable data on these specific attributes for all neighborhoods where members resided in 1990. However, there is reviewed evidence supporting the connection between nSES index and neighborhood attributes (68).

In this study, we had limited information on individual socioeconomic status because baseline education level was missing for ~20% of participants and household income was missing for almost 50% of eligible participants. Our sensitivity analysis comparing estimates between participants with and without data on individual education, showed negligible differences. This suggests that our estimates are likely unbiased from this missing data. However, in terms of individual household income, a total of 1,470,696 of person-years were lost when the start of follow-up changed from 1994 to 2003 and only the participants with this variable are included in the study (48% of the 3,060,125 person-years included in the main analysis). Combined, this missing data may have introduced some level of selection bias and uncontrolled confounding that

could impact our estimates. To avoid making inappropriate comparisons across models with different number of participants, we present our main results by restricting our analysis to those participants with complete variable information. In general, our estimates for the effects of radiation and nSES on CD outcomes remain consistent across all subset of participants.

Our findings contribute to the current literature of the neighborhood-level effects on CD incidence and mortality. Neighborhoods are complex systems that embody several social, physical and economic factors that impact CD development and mortality (80). Even in a relatively homogenous group of radiologic technologists -in terms of gender, race, and occupation-, neighborhood disparities were consistently associated with overall CD mortality, IHD mortality, IHD incidence and CeVD incidence, after adjusting for recognized risk factors. Many other studies have also reported this area-level disparity in the risk of CVD (reviewed by Chaix, 2009; A. V. Diez Roux et al., 2001). However, there is a gap in knowledge on the influences of nSES within an occupational cohort like the USRT, so we are limited on our comparisons with the broader literature.

In our study, we showed that residents of affluent neighborhoods had increased risk of CD mortality compared to similarly exposed technologists in less affluent neighborhoods, after adjusting for educational attainment. This observation was contrary to our initial hypothesis of a double burden between radiation exposure and a deprived neighborhood context. Because we did not collect more detailed information on specific neighborhood attributes more closely linked to CD development (such as food outlets, air pollution, green space, among others), we are unable to fully explain this observation. In addition, there are only limited studies evaluating influences of socioeconomic disparities on worker's health (81–83). A study in the Netherlands evaluated if occupational class was related to perceived health and concluded that health perception was mostly attributed to unequal distribution of work-place hazards, and not social class itself (81).

After accounting for specific job title and industry, a cross-sectional analysis in the US found that levels of occupational exposures varied by sociodemographic characteristics(82). Like us, they initially expected to find an inverse relationship between socioeconomic status and damaging occupational exposures, but the pattern was not clear across professions.

Based on this limited literature on the influence of individual-level social disparities on the impact of occupational exposures, we propose two possible explanations for our observations described below. First, incident and mortality cases occurring among radiologic technologists residing in deprived neighborhoods are likely caused by the strong influence of specific neighborhood-level attributes such as poverty, air pollution, lack of health resources, unhealthy food stores and lack of green space (77,78,84). In this context, occupational radiation is likely playing a small role in the causal pathway of CDs. In contrast, in affluent neighborhoods, where the characteristics of the built environment tend to be protective of CD outcomes, radiation becomes a more influential factor of disease in the absence of others.

In a recent study, Hussein *et al* investigated whether inequalities in incident cardiovascular disease (CVD) are mostly rooted in unequal exposures or unequal vulnerability (85). They showed that the major contributor to CVD disparities is unequal distribution of harmful exposures across the nSES gradient. The disproportionate burden of harmful exposures in deprived neighborhoods is the major cause of disease instead of a higher level of biological vulnerability among low-nSES residents. In light of these observations, our results suggest that residents of low nSES are not more sensitive to radiation exposures, as was initially hypothesized. That said, we do not propose that high income residents are more vulnerable to radiation, but that by limiting our analysis of neighborhood influences to the nSES, we are not accounting for the critical causes of CD in low-income neighborhoods.

Second, there might be differences in reporting of information related to exposure reconstruction, risk factors and incidence outcomes between workers in different social classes (83). Although this is a less likely explanation than the one discussed above, it is possible that low-nSES residents might be misreporting information on contributors to exposure estimates -like apron usage- such that their radiation exposure was overestimated. To exemplify this point, say we observed 20 CD mortality cases in the lowest nSES group and 30 cases in the highest nSES for a 100mGy increase in cumulative radiation dose. If those from low-nSES have an overestimated exposure dose while those in high-nSES areas do not, those 20 observed cases in low nSES could have been caused by a 50mGy increase (erroneously estimated as 100mGy). In this counterfactual scenario, we would expect to see 40 cases for a 100mGy increase in radiation exposure (assuming perfect linearity), which would flip the risk difference by nSES. That said, we are unable to conclusively explain why we observed a higher risk of CD mortality from exposure to radiation among high nSES residents compared to low nSES residents.

Various aspects of the neighborhood have been associated with worse CD outcomes including the built environment, social networks, and the availability and affordability of resources. One of the major contributors of CD and other metabolic diseases is low access to healthy foods. Since the 1990s, areas of low economic resources and poor access to healthy foods, have been called ‘food desserts’(76). Although nSES and these physical attributes of the neighborhood -such as healthy food availability- are closely intertwined, a recent study concluded that adverse cardiovascular outcomes are mainly driven by nSES rather than access to healthy food options (86). This suggests that a construct such as the nSES might act independently of the specific attributes that are often bundled under the nSES proxy. Indeed, a recent study on the neurobiological pathways from socioeconomic disparities to CVD reported that residents of lower SES had increased amygdalar activity (a key component of the stress network), arterial inflammation and a higher prevalence of a major cardiac event(87). This contributes to the

previous evidence supporting a biological mechanism between neighborhood deprivation and CVD including stress and inflammation(36).

Conclusion

In a large cohort of workers occupationally exposed to medical radiation, we showed that residing in an area of low nSES was consistently associated with increased risk of overall CD mortality, IHD mortality, IHD incidence and CeVD incidence compared to residents of more affluent areas. At the same time, we found an independent harmful effect of cumulative radiation exposure on all CD outcomes after adjusting for baseline covariates, educational attainment and nSES. There was evidence suggesting the presence of a multiplicative interaction between cumulative exposure to radiation and nSES for overall CD mortality, IHD mortality and CeVD mortality. Indeed, we observed that the harmful effect of radiation on these outcomes was slightly higher among people from high nSES neighborhoods compared to other areas. Future studies should consider this result and further investigate its causes.

Tables and Figures

Table 7. Characteristics of 105,802* US radiologic technologists by socioeconomic status of their neighborhood of residence in the 1990s

	Low nSES		Middle nSES		High nSES		Total	
Baseline continuous factors	mean	SD	mean	SD	mean	SD	mean	SD
Birth year	1946	10.3	1947	9.8	1946	9.6	1946	9.9
Years worked as Rad. Tech.	21.0	9.4	20.7	9.4	19.4	9.7	20.4	9.5
Cumulative thyroid dose (mGy)	63.0	84.1	59.9	79.5	57.8	74.5	60.2	79.5
BMI at baseline (kg/m2)	24.7	4.8	24.1	4.4	23.6	4.2	24.1	4.5
Years of follow-up	25.5	5.0	25.9	4.2	25.7	4.3	25.7	4.5
Baseline categorical factors	N	%	N	%	N	%	N	%
Gender								
Male	9,134	36.4	8,736	34.8	7,227	28.8	25,097	100
Female	25,364	31.4	27,165	33.7	28,176	34.9	80,705	100
Race								
White	31,424	31.5	34,317	34.4	33,997	34.1	99,738	100
Black	2,095	62.6	750	22.4	504	15.1	3,349	100
Other	933	35.6	812	31.0	873	33.4	2,618	100
Educational level								
Vocational, high school or less	1,765	35.4	1,663	33.3	1,561	31.3	4,989	100
Radiologic technology	15,742	34.0	16,082	34.8	14,445	31.2	46,269	100
Some college	10,409	29.8	11,791	33.7	12,771	36.5	19,573	100
Smoking status								
never	16,466	32.9	17,236	34.4	16,407	32.7	50,109	100
ex-smoker, <=20p-yr	7,168	29.7	8,141	33.7	8,813	36.5	24,122	100
ex-smoker, >20p-yr	4,712	32.3	4,719	32.4	5,135	35.3	14,566	100
current, <=20p-yr	2,802	35.3	2,770	34.9	2,355	29.7	7,927	100
current, >20p-yr	3,267	37.0	2,959	33.5	2,610	29.5	8,836	100
Outcome distribution by 2012								
Circulatory disease mortality								
All CD combined	1,446	38.6	1,189	31.8	1,108	29.6	3,743	100
Ischemic heart disease	765	40.8	567	30.3	541	28.9	1,873	100
Cerebrovascular disease	210	33.6	204	32.6	211	33.8	625	100
Circulatory disease incidence								
Ischemic heart disease	1,336	36.8	1,211	33.3	1,087	29.9	3,634	100
Cerebrovascular disease	635	35.4	576	32.1	585	32.6	1,796	100

*Depending on the outcomes and covariates included in the model, the number of participants included changed but 105,802 was the maximum number of technologists considered in this paper (see *Data analysis* for details)

Neighborhood socioeconomic status (nSES) was standardized for the cohort and divided into tertiles.

Percents are calculated for each row. Some variables have missing information, so the totals vary by covariate.

SD= standard deviation; CD: circulatory disease; p-yr: packs-per-year

Table 8. Associations between cumulative radiation exposure and nSES on circulatory disease mortality after adjusting for educational attainment among 86,147 radiologic technologists

Factors and outcomes	Model 1		Model 2		Model 3		Model 4		Model 5	
All CD mortality	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Thyroid dose (per 100mGy)	1.06	(1.03, 1.09)			1.06	(1.03, 1.08)	1.06	(1.03, 1.09)	1.13	(1.09, 1.17)
nSES tertile										
Low			1.19	(1.08, 1.30)	1.18	(1.08, 1.29)	1.18	(1.08, 1.29)	1.39	(1.24, 1.57)
Middle			1.03	(0.94, 1.13)	1.03	(0.93, 1.12)	1.02	(0.93, 1.12)	1.18	(1.04, 1.33)
High							*Ref.*		*Ref.*	
Education level										
Vocational, high school or less							0.98	(0.87, 1.11)	0.98	(0.87, 1.10)
Radiologic technology							1.01	(0.93, 1.10)	1.01	(0.93, 1.10)
Some college							*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]										
Low									1.03	(0.99, 1.06)
Middle									1.04	(1.00, 1.08)
High									1.13	(1.09, 1.17)
p-value for interaction									*<0.001*	
IHD mortality	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Heart dose (per 100mGy)	1.13	(1.05, 1.22)			1.13	(1.05, 1.21)	1.13	(1.05, 1.22)	1.31	(1.17, 1.46)
nSES tertile										
Low			1.26	(1.12, 1.43)	1.25	(1.11, 1.42)	1.25	(1.11, 1.42)	1.46	(1.26, 1.71)
Middle			0.98	(0.86, 1.12)	0.97	(0.85, 1.11)	0.97	(0.85, 1.11)	1.08	(0.91, 1.28)
High			*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level										
Vocational, high school or less							0.95	(0.81, 1.12)	0.95	(0.81, 1.12)
Radiologic technology							1.02	(0.91, 1.14)	1.02	(0.91, 1.14)
Some college							*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]										
Low									1.05	(0.97, 1.14)
Middle									1.12	(0.98, 1.27)
High									1.31	(1.17, 1.46)
p-value for interaction									*0.003*	
CeVD mortality	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Brain dose (per 100mGy)	1.48	(1.06, 2.07)			1.49	(1.07, 2.10)	1.47	(1.05, 2.07)	2.71	(1.75, 4.18)
nSES tertile										
Low			0.95	(0.77, 1.17)	0.93	(0.75, 1.15)	0.92	(0.75, 1.15)	1.25	(0.94, 1.67)
Middle			0.93	(0.75, 1.15)	0.92	(0.74, 1.14)	0.91	(0.73, 1.13)	1.26	(0.86, 1.55)
High			*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level										
Vocational, high school or less							1.12	(0.86, 1.47)	1.12	(0.85, 1.47)
Radiologic technology							1.11	(0.91, 1.34)	1.09	(0.90, 1.33)
Some college							*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]										
Low									1.08	(0.68, 1.73)
Middle									1.30	(0.77, 2.20)
High									2.71	(1.75, 4.18)
p-value for interaction									*0.004*	

All hazard ratios (HR) and 95% confidence intervals (CI) were estimated using discrete time hazard models with calendar year as a time scale, adjusted by baseline covariates (age as a time-varying covariate, sex, race, ethnicity, BMI and smoking). Follow-up started in 1994 and ended in 2012. All estimates for radiation are for a 100mGy increase in organ dose.
Model 1: baseline covariates + cumulative radiation organ dose
Model 2: baseline covariates + nSES tertiles
Model 3: baseline covariates + cumulative radiation organ dose + nSES tertiles
Model 4: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment

Model 5: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + (radiation * nSES interaction)
[t]Effect of cumulative radiation organ doses stratified by nSES tertile using postestimation commands
CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease

Table 9. Associations between cumulative radiation exposure and nSES on circulatory disease incidence after adjusting for educational attainment among 76,055 radiologic technologists

Factors and outcomes	Model 1		Model 2		Model 3		Model 4		Model 5	
IHD incidence	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Heart dose (per 100mGy)	1.27	(1.12, 1.44)			1.26	(1.11, 1.43)	1.26	(1.11, 1.43)	1.33	(1.11, 1.59)
nSES tertile										
Low			1.22	(1.11, 1.34)	1.22	(1.10, 1.34)	1.21	(1.10, 1.33)	1.24	(1.10, 1.39)
Middle			1.03	(0.94, 1.14)	1.03	(0.93, 1.14)	1.03	(0.93, 1.13)	1.05	(0.93, 1.18)
High			*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level										
Vocational, high school or less							1.02	(0.87, 1.20)	1.02	(0.87, 1.20)
Radiologic technology							1.05	(0.96, 1.14)	1.05	(0.96, 1.14)
Some college							*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ŧ]										
Low									1.21	(1.00, 1.47)
Middle									1.24	(1.26, 1.50)
High									1.33	(1.11, 1.59)
p-value for interaction									*0.73*	
CeVD incidence	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Brain dose (per 100mGy)	1.51	(0.95, 2.38)			1.44	(0.91, 2.28)	1.45	(0.91, 2.30)	1.98	(1.00, 3.94)
nSES tertile										
Low			1.23	(1.07, 1.41)	1.23	(1.07, 1.41)	1.23	(1.07, 1.41)	1.31	(1.09, 1.58)
Middle			1.10	(0.96, 1.25)	1.09	(0.95, 1.25)	1.09	(0.95, 1.25)	1.17	(0.97, 1.42)
High			*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level										
Vocational, high school or less							0.98	(0.78, 1.23)	0.98	(0.78, 1.23)
Radiologic technology							0.99	(0.88, 1.12)	0.99	(0.88, 1.12)
Some college							*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ŧ]										
Low									1.28	(0.67, 2.44)
Middle									1.22	(0.61, 2.43)
High									1.98	(1.00, 3.94)
p-value for interaction									*0.48*	

All hazard ratios (HR) and 95% confidence intervals (CI) were estimated using discrete time hazard models with calendar year as a time scale, adjusted by baseline covariates (age as a time-varying covariate, sex, race, ethnicity, BMI and smoking). Follow-up started in 1994 and ended in 2012. All estimates for radiation are for a 100mGy increase in organ dose.

Model 1: baseline covariates + cumulative radiation organ dose

Model 2: baseline covariates + nSES tertiles

Model 3: baseline covariates + cumulative radiation organ dose + nSES tertiles

Model 4: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment

Model 5: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + (radiation * nSES interaction)

[ŧ]Effect of cumulative radiation organ doses stratified by nSES tertile using postestimation commands

IHD: ischemic heart disease, CeVD: cerebrovascular disease

Table 10. Relative excess risk due to interaction (RERI) and 95% CIs evaluating an additive interaction between cumulative occupational radiation and nSES tertiles on CD mortality and incidence

Outcome	Binary cumulative radiation	RERI*	95% CI
Mortality			
Any CD	Thyroid dose (p50: 40mGy)	0.18	(-0.01, 0.38)
IHD	Heart dose (p50: 11mGy)	0.23	(-0.04, 0.51)
CeVD	Brain dose (p50: 8mGy)	0.40	(-0.11, 0.92)
Incidence			
IHD	Heart dose (p50: 11mGy)	0.15	(-0.01, 0.31)
CeVD	Brain dose (p50: 8mGy)	0.08	(-0.17, 0.33)

Relative risks were estimated using Cox proportional hazard models with year as a time scale, birth year, sex, race, ethnicity, smoking habits, BMI at baseline and educational attainment. 95% CI were estimated using bootstrapping with 400 repetitions.

*The RERI compares the risk difference of high cumulative radiation exposure between the highest nSES tertile and the lowest nSES tertile. Positive estimates indicate that people in high nSES areas have an additional risk of exposure to similar doses of radiation than those in low nSES areas.

CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease; p50: median cumulative dose

Supplemental Tables

Table 11. [Supplemental Table S2] Associations between cumulative radiation exposure and nSES on CD mortality including 105,802 eligible participants (without education in the model

Factors and outcomes+A1:I25	Model 1		Model 2		Model 3		Model 4	
All CD mortality	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Thyroid dose (per 100mGy)	1.05	(1.02, 1.07)			1.05	(1.02, 1.07)	1.08	(1.04, 1.13)
nSES tertile								
Low			1.24	(1.14, 1.34)	1.23	(1.14, 1.34)	1.35	(1.21, 1.50)
Middle			1.05	(0.96, 1.14)	1.04	(0.96, 1.13)	1.14	(1.02, 1.28)
High			*Ref.*		*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]								
Low							1.03	(1.00, 1.06)
Middle							1.03	(0.99, 1.07)
High							1.08	(1.04, 1.13)
p-value for interaction							*0.06*	
IHD mortality								
Heart dose (per 100mGy)	1.10	(1.04, 1.17)			1.10	(1.04, 1.17)	1.18	(1.06, 1.30)
nSES tertile								
Low			1.31	(1.17, 1.47)	1.31	(1.17, 1.47)	1.43	(1.24, 1.64)
Middle			1.01	(0.89, 1.14)	1.01	(0.89, 1.14)	1.07	(0.92, 1.24)
High			*Ref.*		*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]								
Low							1.05	(0.97, 1.13)
Middle							1.08	(0.97, 1.21)
High							1.18	(1.06, 1.30)
p-value for interaction							*0.14*	
CeVD mortality								
Brain dose (per 100mGy)	1.42	(1.07, 1.89)			1.43	(1.07, 1.89)	1.99	(1.36, 2.90)
nSES tertile								
Low			0.97	(0.80, 1.18)	0.96	(0.79, 1.17)	1.14	(0.89, 1.48)
Middle			0.95	(0.78, 1.16)	0.94	(0.77, 1.15)	1.11	(0.86, 1.44)
High			*Ref.*		*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]								
Low							1.17	(0.76, 1.81)
Middle							1.20	(0.76, 1.89)
High							1.99	(1.36, 2.90)
p-value for interaction							*0.08*	

All hazard ratios (HR) and 95% confidence intervals (CI) were estimated using discrete time hazard models with calendar year as a time scale, adjusted by baseline covariates (age as a time-varying covariate, sex, race, ethnicity, BMI and smoking). Follow-up started in 1994 and ended in 2012. All estimates for radiation are for a 100mGy increase in organ dose.

Model 1: baseline covariates + cumulative radiation organ dose

Model 2: baseline covariates + nSES tertiles

Model 3: baseline covariates + cumulative radiation organ dose + nSES tertiles

Model 5*: baseline covariates + cumulative radiation organ dose + nSES tertiles + (radiation * nSES)

[ǂ]Effect of cumulative radiation organ doses stratified by nSES tertile using postestimation commands

CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease

Table 12. [Supplemental Table S3] Associations between cumulative radiation exposure and nSES on CD incidence including 88,989 eligible participants (without education in the model)

Factors and outcomes	Model 1		Model 2		Model 3		Model 4	
IHD incidence	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Heart dose (per 100mGy)	1.16	(1.06, 1.28)			1.16	(1.05, 1.27)	1.19	(1.04, 1.37)
nSES tertile								
Low			1.21	(1.12, 1.32)	1.21	(1.12, 1.32)	1.24	(1.13, 1.37)
Middle			1.05	(0.97, 1.15)	1.05	(0.97, 1.14)	1.06	(0.96, 1.17)
High			*Ref.*		*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]								
Low							1.10	(0.96, 1.28)
Middle							1.17	(1.02, 1.35)
High							1.19	(1.04, 1.37)
p-value for interaction							*0.69*	
CeVD incidence								
Brain dose (per 100mGy)	1.72	(1.20, 2.47)			1.69	(1.17, 2.43)	2.38	(1.44, 3.93)
nSES tertile								
Low			1.16	(1.03, 1.30)	1.15	(1.02, 1.29)	1.27	(1.09, 1.48)
Middle			1.01	(0.90, 1.14)	1.01	(0.90, 1.13)	1.08	(0.92, 1.27)
High			*Ref.*		*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]								
Low							1.30	(0.78, 2.16)
Middle							1.52	(0.86, 2.69)
High							2.38	(1.44, 3.93)
p-value for interaction							*0.16*	

All hazard ratios (HR) and 95% confidence intervals (CI) were estimated using discrete time hazard models with calendar year as a time scale, adjusted by baseline covariates (age as a time-varying covariate, sex, race, ethnicity, BMI and smoking). Follow-up started in 1994 and ended in 2012. All estimates for radiation are for a 100mGy increase in organ dose.
Model 1: baseline covariates + cumulative radiation organ dose
Model 2: baseline covariates + nSES tertiles
Model 3: baseline covariates + cumulative radiation organ dose + nSES tertiles
Model 5*: baseline covariates + cumulative radiation organ dose + nSES tertiles + (radiation * nSES)
[ǂ]Effect of cumulative radiation organ doses stratified by nSES tertile using postestimation commands
CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease

Table 13. [Supplemental Table S4] Associations between cumulative radiation exposure and nSES on circulatory disease mortality after adjusting for educational attainment and individual household income among 45,506 radiologic technologists

Factors and outcomes	Model 4†		Model 5‡		Model 6		Model 7	
All CD mortality	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Thyroid dose (per 100mGy)	1.16	(0.97, 1.39)	1.18	(0.84, 1.64)	1.15	(0.96, 1.37)	1.14	(0.82, 1.59)
nSES tertile								
Low	1.36	(1.08, 1.71)	1.32	(0.90, 1.93)	1.25	(1.00, 1.58)	1.19	(0.81, 1.74)
Middle	0.93	(0.73, 1.19)	1.01	(0.66, 1.53)	0.89	(0.69, 1.13)	0.95	(0.62, 1.44)
High	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level								
Vocational, high school or less	1.22	(0.86, 1.72)	1.22	(0.86, 1.73)	1.17	(0.83, 1.64)	1.17	(0.74, 1.54)
Radiologic technology	1.10	(0.89, 1.35)	1.10	(0.89, 1.35)	1.05	(0.85, 1.29)	1.05	(0.63, 1.44)
Some college	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Household income in Q3								
<$50,000					1.85	(1.28, 2.68)	1.86	(1.29, 2.69)
$50,000-74,999					1.29	(0.90, 1.85)	1.30	(0.91, 1.85)
$75,000-99,999					0.90	(0.59, 1.36)	0.90	(0.59, 1.36)
≥$100,000					*Ref.*		*Ref.*	
Radiation effect by nSES tertile¥								
Low			1.22	(0.97, 1.52)			1.22	(0.97, 1.52)
Middle			1.07	(0.79, 1.44)			1.05	(0.78, 1.41)
High			1.18	(0.84, 1.64)			1.14	(0.82, 1.59)
p-value for interaction			*0.8*				*0.70*	
IHD mortality	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Heart dose (per 100mGy)	1.20	(0.67, 2.14)	1.66	(0.59, 4.66)	1.17	(0.65, 2.11)	1.52	(0.54, 4.31)
nSES tertile								
Low	1.37	(0.99, 1.90)	1.57	(0.97, 2.52)	1.22	(0.88, 1.69)	1.35	(0.84, 2.17)
Middle	0.97	(0.69, 1.37)	1.09	(0.66, 1.81)	0.90	(0.63, 1.27)	1.00	(0.60, 1.65)
High	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level								
Vocational, high school or less	1.15	(0.70, 1.91)	1.15	(0.70, 1.91)	1.08	(0.66, 1.78)	1.08	(0.66, 1.78)
Radiologic technology	1.28	(0.96, 1.73)	1.29	(0.96, 1.73)	1.19	(0.89, 1.60)	1.19	(0.89, 1.60)
Some college	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Household income in Q3								
<$50,000					3.07	(1.76, 5.35)	3.05	(1.75, 5.31)
$50,000-74,999					1.72	(0.98, 3.02)	1.71	(0.98, 3.00)
$75,000-99,999					1.38	(0.74, 2.59)	1.38	(0.74, 2.58)
≥$100,000					*Ref.*		*Ref.*	
Radiation effect by nSES tertile¥								
Low			1.02	(0.47, 2.24)			1.06	(0.48, 2.34)
Middle			1.09	(0.42, 2.84)			1.05	(0.40, 2.75)
High			1.66	(0.59, 4.66)			1.52	(0.54, 4.31)
p-value for interaction			*0.7*				*0.82*	

Supplemental Table S4. *continued*

Factors and outcomes	Model 4†		Model 5‡		Model 6		Model 7	
CeVD mortality	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Brain dose (per 100mGy)	1.16	(0.16, 8.24)	1.57	(0.09, 26.5)	1.14	(0.16, 8.15)	1.53	(0.09, 25.7)
nSES tertile								
Low	0.96	(0.54, 1.67)	0.93	(0.42, 2.08)	0.94	(0.53, 1.66)	0.92	(0.40, 2.05)
Middle	0.79	(0.44, 1.41)	0.95	(0.38, 2.34)	0.78	(0.44, 1.39)	0.94	(0.38, 2.31)
High	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level								
Vocational, high school or less	1.20	(0.48, 3.03)	1.20	(0.48, 3.03)	1.19	(0.48, 2.97)	1.19	(0.48, 2.99)
Radiologic technology	1.35	(0.81, 2.25)	1.35	(0.81, 2.25)	1.34	(0.80, 2.24)	1.34	(0.80, 2.24)
Some college	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Household income in Q3								
<$50,000					1.07	(0.45, 2.57)	1.08	(0.45, 2.57)
$50,000-74,999					0.97	(0.44, 2.15)	0.97	(0.44, 2.16)
$75,000-99,999					0.75	(0.30, 1.93)	0.75	(0.30, 1.93)
≥$100,000					*Ref.*		*Ref.*	
Radiation effect by nSES tertile[ǂ]								
Low			1.76	(0.11, 27.0)			1.76	(0.11, 26.9)
Middle			0.46	(0.01, 26.0)			0.45	(0.01, 25.3)
High			1.57	(0.09, 26.5)			1.53	(0.09, 25.7)
p-value for interaction			*0.8*				*0.84*	

All hazard ratios (HR) and 95% confidence intervals (CI) were estimated using discrete time hazard models with calendar year as a time scale, adjusted by baseline covariates (age as a time-varying covariate, sex, race, ethnicity, BMI and smoking). Follow-up started in 1994 and ended in 2012. All estimates for radiation are for a 100mGy increase in organ dose.

Model 4†: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment (among 45,506 participants with information on household income in Q3)

Model 5‡: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + (radiation * nSES interaction) (among 45,506 participants with information on household income in Q3)

Model 6: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + household income

Model 7: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + household income + (radiation * nSES)

[ǂ]Effect of cumulative radiation organ doses stratified by nSES tertile using postestimation commands

CD: circulatory disease, IHD: ischemic heart disease, CeVD: cerebrovascular disease

Table 14. [Supplemental Table S5] Associations between cumulative radiation exposure and nSES on circulatory disease incidence after adjusting for educational attainment and individual household income among 45,102 radiologic technologists

Factors and outcomes	Model 4†		Model 5‡		Model 6		Model 7	
IHD incidence	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Heart dose (per 100mGy)	1.94	(1.33, 2.82)	1.60	(0.88, 2.94)	1.97	(1.35, 2.86)	1.63	(0.89, 2.99)
nSES tertile								
Low	1.23	(1.05, 1.44)	1.15	(0.93, 1.43)	1.18	(1.00, 1.39)	1.11	(0.89, 1.38)
Middle	0.97	(0.83, 1.14)	0.93	(0.75, 1.17)	0.95	(0.81, 1.12)	0.91	(0.73, 1.14)
High	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level								
Vocational, high school or less	1.06	(0.80, 1.40)	1.06	(0.80, 1.40)	1.03	(0.79, 1.37)	1.03	(0.78, 1.37)
Radiologic technology	1.01	(0.88, 1.16)	1.01	(0.88, 1.16)	0.99	(0.86, 1.14)	0.99	(0.86, 1.14)
Some college	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Household income in Q3								
<$50,000					1.34	(1.09, 1.65)	1.35	(1.10, 1.65)
$50,000-74,999					1.16	(0.96, 1.41)	1.17	(0.96, 1.41)
$75,000-99,999					0.94	(0.76, 1.15)	0.94	(0.76, 1.15)
≥$100,000					*Ref.*		*Ref.*	
Radiation effect by nSES tertile¥								
Low			2.24	(1.28, 3.90)			2.27	(1.30, 3.97)
Middle			1.96	(1.08, 3.57)			1.98	(1.08, 3.60)
High			1.60	(0.88, 2.94)			1.63	(0.89, 2.99)
p-value for interaction			*0.70*				*0.71*	
CeVD incidence	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Brain dose (per 100mGy)	1.76	(0.63, 4.90)	2.35	(0.49, 11.3)	1.70	(0.61, 4.74)	2.24	(0.46, 10.9)
nSES tertile								
Low	1.34	(1.07, 1.68)	1.47	(1.04, 2.07)	1.24	(0.99, 1.55)	1.35	(0.96, 1.91)
Middle	1.18	(0.94, 1.47)	1.18	(0.85, 1.65)	1.12	(0.89, 1.40)	1.13	(0.81, 1.57)
High	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Education level								
Vocational, high school or less	0.94	(0.63, 1.41)	0.94	(0.63, 1.41)	0.91	(0.61, 1.36)	0.91	(0.61, 1.36)
Radiologic technology	0.95	(0.78, 1.15)	0.95	(0.78, 1.15)	0.91	(0.75, 1.11)	0.91	(0.75, 1.11)
Some college	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Household income in Q3								
<$50,000					1.76	(1.30, 2.37)	1.75	(1.30, 2.37)
$50,000-74,999					1.48	(1.11, 1.97)	1.47	(1.10, 1.97)
$75,000-99,999					1.09	(0.79, 1.51)	1.09	(0.79, 1.50)
≥$100,000					*Ref.*		*Ref.*	
Radiation effect by nSES tertile¥								
Low			1.14	(0.22, 5.82)			1.14	(0.22, 5.77)
Middle			2.20	(0.51, 9.48)			2.10	(0.49, 8.97)
High			2.35	(0.49, 11.3)			2.24	(0.46, 10.9)
p-value for interaction			*0.76*				*0.78*	

All hazard ratios (HR) and 95% confidence intervals (CI) were estimated using discrete time hazard models with calendar year as a time scale, adjusted by baseline covariates (age as a time-varying covariate, sex, race, ethnicity, BMI and smoking). Follow-up started in 1994 and ended in 2012. All estimates for radiation are for a 100mGy increase in organ dose.

Model 4†: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment (among 45,506 participants with information on household income in Q3)

Model 5‡: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + (radiation * nSES interaction) (among 45,506 participants with information on household income in Q3)
Model 6: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + household income
Model 7: baseline covariates + cumulative radiation organ dose + nSES tertiles + educational attainment + household income + (radiation * nSES)
ǂEffect of cumulative radiation organ doses stratified by nSES tertile using postestimation commands
IHD: ischemic heart disease, CeVD: cerebrovascular disease

Chapter 4.

Manuscript 3. Impact of sequential selection in a large occupational cohort of medical radiation on estimates of circulatory disease morbidity and mortality: The US Radiologic Technologist (USRT) study

Introduction

The U.S. Radiologic Technologist (USRT) study is the largest longitudinal study of medical occupational radiation exposure to date(18). A total of 146,022 radiologic technologists across the US who had been certified for at least two years by the American Registry of Radiologic Technologists (ARRT) in 1982 were invited to participate (19). The main goal of this cohort was to investigate the effect of protracted exposure to low-dose occupational ionizing radiation on cancer, circulatory disease (CD) and other chronic conditions. More than 110,000 technologists completed at least one of the four comprehensive questionnaire surveys regarding demographic characteristics, health status, employment history and exposure information (20). Over the three decades of the USRT study, participation among living eligible cohort members across study waves was 68% on average(49). If the characteristics of these participants are systematically different from those who did not participate, this might introduce bias to risk estimates through selective mortality and attrition. This might be problematic in this cohort because, although mortality outcomes are obtained through linkage with federal sources, exposure estimation and incidence of disease are dependent on questionnaire completion. Thus, conditioning on participation might be introducing selection bias to this historical cohort.

Selection bias is a common phenomenon in epidemiology that occurs when methods of subject selection (perhaps, recruitment and follow-up) result in a sample of participants for which the effect of interest is different than in the general population(38,40,88). In longitudinal cohort studies, non-participation is the proportion of people who refuse to participate at baseline

(nonresponse) and the proportion of people who enter the study initially, but do not complete one or more of the follow-up steps (attrition)(38). Nonresponse and attrition are ways the analytical sample may not accurately represent the source population and, if attrition continues at each wave, the final sample might not even represent the original cohort.

This issue has been extensively studied, and several demographic, socioeconomic, occupational and health characteristics have been found to differ between people who choose to participate and those who do not. Although not entirely consistent, previous studies show that individual-level characteristics such as participants are more likely to be female(42,45,89,90), white (vs. other races/ethnicities)(45,89), married (vs. other marital status)(41,44,45,47,89,91), have a higher educational level(41,42,45,47,48,89,91), and a higher individual income(42,91). In terms of age, participation appears to increase with age until mid-adulthood (40-50 years) and then declines with increasing age(41,42,44,45,47,48,89–93). Some occupational factors that are associated with participation are higher skilled job grade (vs. manual, or less skilled jobs)(41,93) and more years worked(41,91). In addition, there are several health factors associated with increased participation including never smoking(44,45,47,89), having a normal body mass index (BMI),(44,47) and being generally healthier(41).

Meanwhile, neighborhood or contextual factors have been less frequently studied in relation to participation. Namely, Chaix *et al*. found that the rate of study participation is higher among neighborhoods with higher levels of educational attainment, high median income, and high mean property value after controlling for individual education(48). A Dutch study reported that participation rates increased with urbanity level and household income(93). However, neighborhood predictors of participation have not been thoroughly explored to date. In general, the pattern of participation in the USRT cohort since its conception in 1982 and the potential impact of selection bias on risk estimates have not yet been explored. In response to this concern,

this paper has two main objectives: 1) describe the characteristics of participants and non-participants as they relate to completing the questionnaires at each of the four study waves of the USRT cohort, and 2) estimate the association between occupational radiation and circulatory disease (CD) morbidity and mortality, adjusting for possible selection bias using marginal structural models.

Methods

Study population

To be eligible to participate in the USRT study, radiation technologists had to be certified for at least two years by the American Registry of Radiologic Technologists (ARRT) by 1982 when the cohort was enumerated. The first questionnaire (Q1) was mailed between 1983 and 1990 to all enumerated members alive and the second questionnaire (Q2) was mailed between 1994 and 1998 to all living USRT members regardless of completion of Q1. A total of 110,374 participants responded to one or both questionnaires (Q1/Q2 respondents). The third questionnaire (Q3) was mailed only to Q1/Q2 respondents who were alive between 2003 and 2005, and the fourth questionnaire (Q4) was sent between 2012 and 2014 to Q1/Q2 respondents alive at that time (regardless of Q3 completion). These surveys inquired about demographic information, exposure to ionizing radiation and other risk factors, incidence of disease and general health status. People who responded to each questionnaire were considered participants of that survey. A person was considered a non-participant if they were eligible and alive on the first year of each questionnaire but did not complete the survey, or if they died before answering the questionnaires.

Circulatory disease (CD) outcomes

CD mortality

Vital status of all the original 146,022 ARRT members was determined through annual renewals with ARRT and through linkage with National Death Index (NDI), Social Security

administration and National Change of Address(18) until December 31st, 2012. For all those who died, specific date of death and underlying cause were obtained from NDI-*Plus* using ICD 8, 9 and 10 codes (22). Specific outcomes evaluated were mortality from ischemic heart disease (ICD-8 410–414; ICD-9 410–414; ICD-10 I20–I25) and cerebrovascular diseases (ICD-8 430-438; ICD-9 430-438; ICD-10 I60-I69). Participants were included in the mortality analyses if they were alive in 1983, reported working for at least a year between 1916 and 1997, and completed Q1 and/or Q2. No additional exclusions were made.

CD morbidity

Self-reported incidence data for ischemic heart disease (IHD), myocardial infarction, and stroke were obtained from responses in Q3 and Q4. In each survey, participants were asked to select any medical conditions that they had been diagnosed with by a doctor and report the first year (or age) of diagnosis. Unlike with mortality data, where the exact date of death was known, year of morbidity is only known at the time of survey completion. To unify conditions across questionnaires (with wording differences), we included myocardial infarction as part of ischemic heart disease and stroke as part of cerebrovascular disease (CeVD). Participants who reported multiple CD comorbidities were included in the analysis for each condition. Participants were included in the morbidity analyses if they were alive and CD-free in 1983, reported working for at least a year between 1916 and 1997, completed either Q1 and/or Q2, and completed either Q3 and/or Q4. We excluded participants if: 1) they reported having any of the following conditions in the baseline questionnaire: myocardial infarction, stroke, angina pectoris, or a coronary bypass, or 2) they reported a year of diagnosis earlier than their first questionnaire date or did not report a year of diagnosis.

Cumulative ionizing radiation

Individual cumulative exposure to ionizing radiation was estimated for 110,374 radiation technologists as described elsewhere (54,55). In brief, personal annual doses were estimated for the years 1916-1997 based on data from personnel monitoring badge records, time working as radiation technologists, individual employment practices based on the first three surveys, individual apron usage from the second and third questionnaires (Q2 and Q3), and literature-reported exposure measurements for years when badge doses were not available. Specific annual organ doses (in mGy) for each technologist were estimated using organ dose factors, reported use of personal protective equipment, and body mass index. For the current analyses, we used cumulative heart dose for IHD incidence and mortality, and cumulative brain dose for CeVD outcomes as continuous measures of cumulative radiation exposure.

Predictors of participation at each of the four surveys

Very little information was available regarding technologists who did not participate in this study and consisted only of basic demographic information from ARRT registration (birth year, sex, race and certification year). Survey information gathered from questionnaires was used to identify potential predictors of participation in subsequent waves. These potential predictors were considered *a priori* based on published studies on selection bias (41–43) and they include: birth year, sex, race, certification year, ethnicity, marital status, educational background (highest degree achieved), smoking status, alcohol use, body mass index, hypertension, diabetes, high cholesterol, self-reported health status, and individual household income.

Neighborhood socioeconomic status (nSES)

In addition, we considered rural status and neighborhood socioeconomic status (nSES) of the place of residence as potential predictors of participation. As previously described (94), we used US census block-groups as a proxy for neighborhoods and created a standardized nSES using US census data. Similar to other studies of the effect of nSES on health (24–26,29), we constructed a

composite nSES index for all block-groups in the US for 1990, 2000 and 2010 to correspond with each study wave where addresses are available (Q2, Q3, and Q4). We downloaded tabular sociodemographic data at the block-group level from the Minnesota Population Center: National Historical Geographic Information System(72). Specifically, sociodemographic data were obtained from the 1990 US Census to calculate $nSES_{Q2}$, the 2000 US Census for $nSES_{Q3}$ and the 2008-2012 American Community Survey (ACS) for $nSES_{Q4}$.

To create the nSES index for each wave, we adapted a procedure utilized by Diez Roux *et al*.(29) that combined 6 components of nSES: regionally-adjusted median household income, regionally-adjusted median housing value, percent of households with interest/income, percent of adults who completed high school, percent of adults who completed college, and percent of employed persons in managerial occupations. A z score for each component *j* was calculated using the mean and standard deviation among all block-groups *i* in the US $z_{ij} = (x_{ij} - \bar{x_j})/sd_j$ for each block-group *i* and component *j*. The nSES index for all US block-groups at each time point, *Qn*, was calculated by summing the z scores for each of the 6 components ($nSES_{Qn}$). An nSES index for each time point was assigned to each participant by geocoding their corresponding mailing addresses using ESRI's USA Composite Geocoding service in ArcGIS® to a block-group. Across all three time points, more than 99% of the addresses were successfully geocoded to a latitude and longitude in the US map. The index was then standardized ($nSES_{Q_nstd}$) using the mean nSES index from neighborhoods where USRT participants lived at each point ($nSES_{USRT_{Qn}}$)

$nSES_{Q_nstd} = {(\sum_{j=1}^{6} z_j)}\Big/{\overline{nSES_{USRT_{Qn}}}}$ for each USRT block-group and each time point *Qn*.

Higher $nSES_{Q_nstd}$ scores denote higher neighborhood socioeconomic advantage within the cohort. Finally, $nSES_{Q_nstd}$ was divided into tertiles for each year. Rural status was defined if more than 50% of the blocks within each block-group were categorized as rural for each year.

Data analysis

Participation at each study wave

Characteristics of participants and non-participants were summarized in contingency tables for each of the four study waves (Q1-4). For each characteristic, we calculated risk differences (RD) of participation and 95% confidence intervals (CI) using generalized linear models (GLM) with binomial distribution and an identity link. Due to convergence issues with this model, adjusted RDs and 95%CI were calculated using the marginal probabilities estimated with a GLM model with a logit link. Specifically, for participation in Q1 we calculated the probability of participation conditional on the ARRT variables (birth year, race, ethnicity and certification year). For participation in Q2, we calculated two sets of adjusted probabilities of participating: one for people who participated only in Q2 (not in Q1) compared with technologists who did not participate in either Q1 or Q2. No information was available for these groups from Q1, so the adjusted models only included birth year, gender, race, ethnicity, certification year, nSES and rural status (which was available for all technologists who were sent Q2 regardless of their participation in either questionnaire). The second set of RDs compared technologists who participated in both Q1 and Q2 with technologists who only participated in Q1 (but did not return Q2) and were estimated by adding information from Q1 (education level, marital status, smoking, alcohol use and BMI) to the first model.

Being eligible to participate in Q3 was conditional on completion of either Q1 or Q2, so we estimated RDs for participation in this survey using ARRT characteristics (birth year, race, ethnicity, and certification year), neighborhood factors (rurality and nSES) along with information collected on Q1/Q2 (education level, marital status, smoking, alcohol use, BMI, hypertension, diabetes, high cholesterol, and self-reported health status). For participation in Q4,

we calculated the probability of participation using the same covariates as in Q3 and adding household annual income to the crude model.

Impact of radiation on CD mortality and morbidity

CD morbidity and mortality hazard risks (HR) and 95% confidence intervals (CI) from exposure to occupational ionizing radiation were estimated using discrete time hazard models with calendar year as the time scale adjusted for birth year, sex, race, ethnicity, smoking habits and BMI at baseline. Calendar year was included in the model as an indicator variable to estimate the baseline risk of morbidity or mortality at each year. For mortality outcomes, follow-up started in 1983 and ended at the earliest of the following events: year of death, year of lost-to-follow-up (censored) or 2012 when the latest mortality data were ascertained (censored). For incident outcomes, start of follow-up was the year when the baseline questionnaire was completed (Q1, or Q2 if Q1 was missing) and follow-up ended at the earliest of the following events: year of first diagnosis or year when the latest questionnaire was completed (Q4, or Q3 if Q4 was missing). Cumulative organ doses were treated as time-varying variables such that, at each time point, a person's exposure was the sum of all yearly doses up to and including that year.

Marginal structural models

We used marginal structural models to adjust for the potential effect of selection bias. To model participation at each study wave, we calculated inverse probability weights (IPW) based on a logistic model of participation (yes/no). In Appendix A, we listed the specific variables that were included to model participation at each stage and provided details of the construction of the final weights. Individual survey weights were stabilized using the overall probability of participation calculated using an intercept-only logistic model for participation at each study visit. Final weights were calculated by multiplying individual survey weights (w_{Q1}, $w_{Q2,}$ w_{Q3}, w_{Q4}). A person's participation IPW varied across the four study waves. For example, for outcomes

occurring between Q1 and Q2 (1983-1993) the combined weight for each participant was $w_{Q1} \times w_{Q2}$; for outcomes occurring between Q2 and Q3 (1994-2002) the final weight was calculated considering the probability of participating in Q1, Q2 and Q3 ($w_{Q1} \times w_{Q2} \times w_{Q3}$); and for outcomes occurring between Q3 and Q4 (2003 and 2014) the final weight was $w_{Q1} \times w_{Q2} \times w_{Q3} \times w_{Q4}$.

To construct participation IPWs, we evaluated different marginal structural models that accounted for different number of predictors of participation (Appendix A). When more variables were included, we obtained more information about sequential selection in this cohort at the cost of dropping participants out of the model if they were missing information on any of those predictors. In the end, we prioritized including as many participants in the model as possible and selected the following set of covariates: birth year, race, ethnicity, certification year, rural residence, nSES, marital status, smoking, BMI at baseline, and participation in previous study waves. To check the distribution of the stabilized weights at each wave among the study population, we used descriptive statistics (average, minimum and maximum) (Appendix A, Table 19). Specifically, for the untruncated stabilized IPWs the mean was 0.72 (SD: 1.28), the minimum was 0.20, the 1st percentile was 0.22, the 99th percentile was 4.09, and the maximum value was 214.8. To account for extreme values at each side of the weight distribution, final weights were trimmed to the 1st and 99th percentile to eliminate extreme values (people weighing too much or too little in terms of participation).

Other models that accounted for more predictors were also evaluated in relation to the association between cumulative ionizing radiation and CD outcomes and the results are included in Appendix B. The effect of selection bias was estimated by comparing HRs and 95%CIs estimated from models (adjusted for birth year, sex, race, ethnicity, smoking habits and BMI at baseline as described in the previous section) with and without selection weights. All analyses were performed using Stata/IC v.14.2.

Results

Among eligible living technologists at each time point, participation was 64% for Q1, 73% for Q2, 71% for Q3 and 61% for Q4. Figure 3 provides further detail regarding number of participants, non-respondents and decedents at each of the four study surveys among those eligible at each time point.

[Figure 3]

The differences in the probability of participation according to demographic, occupational, residential and health characteristics of radiologic technologists for each of the four USRT questionnaires are summarized in Tables 15-18. The overall characteristics of participants were generally consistent across the four surveys in the crude and adjusted models. Being younger, female, married, and having a normal BMI was associated with higher probability of participating. On the other hand, being a smoker at baseline, having lower education levels (vocational, high school or less) and being black or other non-white race was associated with a lower probability of participating. In terms of neighborhood-level factors, living in a rural area was associated with a moderate increase in the probability of participating compared to urban areas. Living in the highest tertile of nSES was also associated with increased probability of participating versus the lowest tertile, but there was no clear pattern across nSES tertiles in the adjusted models. People who reported having a fair or poor health status in Q2 were less likely to participate in either Q3 or Q4. Finally, a lower household income reported in Q3 was associated with decreased probability of participating in Q4.

[Tables 15-18]

From the 146,022 original sample, there were a total of 4,719 deaths from ischemic heart disease (IHD) but 2,391 cases were excluded from the analysis because they did not complete either Q1 or Q2, and 63 were excluded because they occurred among technologists who did not work (1,074). There were 2,265 cases of IHD mortality among 109,300 participants included in the mortality analyses. Thus, the prevalence of IHD mortality among non-respondents of Q1/Q2 was 6.7% and 2.1% among Q1/Q2 respondents. Similarly, a total of 1,511 deaths from cerebrovascular disease (CeVD) were observed among 146,022 ARRT registrants but 757 were excluded because they did not complete Q1 or Q2, and 19 were excluded because they reported they never worked as radiation technologists. Thus, a total of 735 cases of CeVD mortality were observed during follow-up. Therefore, the prevalence of CeVD mortality among non-respondents of Q1/Q2 was 0.019% and 0.002% among Q1/Q2 respondents. In terms of morbidity, there were 3,695 incident cases of IHD among respondents who were CD-free at baseline during 2,005,111 person-years of follow-up. During this period, there were 1,824 incident cases of CeVD reported by participants after excluding for baseline conditions.

Figure 4 shows the hazard ratios and 95% CI for a 100mGy increase in cumulative heart dose for IHD mortality and incidence. Without considering participation weights, the HR for IHD mortality was 1.07 (95%CI 1.01-1.13) adjusting for age, sex, race, ethnicity, smoking habits and BMI at baseline (models 1 and 2). When adjusting for predictors of sequential participation through inclusion of IPWs in the model (model 3), the HR decreased 3% points compared to the estimate that did not account for effects of selection (HR: 1.04, 95%CI 0.97 - 1.20). When we used weights truncated to the 1st and 99th percentile, the HR was 1% point smaller than the original estimate (HR: 1.06, 95%CI 1.01, 1.12). A similar pattern was observed for IHD incidence but with more variation in the 95% CI. Specifically, in the model with truncated participation weights, the HR was 4% points smaller than the estimate without selection weights (HR:1.17, 95%CI 1.06 – 1.29 versus HR: 1.13, 95%CI 1.00, 1.28, respectively).

[Figure 4]

In terms of CeVD mortality and incidence, we observed more variation in the effect estimates and wider confidence intervals across all models than for IHD outcomes (Figure 5). Among eligible participants with a final weight available, the HR for CeVD mortality was 1.54 (95%CI: 1.19, 1.99) for 100mGy increase in cumulative brain dose adjusted for age, sex, race, ethnicity, smoking habits and BMI at baseline without adjusting for selection bias (model 2). When IPWs truncated to the 1st and 99th percentile were included in the model, the HR was 4% points smaller (HR:1.50, 95%CI 1.10, 2.01) (model 4). For CeVD incidence, the HR was 1.71 (95% CI: 1.18, 2.48) when weights were not included (model 2), and this decreased in 15% points to an effect estimate of 1.56 (95%CI 0.98, 2.47) if truncated participation weights were included.

[Figure 5]

During sensitivity analysis, we evaluated the effect of different selection weights that included a larger set of covariates related to participation. The effect estimates resulting from the application of each set of weights on the association between cumulative radiation exposure and CD outcomes are detailed in Appendix B. Table 20 in Appendix B shows some differences in estimates depending on the specification of the participation models, but the direction of the association between radiation exposure and CD outcomes remained consistent. In general, the results showed a small percent decrease in the effect estimates when selection weights truncated to the 1st and 99th percentile were used. Effect estimates from untruncated weights showed larger differences from the models without weights and had wider confidence intervals.

Discussion

In this national cohort of radiologic technologists, we found that the pattern of participation, non-response and attrition was not a random process but that it was related to several demographic characteristics. Generally, we found that participation in all surveys was higher among women, whites, married people, technologists in their 50s and 60s at each of the four surveys, those certified after 1950, non-smokers, people with a normal BMI at baseline and those who reported a better health status. Although nSES was not consistently associated with participation, we found that technologists with rural addresses were more likely to complete each questionnaire compared to people in urban areas. Additionally, we found that IHD mortality was 3 times higher in never-participants than ever-participants and CeVD mortality was 10 times higher in never-participants versus ever-participants.

Despite all these differences in the distribution of mortality and risk characteristics of participants and non-participants, we found only a small impact of selection bias on our estimates of the association of cumulative radiation exposure and CD outcomes. After including IPWs of sequential participation in our models, we found a 1%-point difference in the HR of IHD mortality for a 100mGy increase in cumulative heart dose and a 4%-point difference in the estimate of IHC incidence. In terms of CeVD, we found a 4%-point difference in the HR of CeVD mortality for a 100mGy increase in cumulative brain dose and a 15%-point reduction in the HR of CeVD incidence after adjusting for age, sex, race, ethnicity, smoking and BMI. After addition of IPW in the models, the confidence intervals of mortality outcomes remained consistently narrow, while they because visibly wider among incident outcomes.

Consistent with other published studies, USRT participants were more likely to be white(45,89), female(42,45,89,90), married(41,44,45,47,89,91), of higher income(42,91), never smokers(44,45,47,89) and with a normal BMI(44,47). These characteristics are generally related to more socially and economically stable conditions, and being generally healthier(41) which in

turn might influence the likelihood of participating and continuing in a study. In terms of age, we found a slight increase in participation up to 60 years of age and then a decline with increasing age across the study waves which is in agreement with other studies(41,42,44,45,47,48,89–93). Other studies have reported that a longer length of work was associated with increased participation(41,91). Among this group of radiologic technologists, we found that the earliest occupational cohort (certified before 1950) was less likely to complete any of the questionnaires compared to later cohorts, but there was no pattern of increased participation with later certification years.

In terms of neighborhood characteristics, we found that living in more affluent neighborhoods was associated with increased likelihood of participating in all surveys, but this association disappeared after we adjusted for other predictors. Contextual predictors of participation have not been extensively studied, but there is limited evidence to suggest that participation rates increase with neighborhood affluence and urbanity level(48,93,95,96). Unlike these studies, we found that rural residence was consistently associated with increased participation across all time points compared to urban residence after adjusting for other factors. Greater urbanity levels are oftentimes associated with increased access and proximity to resources which encourages participation in studies and other activities(97). Since this is an occupational cohort of mostly employed people, it is possible that technologists residing in rural areas had a better socioeconomic position than their neighbors which might influence their ability to participate. However, we do not have more information on the contextual environment of these participants, so we cannot speculate on the causes of participation.

Using marginal structural models to assess the impact of selection bias on the association between radiation and CD outcomes, we found limited evidence of selection bias. In general, we found that higher chronic exposure to ionizing radiation increased the risk of IHD and CeVD

incidence and mortality after adjusting for age, sex, race, ethnicity, smoking, BMI and potential selection bias. Depending on the specific set of weights and parameters included in the selection model, the precision of the confidence intervals differed and sometimes included the null, but the HR remained consistently above 1. Although we found little evidence of selection bias in our estimates for CD outcomes, this might not necessarily be true for other outcomes in this cohort such as cancer.

A systematic review of participation bias in cohort studies reviewed several studies that evaluated the impact of this phenomenon on circulatory disease outcomes(98). In general, these studies found similar differences in the characteristics of participants and non-participants as those in the USRT cohort. In addition, most studies reported higher prevalence of CD mortality among non-participants than participants consistent with our findings. Despite these differences, we found a negligible impact of selection bias on our estimates of the risk of exposure on CD outcomes consistent with articles summarized in this systematic review. However, only a few studies have quantified the effect of selection processes on the risk estimates of chronic disease using non-simulated data(46,96,99).

A study of various risk factors for cardiovascular disease (CVD) found that HRs for most baseline risk factors (older age, manual social class, obesity, current smoking, heavy drinking, no exercise and history of CVD) were larger among participants than non-participants(99). Although they did not report statistical significance for the interaction between participation status and risk factors on CVD mortality, the results suggest that if non-participants would have been included in the study, the associations reported would have been attenuated. A recent study by Long *et al* (96) conducted a very similar application of IPWs to assess the presence and impact of selection bias on the effect of racial disparities on stroke risk factors. The authors considered several selection models with increasing number of predictors of participation (like those included in this analysis)

and found only a 1-2%-point change in the relative risk of incident hypertension and left ventricular hypertrophy when stabilized weights were included in their models.

Implementation of IPWs to account for selection in this cohort required us to make some assumptions and considerations. First, we had to strike a balance between inclusion of more predictors of participation and the risk of violating the positivity assumption (i.e. a nonzero possibility of finding participants with all combinations of covariates included in the selection model)(96,100). To avoid this latter issue, we included a simple set of covariates in the marginal structural models that maximized the number of participants in the risk models while accounting for sequential selection. However, this meant that we did not include in our final selection model some characteristics that were associated with participation in our study and others. For example, although self-reported health status was strongly associated with participation in Q3 and Q4, we did not include it in the IPW prediction model because only Q2 respondents provided this information. In addition, other studies have consistently reported higher education level as a predictor of participation level(41,42,45,47,48,89,91), but this was not entirely consistent in our cohort and was only inquired in Q1 and not Q2. To test our choice of selection model, we considered the effect of including a more comprehensive set of predictors of participation and found a similar impact on effect estimates as shown in the Appendixes. That said, it is possible that additional predictors of participation that were not considered in the analysis could still be introducing selection bias in our results.

Beyond the limits of IPW, this study had some additional limitations. First, there could be a degree of misclassification bias for radiation exposure, CD outcomes, and other covariates considered. Specifically, annual radiation exposure was not directly measured, but estimated through dosimetry reconstruction (54). Although these dosimetry estimates effectively ranked cohort members with respect to relative radiation exposure, they depended largely on

questionnaire data. Similarly, incidence of IHD and CeVD was determined through questionnaire response and did not include fatal forms of these diseases. We decided to keep fatal and non-fatal cases separated in the analysis because they inform different levels of disease severity.

Conclusion

In conclusion, we show that the pattern of participation and attrition in the USRT cohort was associated with demographic, health and contextual characteristics across the 30 years of follow up. These observations reported here have implications for past and future analyses from this cohort, and other similar occupational studies. The application of IPW in our estimates of the effect of radiation on CD outcomes allowed us to assess the presence and magnitude of selection bias in this study. The results of this analysis of selection bias in the USRT provide further support for the observed elevated risk of CD mortality at low chronic levels of radiation exposure(71). This study shows that the association between low radiation exposure and CD outcomes cannot be attributed to selection processes.

Tables and Figures

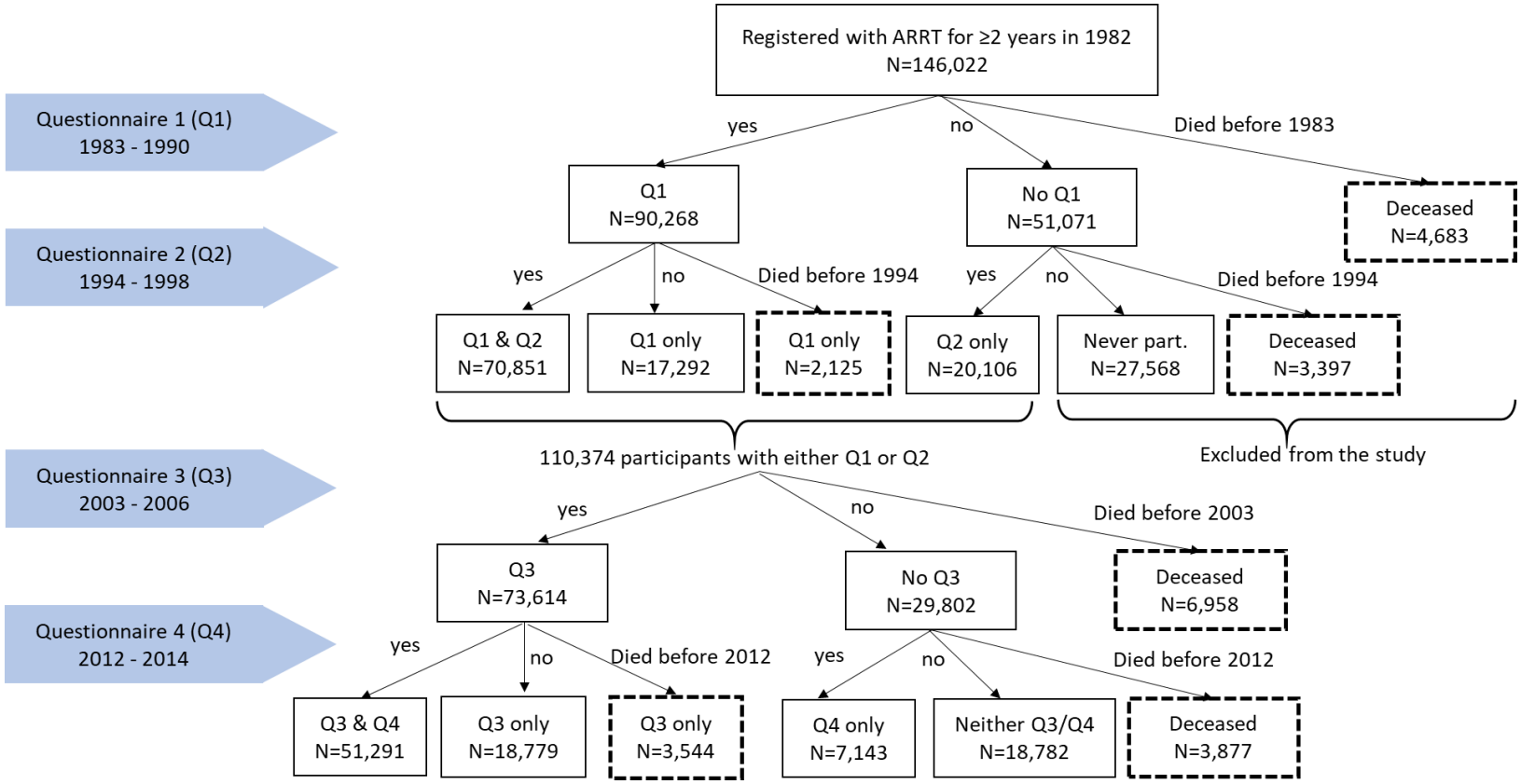

Figure 3. Participation flowchart for each of the four study waves in the US Radiologic Technologists (USRT) study (Q1-4).
The USRT cohort was first enumerated from the American Registry of Radiologic Technologists (ARRT) across the US. 146,022 technologists who had been certified by at least two years in 1982 were sent Q1 and/or Q2. 110,374 participants completed at least one of these two questionnaires (Q1/Q2) and were sent Q3 and Q4. The remaining 35,648 technologists who did not complete Q1 or Q2 were excluded from subsequent waves.

Table 15. Characteristics of 146,022 radiologic technologists by participation status in Questionnaire 1 (Q1), and risk differences (RD) of participating according to these covariates

	Participated in Q1 (1983-1990)						
	Total	Participants		Crude RD		Adjusted* RD	
	n	n	PT‡	RD	95% CI	RD	95% CI
Total	146,022	90,268	0.62				
Basic demographics							
Birth year							
<1930	18,010	7,601	0.42	*Ref.*		*Ref.*	
1930-39	20,113	11,826	0.59	0.17	(0.16, 0.18)	-0.03	(-0.04, -0.02)
1940-49	46,651	29,446	0.63	0.21	(0.20, 0.22)	-0.01	(-0.02, 0.00)
1950+	61,209	41,395	0.68	0.25	(0.25, 0.26)	0.02	(0.00, 0.03)
missing	39	0	0.00				
Gender							
male	39,069	20,766	0.53	*Ref.*		*Ref.*	
female	106,953	69,502	0.65	0.12	(0.11, 0.12)	0.04	(0.04, 0.05)
missing	0	0	0.00				
Race							
white	127,912	85,588	0.67	*Ref.*		*Ref.*	
black	6,176	2,395	0.39	-0.28	(-0.29, -0.27)	-0.13	(-0.15, -0.12)
other	3,435	2,274	0.66	-0.01	(-0.02, 0.01)	0.02	(0.01, 0.04)
missing	8,499	11	0.00				
Hispanic							
no	107,250	88,248	0.82	*Ref.*		*Ref.*	
yes	2,709	1,947	0.72	-0.10	(-0.12, -0.09)	-0.09	(-0.10, -0.07)
missing	36,063	73	0.20				
Certification year							
<1950	8,006	2,685	0.34	*Ref.*		*Ref.*	
1950-59	19,142	10,774	0.56	0.23	(0.21, 0.24)	-0.01	(-0.03, 0.01)
1960-69	40,973	25,868	0.63	0.30	(0.28, 0.31)	-0.01	(-0.02, 0.01)
1970-79	70,457	46,057	0.65	0.32	(0.31, 0.33)	-0.03	(-0.05, -0.01)
1980+	7,444	4,884	0.66	0.32	(0.31, 0.34)	-0.04	(-0.06, -0.02)
missing	0	0	0.00				
Vital status in 1983							
alive	141,339	90,268	0.64				
dead from CD	1,689	0	0.00				
dead from other cause	2,994	0	0.00				

Risk differences (RD) and 95% confidence intervals (CI) were calculated using a generalized linear model (GLM) with a binomial distribution and an identity link.
* Adjusted simultaneously for all variables
CD: Circulatory disease
‡PT: Proportion of participants among people of that strata.

Table 16. Characteristics of 146,022 radiologic technologists by participation status in Questionnaire 2 (Q2), and risk differences (RD) of participating according to these covariates

	Participation in Q2 (1994-1998)											
						Q2 only vs. non-participant				Q1 and Q2 vs. Q1 only			
	Total	Q2 only		Q1 and Q2		Crude RD		Adjusted* RD		Crude RD		Adjusted* RD	
	n	n	PT‡	n	PT‡	RD	95% CI	RD	95% CI	RD	95% CI	RD	95% CI
Total	146,022	20,196	0.14	70,851	0.49								
Basic demographics													
Birth year													
<1930	18,010	1,607	0.09	4,800	0.27	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
1930-39	20,113	3,111	0.15	9,407	0.47	0.17	(0.16, 0.18)	0.17	(0.14, 0.19)	0.26	(0.25, 0.27)	0.10	(0.08, 0.11)
1940-49	46,651	6,812	0.15	23,539	0.50	0.17	(0.16, 0.18)	0.14	(0.11, 0.17)	0.30	(0.29, 0.31)	0.09	(0.08, 0.11)
1950+	61,209	8,576	0.14	33,105	0.54	0.18	(0.18, 0.19)	0.10	(0.07, 0.14)	0.33	(0.33, 0.34)	0.09	(0.07, 0.11)
missing	39	0	0.00	0	0.00								
Gender													
male	39,069	5,888	0.15	15,084	0.39	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
female	106,953	14,218	0.13	55,767	0.52	0.03	(0.03, 0.04)	0.00	(-0.01, 0.01)	0.15	(0.14, 0.15)	0.06	(0.05, 0.07)
missing	0	0	0.00	0	0.00								
Race													
white	127,912	18,340	0.14	67,731	0.53	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
black	6,176	1,149	0.19	1,627	0.26	-0.05	(-0.07, -0.04)	0.07	(0.05, 0.10)	-0.29	(-0.31, -0.28)	-0.09	(-0.10, -0.07)
other	3,435	510	0.15	1,493	0.43	-0.04	(-0.06, -0.02)	-0.20	(-0.23, -0.18)	-0.11	(-0.13, -0.09)	-0.15	(-0.18, -0.13)
missing	8,499	107	0.01	0	0.00								
Hispanic													
no	107,250	18,961	0.18	69,288	0.65	*Ref.*		*Ref.*		*Ref.*			
yes	2,709	760	0.28	1,556	0.57	0.16	(0.13, 0.19)	0.27	(0.23, 0.31)	0.01	(-0.00, 0.03)	0.08	(0.06, 0.09)
missing	36,063	385	0.01	7	0.00								
Certification year													
<1950	8,006	509	0.06	1,524	0.19	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
1950-59	19,142	2,582	0.13	8,205	0.43	0.16	(0.15, 0.17)	0.10	(0.06, 0.12)	0.29	(0.28, 0.30)	0.09	(0.07, 0.11)
1960-69	40,973	5,785	0.14	20,717	0.51	0.21	(0.20, 0.22)	0.09	(0.06, 0.12)	0.38	(0.38, 0.40)	0.09	(0.06, 0.11)
1970-79	70,457	10,101	0.14	36,536	0.52	0.22	(0.21, 0.23)	0.10	(0.07, 0.14)	0.40	(0.39, 0.41)	0.08	(0.05, 0.10)
1980+	7,444	1,129	0.15	3,869	0.52	0.24	(0.22, 0.25)	0.13	(0.08, 0.17)	0.41	(0.39, 0.42)	0.08	(0.05, 0.10)
missing	0	0	0.00	0	0.00								
Vital status in 1994													
alive	135,817	20,106	0.15	79,851	0.59								
dead from CD	3,584	0	0.00	0	0.00								
dead from other cause	6,621	0	0.00	0	0.00								

Table 16. *continued.*

	Total	Q2 only		Q1 and Q2		Q2 only vs. non-participant				Q1 and Q2 vs. Q1 only			
						Crude RD		Adjusted* RD		Crude RD		Adjusted* RD	
	n	n	PT‡	n	PT‡	RD	95% CI	RD	95% CI	RD	95% CI	RD	95% CI
Neighborhood of residence													
Tertiles of nSES in 1990													
low nSES	47,431	6,287	0.13	22,080	0.47	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
middle nSES	47,431	6,241	0.13	24,513	0.52	0.02	(0.02, 0.03)	0.00	(-0.01, 0.01)	0.06	(0.05, 0.07)	0.01	(-0.00, 0.01)
high nSES	47,430	6,589	0.14	23,942	0.50	0.03	(0.02, 0.04)	0.01	(0.00, 0.03)	0.05	(0.04, 0.06)	0.00	(-0.01, 0.01)
missing	3,730	989	0.27	316	0.08								
Rural status in 1990													
urban	121,602	16,583	0.14	58,711	0.48	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
rural	20,702	2,535	0.12	11,824	0.57	0.02	(0.01, 0.03)	-0.03	(-0.04, -0.01)	0.09	(0.08, 0.10)	0.01	(0.00, 0.02)
missing	3,718	988	0.27	316	0.08								
Data collected in Q1													
Education level in Q1													
vocational or less	5,421	0	0.00	3,994	0.74					0.07	(0.05, 0.08)	0.01	(0.00, 0.03)
radiation technology	47,803	0	0.00	38,394	0.80					0.03	(0.02, 0.05)	0.01	(0.00, 0.02)
some college	36,414	0	0.00	28,058	0.77					*Ref.*		*Ref.*	
missing	56,384	20,106	0.36	450	0.01								
Marital status in Q1													
never	10,792	0	0.00	7,999	0.74					*Ref.*		*Ref.*	
married	67,766	0	0.00	54,228	0.80					0.06	(0.05, 0.07)	0.05	(0.04, 0.06)
widowed	1,641	0	0.00	1,041	0.63					-0.11	(-0.13, -0.08)	-0.03	(-0.05, -0.01)
div/sep	9,060	0	0.00	6,850	0.76					0.01	(0.00, 0.03)	0.01	(-0.00, 0.02)
missing	56,763	20,106	0.35	733	0.01								
Smoking status in Q1													
no	42,360	0	0.00	34,253	0.81					*Ref.*		*Ref.*	
yes	47,756	0	0.00	36,503	0.76					-0.04	(-0.05, -0.04)	-0.04	(-0.05, -0.04)
missing	55,906	20,106	0.36	95	0.00								
Alcohol use in Q1													
none	16,209	0	0.00	12,280	0.76					*Ref.*		*Ref.*	
<1 per week	36,344	0	0.00	28,979	0.80					0.04	(0.03, 0.05)	0.03	(0.02, 0.04)
1-2 per week	13,930	0	0.00	11,126	0.80					0.04	(0.03, 0.05)	0.04	(0.03, 0.04)
3-6 per week	13,335	0	0.00	10,449	0.78					0.03	(0.02, 0.04)	0.03	(0.02, 0.04)
≥7 per week	9,826	0	0.00	7,544	0.77					0.01	(0.00, 0.02)	0.03	(0.02, 0.04)
missing	56,378	20,106	0.36	473	0.01								
BMI in Q1													
underweight	3,082	0	0.00	2,371	0.77					-0.03	(-0.04, -0.01)	-0.03	(-0.04, -0.01)
normal weight	57,982	0	0.00	46,125	0.80					*Ref.*		*Ref.*	
overweight	19,721	0	0.00	15,217	0.77					-0.02	(-0.03, -0.02)	0.00	(-0.01, 0.01)
obese	9,483	0	0.00	7,138	0.75					-0.04	(-0.05, -0.03)	-0.02	(-0.03, -0.01)
missing	55,754	20,106	0.36	0	0.00								

Risk differences (RD) and 95% confidence intervals (CI) were calculated using a generalized linear model (GLM) with a binomial distribution and an identity link. Due to convergence issues, adjusted RDs and 95%CI were estimated using the marginal probabilities estimated with a GLM model with a logit link. The middle columns present comparisons between technologists who participated only in Q2 (not in Q1) versus technologists who did not participate in either Q1 or Q2. No information was available for them from Q1, so the adjusted models only include birth year, gender, race, ethnicity, certification year, nSES and rural status (which was available for all technologists who were sent Q2 regardless of their participation in Q1). The right columns present comparisons between technologists who participated in both Q1 and Q2 versus technologists who participated in Q1 but not Q2. All variables in the column were included in the adjusted model.
*Adjusted simultaneously for all variables
CD: Circulatory disease; nSES: neighborhood socioeconomic status
‡PT: Proportion of participants among people of that strata.

Table 17. Characteristics of 110,374 radiologic technologists who responded to either Q1 or Q2 by participation status in Questionnaire 3 (Q3), and risk differences (RD) of participating according to these covariates

Participated in Q3 (2003-2006; N=110,374 eligible)							
	Total	Participants		Crude RD		Adjusted* RD	
	n	n	PT‡	RD	95%CI	RD	95%CI
Total	110,374	73,614	0.67				
Basic demographics							
Birth year							
<1930	9,208	3,399	0.37	*Ref.*		*Ref.*	
1930to39	14,937	9,933	0.66	0.30	(0.28, 0.31)	0.17	(0.15, 0.19)
1940to49	36,258	25,343	0.70	0.33	(0.32, 0.34)	0.19	(0.17, 0.21)
1950+	49,971	34,939	0.70	0.33	(0.32, 0.34)	0.17	(0.14, 0.19)
missing	0	0					
Sex							
male	26,654	15,755	0.59	*Ref.*		*Ref.*	
female	83,720	57,859	0.69	0.10	(0.09, 0.11)	0.06	(0.05, 0.07)
missing	0	0					
Race							
white	103,928	69,922	0.67	*Ref.*		*Ref.*	
black	3,544	1,982	0.56	-0.11	(-0.13, -0.10)	-0.04	(-0.06, -0.02)
other	2,784	1,658	0.60	-0.08	(-0.10, -0.06)	-0.01	(-0.03, -0.01)
missing	118	52	0.44				
Hispanic							
no	107,209	71,598	0.67	*Ref.*		*Ref.*	
yes	2,707	1,777	0.66	-0.01	(-0.03, 0.01)	0.01	(-0.01, 0.03)
missing	458	239	0.52				
Certification year							
<1950	3,194	941	0.29	*Ref.*		*Ref.*	
1950-59	13,356	7,907	0.59	0.30	(0.28, 0.32)	0.09	(0.06, 0.11)
1960-69	31,653	21,750	0.69	0.39	(0.38, 0.41)	0.09	(0.06, 0.12)
1970-79	56,158	38,870	0.69	0.40	(0.38, 0.41)	0.09	(0.06, 0.12)
1980+	6,013	4,146	0.69	0.39	(0.38, 0.41)	0.09	(0.06, 0.12)
missing	0	0	0.00				
Vital status in 2003							
alive	103,440	73,614	0.71				
dead from CD	2,171	0	0.00				
dead from other cause	4,763	0	0.00				
Previous participation							
Q1 only	19,417	6,358	0.33	*Ref.*		N/A	N/A
Q2 only	20,106	12,023	0.60	0.27	(0.26, 0.28)	N/A	N/A
Q1 and Q2	70,851	55,233	0.78	0.45	(0.44, 0.46)	N/A	N/A
Neighborhood of residence							
Tertiles of nSES in 2000							
low nSES	33,950	21,520	0.63	*Ref.*		*Ref.*	
middle nSES	38,021	25,851	0.68	0.06	(0.05, 0.07)	0.01	(0.00, 0.02)
high nSES	38,085	26,084	0.68	0.07	(0.06, 0.08)	0.00	(-0.00, 0.02)
missing	318	159	0.50				
Rural status in 2000							
urban	89,159	58,770	0.66	*Ref.*		*Ref.*	
rural	20,899	14,686	0.70	0.04	(0.04, 0.05)	0.02	(0.01, 0.02)
missing	316	158	0.50				

Table 17. continued.

Participated in Q3 (2003-2006; N=110,374 eligible)							
	Total	Participants		Crude RD		Adjusted* RD	
	n	n	PT‡	RD	95%CI	RD	95%CI
Data collected in Q1 or Q2							
Education level at baseline							
vocational or less	5,421	3,209	0.59	-0.08	(-0.09, -0.06)	-0.01	(-0.02, 0.00)
radiation technology	47,803	33,608	0.70	0.03	(0.03, 0.04)	0.00	(-0.01, 0.00)
some college	36,414	24,388	0.67	*Ref.*		*Ref.*	
missing	20,736	12,409	0.60				
Marital status at baseline	0						
never	9,099	4,981	0.55	*Ref.*		*Ref.*	
married	80,586	55,525	0.69	0.14	(0.13, 0.15)	0.05	(0.04, 0.07)
widowed	8,076	5,184	0.64	0.09	(0.08, 0.11)	0.00	(-0.01, 0.03)
div/sep	12,095	7,711	0.64	0.09	(0.08, 0.10)	0.02	(0.00, 0.03)
missing	518	213	0.41				
Smoking status at baseline							
no	51,940	36,135	0.70	*Ref.*		*Ref.*	
yes	58,153	37,349	0.64	-0.05	(-0.06, -0.05)	-0.03	(-0.03, -0.02)
missing	281	130	0.46				
Alcoholic drinks at baseline							
none	16,209	12,280	0.76	*Ref.*		*Ref.*	
<1 per week	36,344	28,979	0.80	0.06	(0.05, 0.07)	0.02	(0.01, 0.03)
1-2 per week	13,930	11,129	0.80	0.06	(0.05, 0.08)	0.03	(0.02, 0.04)
3-6 per week	13,335	10,449	0.78	0.04	(0.03, 0.05)	0.02	(0.01, 0.03)
≥7 per week	9,826	7,544	0.77	0.00	(-0.01, 0.01)	0.02	(0.00, 0.03)
missing	56,378	20,579	0.37				
BMI at baseline							
underweight	3,454	2,229	0.65	-0.04	(-0.06, -0.03)	-0.03	(-0.05, -0.02)
normal weight	68,269	47,114	0.69	*Ref.*		*Ref.*	
overweight	26,740	17,184	0.64	-0.05	(-0.05, -0.04)	0.00	(-0.00, 0.01)
obese	11,911	7,087	0.59	-0.10	(-0.10, -0.09)	-0.02	(-0.03, -0.01)
missing	0	0	0.00				
Self-reported health status							
excellent	24,140	18,827	0.78	*Ref.*		*Ref.*	
good	55,276	41,315	0.75	-0.03	(-0.04, -0.03)	-0.02	(-0.03, -0.02)
fair	9,898	6,317	0.64	-0.14	(-0.15, -0.13)	-0.09	(-0.11, -0.08)
poor	1,063	450	0.42	-0.36	(-0.39, -0.33)	-0.28	(-0.32, -0.24)
missing	19,997	6,705	0.34				

Risk differences (RD) and 95% confidence intervals (CI) were calculated using a generalized linear model (GLM) with a binomial distribution and an identity link. Due to convergence issues, adjusted RDs and 95%CI were estimated using the marginal probabilities estimated with a GLM model with a logit link.
*Adjusted simultaneously for all variables
CD: Circulatory disease; nSES: neighborhood socioeconomic status
‡PT: Proportion of participants among people of that strata.

Table 18. Characteristics of 110,374 radiologic technologists who responded to either Q1 or Q2 by participation status in Questionnaire 4 (Q4), and risk differences (RD) of participating according to these covariates

Participated in Q4 (2012-2014; N=110,374 eligible)							
	Total	Participants		Crude RD		Adjusted* RD	
	n	n	PT‡	RD	95%CI	RD	95%CI
Total	110374	58,434	0.53				
Basic demographics							
Birth year							
<1930	9,208	1,523	0.17	*Ref.*		*Ref.*	
1930to39	14,937	7,421	0.50	0.33	(0.32, 0.34)	0.24	(0.22, 0.26)
1940to49	36,258	20,912	0.58	0.41	(0.40, 0.42)	0.31	(0.29, 0.33)
1950+	49,971	28,578	0.57	0.41	(0.40, 0.42)	0.30	(0.27, 0.33)
missing	0	0					
Sex							
male	26,654	12,109	0.45	*Ref.*		*Ref.*	
female	83,720	46,325	0.55	0.10	(0.09, 0.11)	0.03	(0.02, 0.04)
missing	0	0					
Race							
white	103,928	55,657	0.54	*Ref.*		*Ref.*	
black	3,544	1,422	0.40	-0.13	(-0.15, -0.12)	-0.06	(-0.08, -0.04)
other	2,784	1,319	0.47	-0.06	(-0.08, -0.04)	0.02	(-0.01, 0.04)
missing	118	36	0.31				
Hispanic							
no	107,209	56,893	0.53	*Ref.*		*Ref.*	
yes	2,707	1,388	0.51	-0.02	(-0.04, 0.00)	0.00	(-0.02, 0.03)
missing	458	153	0.33				
Certification year							
<1950	3,194	372	0.12	*Ref.*		*Ref.*	
1950-59	13,356	5,475	0.41	0.29	(0.28, 0.31)	0.07	(0.04, 0.10)
1960-69	31,653	17,633	0.56	0.44	(0.43, 0.45)	0.06	(0.03, 0.10)
1970-79	56,158	31,573	0.56	0.45	(0.43, 0.46)	0.05	(0.01, 0.09)
1980+	6,013	3,381	0.56	0.45	(0.43, 0.46)	0.04	(0.01, 0.08)
missing	0	0					
Vital status in 2012							
alive	95,995	58,434	0.61				
dead from CD	4,348	0	0.00				
dead from other cause	10,031	0	0.00				
Previous participation							
Q1 and/or Q2 only	36,760	7,143	0.19	*Ref.*		*Ref.*	
Q1 or Q2, and Q3	15,439	9,048	0.59	0.39	(0.38, 0.40)	NA	NA
Q1, Q2 and Q3	58,175	42,243	0.73	0.53	(0.53, 0.54)	0.45	(0.44, 0.45)
Neighborhood of residence							
Tertiles of nSES in 2010							
low nSES	34,084	16,391	0.48	*Ref.*		*Ref.*	
middle nSES	38,014	20,719	0.55	0.06	(0.06, 0.07)	0.01	(0.00, 0.02)
high nSES	38,045	21,232	0.56	0.08	(0.07, 0.08)	0.02	(0.01, 0.02)
missing							
Rural residence in 2010							
urban	91,370	47,512	0.52	*Ref.*		*Ref.*	
rural	18,784	10,834	0.58	0.04	(0.03, 0.05)	0.01	(0.00, 0.02)
missing	220	88	0.40				

Table 18. *Continued.*

Participated in Q4 (2012-2014; N=110,374 eligible)							
	Total	Participants		Crude RD		Adjusted* RD	
	n	n	PT‡	RD	95%CI	RD	95%CI
Data from previous surveys							
Education level at baseline							
vocational or less	5,421	2,412	0.44	-0.10	(-0.12, -0.09)	-0.02	(-0.03, -0.01)
rad-tech	47,803	26,876	0.56	0.02	(0.01, 0.02)	-0.02	(-0.03, -0.01)
some college	36,414	19,886	0.55	*Ref.*		*Ref.*	
missing	20,736	9,260	0.45				
Marital status at baseline							
never	9,099	3,724	0.41	*Ref.*			
married	80,586	44,608	0.55	0.14	(0.13, 0.15)	0.04	(0.03, 0.05)
widowed	8,076	4,144	0.51	0.10	(0.09, 0.12)	0.03	(0.01, 0.04)
div/sep	12,095	5,812	0.48	0.07	(0.06, 0.08)	0.01	(-0.01, 0.02)
missing	518	146	0.28				
Smoking status at baseline							
no	51,940	29,745	0.57	*Ref.*		*Ref.*	
yes	58,153	28,591	0.49	-0.08	(-0.09, -0.08)	-0.05	(-0.05, -0.04)
missing	281	98	0.35				
Alcoholic drinks at baseline							
none	16,203	8026	0.50	*Ref.*			
<1 per week	36,332	20769	0.57	0.08	(0.07, 0.09)	0.03	(0.02, 0.04)
1-2 per week	13,921	7998	0.57	0.08	(0.07, 0.09)	0.03	(0.02, 0.04)
3-6 per week	13,333	7475	0.56	0.07	(0.05, 0.08)	0.04	(0.03, 0.05)
≥7 per week	9,823	4878	0.50	0.00	(-0.01, 0.01)	0.01	(0.00, 0.03)
missing	69,908	58434	0.84				
BMI at baseline							
underweight	3,454	1,787	0.52	-0.04	(-0.06, -0.02)	-0.02	(-0.04, -0.00)
normal weight	68,269	37,986	0.56	*Ref.*		*Ref.*	
overweight	26,740	13,375	0.50	-0.06	(-0.06, -0.05)	0.00	(-0.00, 0.01)
obese	11,911	5,286	0.44	-0.11	(-0.12, -0.10)	-0.02	(-0.03, -0.01)
missing	0	0					
Self-reported health status							
excellent	24,140	15,828	0.66	*Ref.*		*Ref.*	
good	55,276	32,997	0.60	-0.06	(-0.07, -0.05)	-0.03	(-0.04, -0.02)
fair	9,898	4,520	0.46	-0.20	(-0.21, -0.19)	-0.09	(-0.11, -0.08)
poor	1,063	261	0.25	-0.41	(-0.44, -0.38)	-0.22	(-0.26, -0.18)
missing	19,997	4,828	0.24				
Household annual income							
< $25,000	2,638	1,582	0.60	-0.17	(-0.19, -0.15)	N/A	N/A
$25,000 - $49,999	9,732	7,093	0.73	-0.04	(-0.05, -0.03)	N/A	N/A
$50,000 - $74,999	14,641	11,180	0.76	-0.01	(-0.02, 0.00)	N/A	N/A
$80,000 - $99,999	12,021	9,421	0.78	0.01	(0.00, 0.02)	N/A	N/A
>$100,000	15,271	11,795	0.77	*Ref.*			
missing	56,071	17,363	0.31				

Risk differences (RD) and 95% confidence intervals (CI) were calculated using a generalized linear model (GLM) with a binomial distribution and an identity link. Due to convergence issues, adjusted RDs and 95%CI were estimated using the marginal probabilities estimated with a GLM model with a logit link. *Adjusted simultaneously for all variables, except household income because this was only available for 54,303 people. CD: Circulatory disease; nSES: neighborhood socioeconomic status; ‡PT: Proportion of participants among people of that strata.

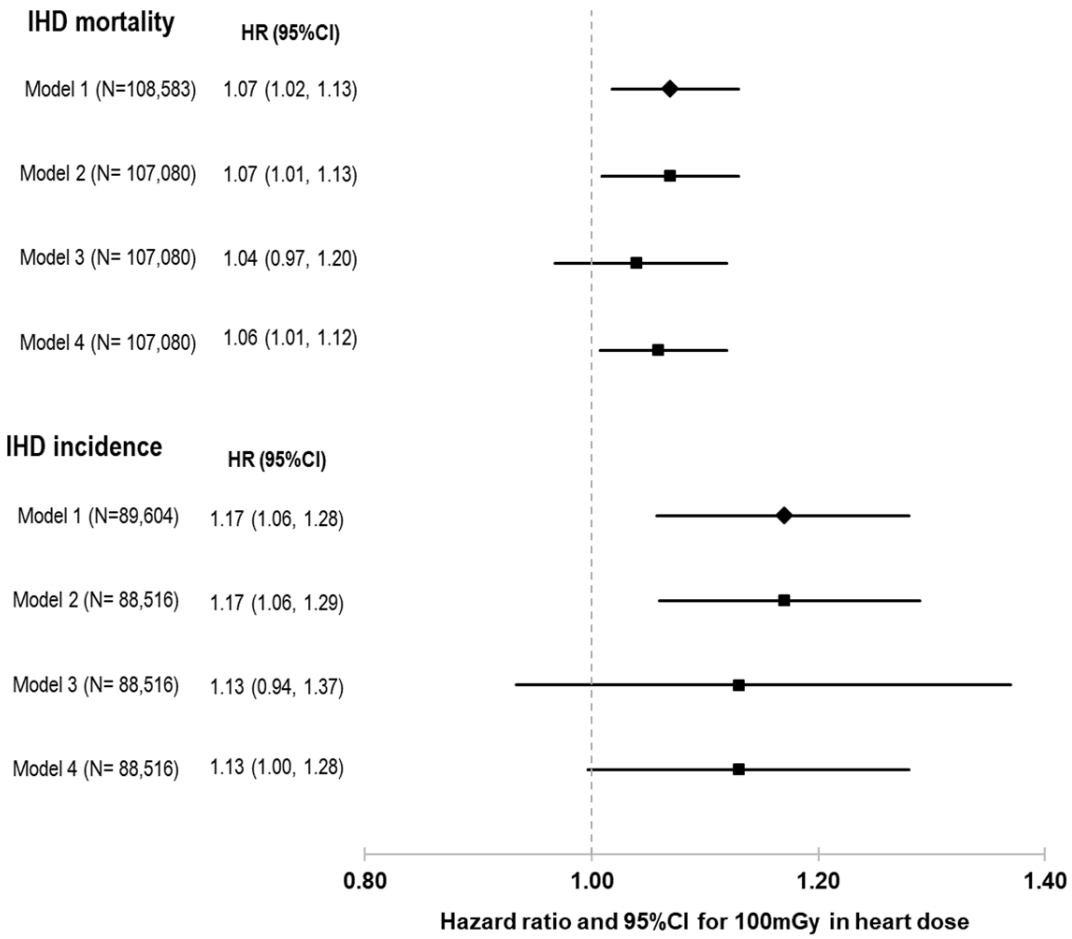

Figure 4. Effect estimates and 95% confidence intervals for IHD mortality and incidence for a 100mGy increase in cumulative heart dose.

HRs and 95%CI were estimated using discrete time hazard models with calendar year as the time scale adjusted for birth year, sex, race, ethnicity, smoking habits and BMI at baseline. Model 1 includes all eligible observations and does not include participation weights. Model 2 restricts this analysis to participants with available weights but does not add participation weight to the model. Model 3 includes untruncated participation weights and Model 4 used weights truncated to the 1st and 99th percentile. Final participation weights included: birth year, sex, certification year, race, ethnicity, marital status, smoking status, BMI at baseline, neighborhood socioeconomic status and rural status and participation status in the previous questionnaire.

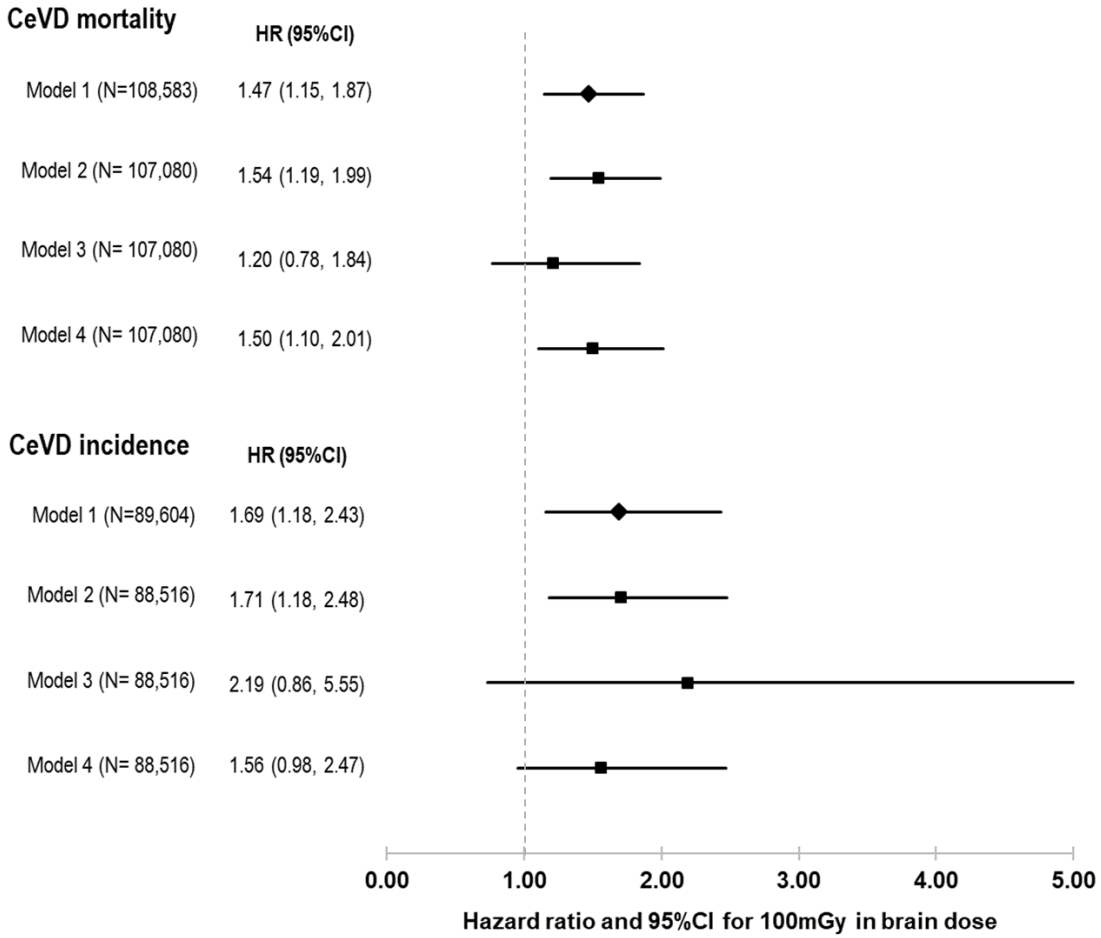

Figure 5. Effect estimates and 95% confidence intervals for CeVD mortality and incidence for a 100mGy increase in cumulative brain dose.

HRs and 95%CI were estimated using discrete time hazard models with calendar year as the time scale adjusted for birth year, sex, race, ethnicity, smoking habits and BMI at baseline. Model 1 includes all eligible observations and does not include participation weights. Model 2 restricts this analysis to participants with available weights but does not add participation weight to the model. Model 3 includes untruncated participation weights and Model 4 used weights truncated to the 1st and 99th percentile. Final participation weights included: birth year, sex, certification year, race, ethnicity, marital status, smoking status, BMI at baseline, neighborhood socioeconomic status and rural status and participation status in the previous questionnaire.

General discussion

In this longitudinal cohort of radiologic technologists exposed to chronic low-to-moderate levels of ionizing radiation, we found a dose-response relationship between cumulative exposure to radiation and CD mortality and incidence. This association was robust to adjustment by residential nSES and selection bias. In ***manuscript 1***, there was consistent evidence that higher doses of cumulative radiation increased the CD mortality, independent of whether badge dose or organ doses were used in the model. Categorical analysis of radiation doses on CD outcomes was consistent with the continuous models suggesting that higher levels of cumulative medical radiation increase the risk of CD, IHD and CeVD mortality. Restricting our analysis to lower doses, we found that cumulative radiation was associated with increased CD mortality at doses below 200mSv of badge dose.

Our results contribute to the expanding literature supporting an elevated risk of CD mortality from low protracted doses of ionizing radiation below 0.5Gy. Two meta-analyses provided evidence to support a linear-no-threshold relationship between radiation and circulatory disease at cumulative doses under 0.5Gy consistent with our results (11,59). Among Japanese atomic bomb survivors, there was evidence of a linear dose-response association for all heart disease mortality (ERR/Gy: 0.14, 95%CI= 0.06, 0.23) (60). More relevantly for this occupational cohort, studies of populations occupationally exposed to radiation, such as nuclear workers, found similar evidence of a dose-response relationship between cumulative radiation and CD outcomes even below 0.7Sv (61–63).

In addition to the consistent association between radiation and CD incidence and mortality, in ***manuscript 2*** we found that a lower socioeconomic status of the neighborhood of residence was

associated with a 20 – 30% increase in the risk of CD incidence and mortality independently of radiation. The association between neighborhood deprivation and CD outcomes has been extensively studied in the general population, with results that are similar in magnitude and direction to those reported in the USRT cohort (23,31,101). Our study uniquely contributes to the existing neighborhood literature because it shows that area-level disparities are linked to CD outcomes even in of relatively homogenous cohort in terms of demographics and occupation.

Statistical evidence of multiplicative interaction between cumulative exposure to radiation and nSES, suggested that the harmful effect of radiation on CD mortality was slightly higher among people from high nSES neighborhoods compared to other areas. There is a striking knowledge gap regarding how the social and economic context of workers may influence the impact of occupational exposures (81–83). Based on this limited literature, we proposed that CD cases occurring among radiologic technologists residing in deprived neighborhoods are likely caused by the strong influence of specific neighborhood-level attributes such as poverty, air pollution, lack of health resources, unhealthy food stores and lack of green space (77,78,84). In this context, occupational radiation is likely playing a small role in the causal pathway of CDs. In contrast, in affluent neighborhoods where the characteristics of the built environment tend to be protective of CD outcomes, radiation becomes a more influential factor of disease in the absence of other harmful exposures. Future studies on this and other occupational cohorts should explore the specific neighborhood attributes that might be accounting for this difference in sensitivity to radiation between affluent and deprived neighborhoods.

Finally, in ***manuscript 3***, we reported that the pattern of non-participation and attrition was not a random process but that it was related to several demographic characteristics. Consistent with previous studies, USRT participants were more likely to be white (45,89), female (42,45,89,90), married (41,44,45,47,89,91), of middle age(41,42,44,45,47,48,89–93), of higher

income (42,91), never smokers (44,45,47,89) and with a normal BMI (44,47). Despite all these differences in risk characteristics of participants and non-participants, we found only a small impact of selection bias on our estimates of the association of cumulative radiation exposure and CD outcomes after including participation IPWs.

Conclusions

Although medical radiation use has steeply increased around the world in the recent decades (67), this particular worker population has been underrepresented among radiation-related studies. Our results from the USRT cohort indicate an association between CD mortality and occupational ionizing radiation exposures below the current radiation protection standards. In addition, nSES was independently associated with CD mortality and incidence in a group of US technologists occupationally exposed to low-doses of radiation, but there was no consistent evidence that it confounded the association between radiation and CD outcomes. Furthermore, there was a multiplicative two-way interaction between radiation and nSES, where residents of high nSES areas had higher risk of CD mortality than residents of low nSES exposed to the same radiation dose. In terms of our selection bias analysis, we observed only a small impact of selection bias on our estimates of the association of cumulative radiation exposure and CD outcomes despite consistent differences in the characteristics of participants and non-participants.

Bibliography

1. Linet MS, Kim KP, Miller DL, Kleinerman RA, Simon SL, de Gonzalez AB. Historical Review of Occupational Exposures and Cancer Risks in Medical Radiation Workers. Radiat Res. 2010 Dec 8;174(6b):793–808.
2. Schauer DA, Linton OW. NCRP Report No. 160, Ionizing Radiation Exposure of the Population of the United States, medical exposure--are we doing less with more, and is there a role for health physicists? Health Phys. 2009 Jul 1;97(1):1–5.
3. Chung JH, Duszak R, Hemingway J, Hughes DR, Rosenkrantz AB. Increasing Utilization of Chest Imaging in US Emergency Departments From 1994 to 2015. J Am Coll Radiol. 2019 May;16(5):674–82.
4. ARRT. The American Registry of Radiologic Technologists [Internet]. 2019 [cited 2019 Jul 29]. Available from: https://www.arrt.org/
5. UNSCEAR. Sources and effects of ionizing radiation: Report to the General Assembly with Scientific Annexes,Volume 1 [Internet]. 2010 [cited 2019 May 30]. Available from: https://www.unscear.org/docs/reports/2008/09-86753_Report_2008_GA_Report.pdf
6. Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci U S A. 2003 Nov 25;100(24):13761–6.
7. Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, et al. A systematic review of epidemiological associations between low and moderate doses of ionizing radiation and late cardiovascular effects, and their possible mechanisms. Radiat Res. 2008;169(1).
8. Vrijheid M, Cardis E, Ashmore P, Auvinen A, Bae J-M, Engels H, et al. Mortality from diseases other than cancer following low doses of ionizing radiation: Results from the 15-Country Study of nuclear industry workers. Int J Epidemiol. 2007;36(5).
9. Mohan AK, Hauptmann M, Freedman DM, Ron E, Matanoski GM, Lubin JH, et al. Cancer and other causes of mortality among radiologic technologists in the United States. Int J Cancer. 2003 Jan 10;103(2):259–67.
10. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the Mortality of Atomic Bomb Survivors, Report 14, 1950–2003: An Overview of Cancer and Noncancer Diseases. Radiat Res. 2012 Mar 15;177(3):229–43.
11. Little MP, Azizova TV, Bazyka D, Bouffler SD, Cardis ESC, Chekin S, et al. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect. 2012;120(11).
12. Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. BMJ. 2010;340(7739).
13. Cousins C, Miller DL, Bernardi G, Rehani MM, Schofield P, Vañó E, et al. ICRP Publication 120: Radiological Protection in Cardiology. Ann ICRP. 2013 Feb 1;42(1):1–125.
14. Borghini A, Luca Gianicolo EA, Picano E, Andreassi MG. Ionizing radiation and atherosclerosis: Current knowledge and future challenges. Atherosclerosis. 2013;230(1).
15. Hayashi T, Kusunoki Y, Hakoda M, Morishita Y, Kubo Y, Maki M, et al. Radiation dose-dependent increases in inflammatory response markers in A-bomb survivors. Int J Radiat Biol. 2003 Jan 1;79(2):129–36.
16. McMillan TJ, Bennett MR, Bridges BA, Hendry J, Jones B, Kanthou C, et al. Circulatory disease risk : report of the independent Advisory Group on Ionising Radiation. London: Subgroup on Circulatory Disease Risk Health Protection Agency (Great Britain); 2010.
17. Al-Massarani G, Najjar F, Aljapawe A, Ikhtiar A. Evaluation of circulating microparticles

in healthy medical workers occupationally exposed to ionizing radiation: A preliminary study. Int J Occup Med Environ Health. 2018 Dec 18;31(6):783–93.
18. USRT. United States Radiologic Technologist (USRT) Study [Internet]. 2018 [cited 2016 Sep 26]. Available from: https://radtechstudy.nci.nih.gov/index.html
19. Boice JD, Mandel JS, Doody MM, Yoder RC, McGowan R. A health survey of radiologic technologists. Cancer. 1992;69(2):586–98.
20. Doody MM, Mandel JS, Lubin JH, Boice JD. Mortality among United States radiologic technologists, 1926-90. Cancer Causes Control. 1998;9(1):67–75.
21. Hauptmann M, Mohan AK, Doody MM, Linet MS, Mabuchi K. Mortality from diseases of the circulatory system in radiologic technologists in the United States. Am J Epidemiol. 2003;157(3).
22. Rajaraman P, Doody MM, Yu CL, Preston DL, Miller JS, Sigurdson AJ, et al. Incidence and mortality risks for circulatory diseases in US radiologic technologists who worked with fluoroscopically guided interventional procedures, 1994-2008. Occup Environ Med. 2016;73(1):21–7.
23. Diez Roux AV, Mair C. Neighborhoods and health. Ann N Y Acad Sci. 2010;1186.
24. Roblin DW. Validation of a Neighborhood SES Index in a Managed Care Organization. Med Care. 2013;51(1).
25. Winkleby MA, Cubbin C. Influence of individual and neighbourhood socioeconomic status on mortality among black, Mexican-American, and white women and men in the United States. J Epidemiol Community Health. 2003;57(6).
26. Winkleby M, Cubbin C, Ahn D. Effect of cross-level interaction between individual and neighborhood socioeconomic status on adult mortality rates. Am J Public Health. 2006;96(12).
27. Dragano N, Bobak M, Wege N, Peasey A, Verde PE, Kubinova R, et al. Neighbourhood socioeconomic status and cardiovascular risk factors: A multilevel analysis of nine cities in the Czech Republic and Germany. BMC Public Health. 2007;7.
28. Morenoff JD, House JS, Hansen BB, Williams DR, Kaplan GA, Hunte HE. Understanding social disparities in hypertension prevalence, awareness, treatment, and control: The role of neighborhood context. Soc Sci Med. 2007;65(9).
29. Diez Roux AV, Merkin SS, Arnett D, Chambless L, Massing M, Nieto FJ, et al. Neighborhood of residence and incidence of coronary heart disease. N Engl J Med. 2001;345(2).
30. Institute for Health Metrics and Evaluation U of W. GBD Compare | IHME Viz Hub. 2019.
31. De Mestral C, Stringhini S. Socioeconomic Status and Cardiovascular Disease: an Update. Curr Cardiol Rep. 2017;19(115).
32. Chaix B. Geographic life environments and coronary heart disease: A literature review, theoretical contributions, methodological updates, and a research agenda. Annu Rev Public Health. 2009;30.
33. MTO. Moving to Opportunity (MTO) for Fair Housing Demonstration Program [Internet]. [cited 2017 Apr 18]. Available from: http://www.nber.org/mtopublic/
34. Ludwig J, Sanbonmatsu L, Gennetian L, Adam E, Duncan GJ, Katz LF, et al. Neighborhoods, Obesity, and Diabetes — A Randomized Social Experiment. N Engl J Med. 2011 Oct 20;365(16):1509–19.
35. National Insitutite of Occupational Health and Safety. Total Worker Health [Internet]. 2018. Available from: https://www.cdc.gov/niosh/twh/totalhealth.html
36. Daniel M, Moore S, Kestens Y. Framing the biosocial pathways underlying associations between place and cardiometabolic disease. Heal Place. 2008;14(2).
37. Clark C, Ridker P, Ommerborn M, Huisingh C, Coull B, Buring J, et al. Cardiovascular inflammation in healthy women: Multilevel associations with state-level prosperity,

productivity and income inequality. BMC Public Health. 2012;12(1).
38. Greenland S. Response and follow-up bias in cohort studies. Am J Epidemiol. 1977;106(3).
39. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004 Sep;15(5):615–25.
40. Hernán MA. Invited Commentary: Selection Bias Without Colliders. Am J Epidemiol. 2017 Jun 1;185(11):1048–50.
41. Goldberg M, Chastang JF, Leclerc A, Zins M, Bonenfant S, Bugel I, et al. Socioeconomic, demographic, occupational, and health factors associated with participation in a long-term epidemiologic survey: A prospective study of the French GAZEL cohort and its target population. Am J Epidemiol. 2001;154(4):373–84.
42. Langley JD, Lilley R, Wilson S, Derrett S, Samaranayaka A, Davie G, et al. Factors associated with non-participation in one or two follow-up phases in a cohort study of injured adults. Inj Prev. 2013;19(6).
43. Yu S, Brackbill RM, Stellman SD, Ghuman S, Farfel MR. Evaluation of non-response bias in a cohort study of World Trade Center terrorist attack survivors. BMC Res Notes. 2015;8(1).
44. Alonso A, Seguí-Gómez M, De Irala J, Sánchez-Villegas A, Beunza JJ, Martínez-Gonzalez MÁ. Predictors of follow-up and assessment of selection bias from dropouts using inverse probability weighting in a cohort of university graduates. Eur J Epidemiol. 2006;21(5):351–8.
45. Littman AJ, Boyko EJ, Jacobson IG, Horton J, Gackstetter GD, Smith B, et al. Assessing nonresponse bias at follow-up in a large prospective cohort of relatively young and mobile military service members. BMC Med Res Methodol. 2010;10.
46. Rinsky JL, Richardson DB, Wing S, Beard JD, Alavanja M, Beane Freeman LE, et al. Assessing the Potential for Bias From Nonresponse to a Study Follow-up Interview: An Example From the Agricultural Health Study. Am J Epidemiol. 2017 Aug 15;186(4):395–404.
47. Tolonen H, Dobson A, Kulathinal S. Effect on trend estimates of the difference between survey respondents and non-respondents: Results from 27 populations in the WHO MONICA Project. Eur J Epidemiol. 2005;20(11):887–98.
48. Chaix B, Billaudeau N, Thomas F, Havard S, Evans D, Kestens Y, et al. Neighborhood effects on health: Correcting bias from neighborhood effects on participation. Epidemiology. 2011;22(1).
49. USRT. Cohort Description and Participation [Internet]. 2018 [cited 2019 Jul 22]. Available from: https://radtechstudy.nci.nih.gov/cohort/cohortdesc.html
50. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid Cancer Incidence in Atomic Bomb Survivors: 1958–1998. Radiat Res. 2007 Jul 1;168(1):1–64.
51. GAO. Low-Dose Radiation: Interagency Collaboration on Planning Research Could Improve Information on Health Effects. Washington, D.C.; 2017.
52. Occupational Safety and Health Administration. Ionizing Radiation - Maximum Permissible Dose Equivalent for Occupational Exposure [Internet]. Maximum Permissible Dose Equivalent for Occupational Exposure. 1975 [cited 2019 May 6]. Available from: https://www.osha.gov/SLTC/radiationionizing/introtoionizing/ionizingattachmentsix.html
53. Kitahara CM, Linet MS, Rajaraman P, Ntowe E, Berrington de González A. A New Era of Low-Dose Radiation Epidemiology. Curr Environ Heal reports. 2015;2(3).
54. Simon SL, Preston DL, Linet MS, Miller JS, Sigurdson AJ, Alexander BH, et al. Radiation organ doses received in a nationwide cohort of U.S. radiologic technologists: Methods and findings. Radiat Res. 2014;182(5).
55. Simon SL, Weinstock RM, Doody MM, Neton J, Wenzl T, Stewart P, et al. Estimating historical radiation doses to a cohort of U.S. Radiologic Technologists. Radiat Res.

2006;166(1 II).
56. Bhatti P, Preston DL, Doody MM, Hauptmann M, Kampa D, Alexander BH, et al. Retrospective Biodosimetry among United States Radiologic Technologists. Radiat Res. 2007 Jun;167(6):727–34.
57. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of Death Certificates for Coding Coronary Heart Disease as the Cause of Death. Ann Intern Med. 1998 Dec 15;129(12):1020.
58. Pagidipati NJ, Gaziano TA. Estimating Deaths From Cardiovascular Disease: A Review of Global Methodologies of Mortality Measurement. Circulation. 2013 Feb 12;127(6):749–56.
59. Little MP. Radiation and circulatory disease. Mutat Res Mutat Res. 2016 Oct 1;770:299–318.
60. Takahashi I, Shimizu Y, Grant EJ, Cologne J, Ozasa K, Kodama K. Heart Disease Mortality in the Life Span Study, 1950–2008. Radiat Res. 2017 Feb 7;187(3):319.
61. Simonetto C, Schöllnberger H, Azizova T V, Grigoryeva ES, Pikulina M V, Eidemüller M. Cerebrovascular Diseases in Workers at Mayak PA: The Difference in Radiation Risk between Incidence and Mortality. Fei P, editor. PLoS One. 2015 May 1;10(5):e0125904.
62. Gillies M, Richardson DB, Cardis E, Daniels RD, O'Hagan JA, Haylock R, et al. Mortality from Circulatory Diseases and other Non-Cancer Outcomes among Nuclear Workers in France, the United Kingdom and the United States (INWORKS). Radiat Res. 2017 Sep 10;188(3):276–90.
63. Zhang W, Haylock RGE, Gillies M, Hunter N. Mortality from heart diseases following occupational radiation exposure: analysis of the National Registry for Radiation Workers (NRRW) in the United Kingdom. J Radiol Prot. 2019 Jun 12;39(2):327–53.
64. Tran V, Zablotska LB, Brenner A V., Little MP. Radiation-associated circulatory disease mortality in a pooled analysis of 77,275 patients from the Massachusetts and Canadian tuberculosis fluoroscopy cohorts. Sci Rep. 2017 Apr 13;7(1):44147.
65. Zhivin S, Guseva Canu I, Davesne E, Blanchardon E, Garsi J-P, Samson E, et al. Circulatory disease in French nuclear fuel cycle workers chronically exposed to uranium: a nested case-control study. Occup Environ Med. 2018 Apr 1;75(4):270–6.
66. Zielinski J, Ashmore P, Band P, Jiang H, Shilnikova N, Tait V, et al. Low dose ionizing radiation exposure and cardiovascular disease mortality: cohort study based on Canadian national dose registry of radiation workers. Int J Occup Med Environ Health. 2009 Jan 1;22(1).
67. Shannoun F. Medical exposure assessment: the global approach of the United Nations Scientific Committee on the Effects of Atomic Radiation. Radiat Prot Dosimetry. 2015;165(1–4):125–8.
68. Bhatnagar A. Environmental Determinants of Cardiovascular Disease. Circ Res. 2017 Jul 7;121(2):162–80.
69. Roberts EM. Neighborhood social environments and the distribution of low birthweight in Chicago. Am J Public Health. 1997 Apr;87(4):597–603.
70. Pickett KE, Pearl M. Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. J Epidemiol Community Health. 2001 Feb 1;55(2):111–22.
71. Bustamante G, MacLehose R, Ramirez M, Osypuk T, Kitahara C, Linet MS, et al. Effects of low-to-moderate chronic radiation exposure on circulatory disease mortality in a large cohort of radiologic technologists. 2019;(Unpublished).
72. Minnesota Population Center. National Historical Geographic Information System. Version 11.0 [Database]. Minneapolis; 2016.
73. CDC. Defining Adult Overweight and Obesity [Internet]. 2017 [cited 2019 Jul 30]. Available from: https://www.cdc.gov/obesity/adult/defining.html

74. Richardson DB, Kaufman JS. Estimation of the Relative Excess Risk Due to Interaction and Associated Confidence Bounds. Am J Epidemiol. 2009 Mar 15;169(6):756–60.
75. Engstrom R, Ofiesh C, Rain D, Jewell H, Weeks J. Defining neighborhood boundaries for urban health research in developing countries: a case study of Accra, Ghana. J Maps. 2013 Mar;9(1):36–42.
76. Cummins S, Macintyre S. "Food deserts"--evidence and assumption in health policy making. BMJ. 2002 Aug 24;325(7361):436–8.
77. Hajat A, Diez-Roux A V., Adar SD, Auchincloss AH, Lovasi GS, O'Neill MS, et al. Air Pollution and Individual and Neighborhood Socioeconomic Status: Evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). Environ Health Perspect. 2013 Nov;121(11–12):1325–33.
78. Bell ML, Ebisu K. Environmental Inequality in Exposures to Airborne Particulate Matter Components in the United States. Environ Health Perspect. 2012 Dec;120(12):1699–704.
79. Gascon M, Triguero-Mas M, Martínez D, Dadvand P, Rojas-Rueda D, Plasència A, et al. Residential green spaces and mortality: A systematic review. Environ Int. 2016 Jan;86:60–7.
80. Diez Roux AV, Mujahid MS, Hirsch JA, Moore K, Moore L V. The Impact of Neighborhoods on CV Risk. Glob Heart. 2016 Sep;11(3):353–63.
81. Schrijvers C, van de Mheen HD, Stronks K, Mackenbach JP. Socioeconomic inequalities in health in the working population: the contribution of working conditions. Int J Epidemiol. 1998 Dec 1;27(6):1011–8.
82. Quinn MM, Sembajwe G, Stoddard AM, Kriebel D, Krieger N, Sorensen G, et al. Social disparities in the burden of occupational exposures: Results of a cross-sectional study. Am J Ind Med. 2007 Dec 1;50(12):861–75.
83. Neilson HK, Sass-Kortsak A, Lou WW, Purdham JT. Personal factors influencing agreement between expert and self-reported assessments of an occupational exposure. Chronic Dis Can. 2007;28(1–2):1–9.
84. Schüle SA, Bolte G. Interactive and Independent Associations between the Socioeconomic and Objective Built Environment on the Neighbourhood Level and Individual Health: A Systematic Review of Multilevel Studies. Ojima T, editor. PLoS One. 2015 Apr 7;10(4):e0123456.
85. Hussein M, Diez Roux A V, Mujahid MS, Hastert TA, Kershaw KN, Bertoni AG, et al. Unequal Exposure or Unequal Vulnerability? Contributions of Neighborhood Conditions and Cardiovascular Risk Factors to Socioeconomic Inequality in Incident Cardiovascular Disease in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2018 Jul 1;187(7):1424–37.
86. Kelli HM, Kim JH, Samman Tahhan A, Liu C, Ko Y-A, Hammadah M, et al. Living in Food Deserts and Adverse Cardiovascular Outcomes in Patients With Cardiovascular Disease. J Am Heart Assoc. 2019 Feb 19;8(4):e010694.
87. Tawakol A, Osborne MT, Wang Y, Hammed B, Tung B, Patrich T, et al. Stress-Associated Neurobiological Pathway Linking Socioeconomic Disparities to Cardiovascular Disease. J Am Coll Cardiol. 2019 Jul 2;73(25):3243–55.
88. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004;15(5).
89. Rinsky JL, Richardson DB, Wing S, Beard JD, Alavanja M, Beane Freeman LE, et al. Assessing the potential for bias from nonresponse to a study follow-up interview: An example from the agricultural health study. Am J Epidemiol. 2017;186(4):395–404.
90. Ronckers C, Land C, Hayes R, Verduijn P, Leeuwen FV. Factors impacting questionnaire response in a dutch retrospective cohort study. Ann Epidemiol. 2004;14(1):66–72.
91. Tjønneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, et al. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and

Health: A population-based prospective cohort study of 57,053 men and women in Denmark. Scand J Public Health. 2007;35(4):432–41.
92. Santin G, Geoffroy B, Bénézet L, Delézire P, Chatelot J, Sitta R, et al. In an occupational health surveillance study, auxiliary data from administrative health and occupational databases effectively corrected for nonresponse. J Clin Epidemiol. 2014;67(6):722–30.
93. Boshuizen HC, Viet AL, Picavet HSJ, Botterweck A, van Loon AJM. Non-response in a survey of cardiovascular risk factors in the Dutch population: Determinants and resulting biases. Public Health. 2006;120(4):297–308.
94. Bustamante G, Osypuk T, Ramirez M, MacLehose R, Kitahara C, Linet MS, et al. Where you live matters: impact of the neighborhood socioeconomic status on the association between ionizing radiation and circulatory disease morbidity and mortality. 2019;(Unpublished).
95. Paul PG, George RJ, Baskaran M, Arvind H, Raj M, Augustian, et al. A Comparison of Participants and Non-Participants in the Chennai Glaucoma Study—Rural Population. Ophthalmic Epidemiol. 2005 Jan 8;12(2):125–32.
96. Long DL, Howard G, Long DM, Judd S, Manly JJ, McClure LA, et al. An Investigation of Selection Bias in Estimating Racial Disparity in Stroke Risk Factors. Am J Epidemiol. 2019 Mar 1;188(3):587–97.
97. Strobl R, Maier W, Ludyga A, Mielck A, Grill E. Relevance of community structures and neighbourhood characteristics for participation of older adults: a qualitative study. Qual Life Res. 2016 Jan 17;25(1):143–52.
98. Henrique Almeida da Silva Junior S, Santos SM, Medina Coeli C, Sá Carvalho M, Junior SHA S. Assessment of participation bias in cohort studies: systematic review and meta-regression analysis. Cad Saude Publica. 2015;31(11):2259–74.
99. Batty GD, Gale CR. Impact of resurvey non-response on the associations between baseline risk factors and cardiovascular disease mortality: prospective cohort study. J Epidemiol Community Health. 2009 Nov 1;63(11):952–5.
100. Hernán MA, Robins JM. Causal Inference [Internet]. 2019 [cited 2019 Jul 25]. Available from: https://cdn1.sph.harvard.edu/wp-content/uploads/sites/1268/2019/02/hernanrobins_v1.10.38.pdf
101. Chaix B, Leal C, Evans D. Neighborhood-level confounding in epidemiologic studies: Unavoidable challenges, uncertain solutions. Epidemiology. 2010;21(1).

Appendix A.

Inverse Probability Weighting (IPW)- Specific variables included in the logistic models used to predict the probability of participating in each of the four questionnaires.

With the exception of participation in Questionnaire 1, two weights were created for participation in each study survey: weights A included a minimum set of covariates available for the majority of technologists eligible for each survey, while weights B included more predictors of participation that were available only for respondents of the previous survey(s). Specific variables are listed below.

Questionnaire 1 (Q1)

- Weight 1A: birth year, sex, race, and certification year
    - Predicted probabilities were calculated for all ARRT members with this information available (n=137,523)

Questionnaire 2 (Q2)

- Weight 2A: birth year, sex, race, certification year, participation in Q1, nSES in 1990, and rural status in 1990.
    - Predicted probabilities were calculated for all ARRT members with this information available (n=135,065)
- Weight 2B: birth year, sex, race, ethnicity, certification year, participation in Q1, nSES in 1990, rural status in 1990, education level, marital status, ever smoke, alcohol consumption, and BMI reported in Q1
    - Predicted probabilities were calculated only for Q1 participants with this available information (n=88,221)

Questionnaire 3 (Q3)

- Weight 3A: birth year, sex, race, ethnicity, certification year, participation in Q1 and/or Q2, nSES in 1990, rural status in 1990, nSES in 2000, rural status in 2000, marital status, ever smoke, and BMI reported in either Q1 or Q2
    - Predicted probabilities were calculated for people who completed either Q1 or Q2 and had this information available (n=107,644)
- Weight 3B: birth year, sex, race, ethnicity, certification year, participation in Q1 and/or Q2, nSES in 1990, rural status in 1990, nSES in 2000, rural status in 2000, marital status, ever smoke, alcohol consumption, BMI reported in Q1 or Q2, education level, diagnosis of hypertension, diagnosis of diabetes, diagnosis of high cholesterol, and self-reported health status
    - Predicted probabilities were calculated only for people who participated in both Q1 AND Q2 (n=67,384)
    - Education level and alcohol consumption were collected only in Q1; self-reported health status and diagnoses of diabetes, cholesterol, and hypertension were collected only in Q2

Questionnaire 4 (Q4)

- Weight 4A: birth year, sex, race, ethnicity, certification year, participation in Q1 and/or Q2, participation in Q3, nSES in 1990, rural status in 1990, nSES in 2000, rural status in 2000, nSES in 2010, rural status in 2010, marital status, ever smoke, and BMI reported in either Q1 or Q2
    - Predicted probabilities were calculated for people who completed either Q1 or Q2, regardless of Q3 participation, and had this information available (n=107,524)

- Weight 4B: birth year, sex, race, ethnicity, certification year, participation in Q1 and/or Q2, participation in Q3, nSES in 1990, rural status in 1990, nSES in 2000, rural status in 2000, nSES in 2010, rural status in 2010, marital status, ever smoke, and BMI reported in either Q1 or Q2, education level, diagnosis of hypertension, diagnosis of diabetes, diagnosis of high cholesterol, self-reported health status and individual annual household income reported in Q3
    - Predicted probabilities were calculated only for people who participated in all previous questionnaires (Q1, Q2 and Q3) and reported this information (n=38,499)
    - Education level and alcohol consumption were collected only in Q1; self-reported health status and diagnoses of diabetes, cholesterol, and hypertension were collected only in Q2; household annual income only collected in Q3

Final weights

Final weights were calculated by multiplying individual survey weights (w_{Q1}, w_{Q2}, w_{Q3}, w_{Q4}). A person's weight varied over time such that for outcomes occurring between Q1 and Q2 (1983-1993) the combined weight for each participant was $w_{Q1} \times w_{Q2}$; for outcomes occurring between Q2 and Q3 (1994-2002) the final weight was calculated considering the probability of participating in Q1, Q2 and Q3 ($w_{Q1} \times w_{Q2} \times w_{Q3}$); and for outcomes occurring between Q3 and Q4 (2003 and 2014) the final weight was $w_{Q1} \times w_{Q2} \times w_{Q3} \times w_{Q4}$.

- **Final weights A** – they maximized people with weights, at the cost of variable inclusion. ** *This weight was presented in the main analysis*
    - Final weight for years between first questionnaire completion and 1994: *wt_q1a*wt_q2a*
    - Final weight for years between 1994 and 2003: *wt_q1a*wt_q2a*wt_q3a*
    - Final weight for years after 2003: *wt_q1a*wt_q2a*wt_q3a*wt_q4a*
    - Total people with weights A: 107,080

- **Final weights B** – they maximized variable inclusion, at the cost of including participants in the analyses.
    - Final weight for years between first questionnaire completion and 1994: *wt_q1b*wt_q2b*
    - Final weight for years between 1994 and 2003: *wt_q1b*wt_q2b*wt_q3b*
    - Final weight for years after 2003: *wt_q1b*wt_q2b*wt_q3b*wt_q4b*
    - Total people with weights B: 87,284

- **Final weights C** – A combination of the final weights A and B which used weights B for people with these weights available and weights A if they were missing information in any of the parameters in weight B
    - Final weight for years between first questionnaire completion and 1994: *wt_q1a*wt_q2a*
        - If available: *wt_q1b*wt_q2b*
    - Final weight for years between 1994 and 2003: *wt_q1a*wt_q2a*wt_q3a*
        - If available *wt_q1b*wt_q2b*wt_q3b*
    - Final weight for years after 2003: *wt_q1a*wt_q2a*wt_q3a*wt_q4a*
        - If available *wt_q1b*wt_q2b*wt_q3b *wt_q4b*
    - Total people with weights A: 105,979

Table 19. Characteristics of the final Inverse Probability Weights (IPW) and IPW truncated to the 1st and 99th percentile

Final weights	Obs	Mean	SD	Min	P1	P99	Max
A	2,519,475	0.72	1.28	0.20	0.22	4.06	214.8
B	1,753,218	0.56	0.31	0.16	0.17	1.74	9.80
C	2,313,837	0.70	1.12	0.16	0.17	3.47	214.8
Truncated							
A_trunc	2,519,475	0.68	0.54	0.22	0.22	4.06	4.06
B_trunc	1,753,218	0.56	0.28	0.17	0.17	1.74	1.74
C_trunc	2,313,837	0.66	0.47	0.17	0.17	3.47	3.47

Obs: number of observations, SD: standard deviation, Min: minimum, P1: 1st percentile, P99: 99th percentile, Max: maximum

Appendix B.

Models with alternative Inverse Probability Weights

Table 20. Incidence and mortality risk estimates from cumulative radiation exposure using different sets of Inverse Probability Weights (IPW)

	IHD mortality (per 100mGy increase in heart dose)			CeVD mortality (per 100mGy increase in brain dose)		
	n	**HR**	**95% CI**	**n**	**HR**	**95% CI**
All obs., no weights	108,583	1.07	(1.02, 1.13)	108,583	1.47	(1.15, 1.87)
Only obs. with Weight A						
No weights in the model	107,080	1.07	(1.01, 1.13)	107,080	1.54	(1.19, 1.99)
Untruncated weight A		1.04	(0.97, 1.12)		1.20	(0.78, 1.84)
Truncated weight A		1.06	(1.01, 1.12)		1.50	(1.11, 2.01)
Only obs. with Weight B						
No weights in the model	87,284	1.12	(1.04, 1.21)	87,284	1.34	(0.90, 1.99)
Untruncated weight B		1.16	(1.07, 1.25)		1.36	(0.87, 2.12)
Truncated weight B		1.13	(1.05, 1.22)		1.38	(0.90, 2.10)
Only obs. with Weight C						
No weights in the model	105,979	1.08	(1.03, 1.14)	105,979	1.36	(1.04, 1.78)
Untruncated weight C		1.03	(0.96, 1.10)		1.00	(0.64, 1.59)
Truncated weight C		1.06	(1.00, 1.12)		1.26	(0.93, 1.71)
	IHD incidence (per 100mGy increase in heart dose)			**CeVD incidence** (per 100mGy increase in brain dose)		
	n	**HR**	**95% CI**	**n**	**HR**	**95% CI**
All obs., no weights	89,604	1.17	(1.06, 1.28)	89,604	1.69	(1.18, 2.43)
Only obs. with Weight A						
No weights in the model	88,516	1.17	(1.06, 1.29)	88,516	1.71	(1.18, 2.48)
Untruncated weight A		1.13	(0.94, 1.37)		2.19	(0.86, 5.55)
Truncated weight A		1.13	(1.00, 1.28)		1.56	(0.98, 2.47)
Only obs. with Weight B						
No weights in the model	75,307	1.20	(1.08, 1.33)	75,307	1.72	(1.12, 2.63)
Untruncated weight B		1.09	(0.94, 1.27)		1.54	(0.94, 2.54)
Truncated weight B		1.08	(0.96, 1.22)		1.57	(0.96, 2.59)
Only obs. with Weight C						
No weights in the model	88,128	1.19	(1.08, 1.32)	88,128	1.79	(1.21, 2.66)
Untruncated weight C		1.13	(0.94, 1.36)		1.77	(1.06, 2.94)
Truncated weight C		1.08	(0.95, 1.23)		1.64	(1.03, 2.62)

HRs and 95%CI were estimated using discrete time hazard models with calendar year as the time scale adjusted for birth year, sex, race, ethnicity, smoking habits and BMI at baseline. For each outcome, we calculated the HR (and 95%CI) for all eligible observations (obs.) regardless of availability of IPW of participation. For each set of weights, we first recalculated the HR and 95%CI without weights but only among observations who had a final weight available. We also included the effect estimates after including in the model untruncated weights and weights truncated to the 1st and 99th percentile.

Specific variables included in each final weight are detailed in Appendix 1. Briefly, final participation weights A included: birth year, sex, certification year, race, ethnicity, marital status, smoking status, BMI at baseline, neighborhood socioeconomic status and rural status and participation status in the previous questionnaire. Final participation weights B included: birth

year, sex, race, ethnicity, certification year, participation in Q1 and/or Q2, participation in Q3, nSES in 1990, rural status in 1990, nSES in 2000, rural status in 2000, nSES in 2010, rural status in 2010, marital status, ever smoke, and BMI reported in either Q1 or Q2, education level, diagnosis of hypertension, diagnosis of diabetes, diagnosis of high cholesterol, self-reported health status and individual annual household income reported in Q3. Final participation weights C were created by giving everyone weights A and replacing them with weights B, if they were available at each stage.