Comparison of Cancer Risk Associated With Low-Dose Ionizing Radiation from Cardiac Imaging and Therapeutic Procedures After Acute Myocardial Infarction in Women Versus Men

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Patients with cardiovascular disease are increasingly exposed to low-dose ionizing radiation (LDIR) from diagnostic and therapeutic procedures. Previous studies have suggested that the malignancy risk associated with LDIR may be greatest in women and in young patients. We sought to compare the effect of LDIR on incident cancer across gender and age strata in a population-based cohort of patients with myocardial infarction (MI). All initially cancer-free patients with MI from 1996 to 2006 were identified in a province-wide administrative database. Procedure-specific LDIR dose estimates were used to generate a cumulative cardiac LDIR exposure variable. Time-dependent multivariate Cox regression was used to determine the relation between cardiac LDIR and incident cancer. A time-lag covariate of 3 years was used wherein a de novo cancer could only be attributed to LDIR incurred at least 3 years earlier. The effect of age and gender on LDIR-associated risk of cancer was evaluated with stratified models and the addition of interaction terms. The study cohort consisted of 56,606 men and 26,255 women. For each millisievert of cardiac LDIR, women were more likely to develop a cancer (hazard ratio 1.005, 95% confidence interval 1.002 to 1.008) than men (hazard ratio 1.002, 95% confidence interval 1.001 to 1.004) after adjusting for age, noncardiac LDIR, and covariates (p for interaction = 0.014). Contrarily, over the range studied (predominantly patients aged >50 years), age was not a determinant of LDIR-associated risk of cancer. In conclusion, women exposed to LDIR from cardiac imaging and therapeutic procedures after MI are at a greater risk of incident cancer compared with men after similar exposure. The extrapolated absolute risk from LDIR exposure would nonetheless be expected to be low. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;112:1545–1550)

Women have been found to have a greater risk than men of developing malignancy after similar exposure to low-dose ionizing radiation (LDIR), as have been younger patients. The risk in younger patients declines asymptotically with age, reaching a constant nadir at around the third decade of life. Using a large longitudinal population-based cohort, we previously suggested an association between LDIR exposure from medical cardiac imaging and therapeutic procedures after myocardial infarction (MI) and subsequent risk of malignancy. In the present study, we aimed to determine the risks posed to women and younger patients from LDIR exposure. We hypothesized, based on the findings from previous studies, that women would be at greater relative risk (RR) than men and that over the age range studied in our cohort (primarily >50 years of age), there would not be an interaction between age at exposure and cancer risk.

Methods

We previously described the creation of a cohort comprised of all patients with an MI in Quebec, Canada, from January 1, 1996 to March 31, 2006. Briefly, this was a population-based longitudinal cohort created by linking the Quebec hospital discharge summary database to provincial physicians’ services and drug claims databases as well as to vital status information. Linkage was done anonymously using patients’ unique, encrypted health-care insurance numbers. Patients with MI were identified by International Classification of Diseases-9 and -10 codes 410 and I21, respectively. This initial cohort contained 94,672 patients. We then excluded all patients with a concurrent or recent cancer diagnosis. Patients were excluded if, in the year preceding entry into the cohort or for 1 year thereafter, they had (1) an admission to hospital for a cancer diagnosis, (2) a cancer co-morbidity listed as a secondary diagnosis for a noncancer-related admission, (3) any outpatient visit with a cancer diagnosis, or (4) any visit billed by an oncologist, regardless of diagnosis. After exclusions, 82,861 patients remained. Figure 1 outlines the study design, which differed from the original design by incorporating a longer time-lag...
co-variate, resulting in the exclusion of cancers previously included by the initial study design.

After index MI, exposure to 4 tests of interest was collected, and their respective LDIR doses estimated from published sources; myocardial perfusion imaging (15.6 mSv), diagnostic cardiac catheterization without intervention (7 mSv), cardiac catheterization with percutaneous coronary intervention (15 mSv), and cardiac resting ventriculography/multiple gated acquisition scan (7.8 mSv). The study did not incorporate gender-, body surface area-, or year-based LDIR dose estimates. Exposure to other common sources of medical LDIR was also collected for adjustment in multivariate analyses as some of these noncardiac tests could have been performed for work-up of cancer. Analyses were done with cumulative LDIR exposure expressed as continuous variables or in tertiles.

Follow-up began at the time of index MI. Cancer diagnoses were identified using International Classification of Diseases -9 and -10 codes. The criteria used for cancer diagnosis included (1) an admission for a cancer diagnosis, (2) a cancer co-morbidity listed as a secondary diagnosis for a noncancer-related admission, or (3) any outpatient visit for a cancer diagnosis.

Given that previous studies had shown a 5- to 10-year latency between LDIR exposure and cancer development, a 3-year time lag was subtracted from the time of cancer diagnosis to exclude all radiation within the 3 years preceding the cancer diagnosis (Figure 1). As such, an incident cancer could only be attributed to LDIR exposure if the cancer occurred at least 3 years after the attributed radiation exposure. Three years was chosen to reflect the previously observed cancer latency time but was intentionally shorter to not exclude the possibility of earlier detection due to increased cancer risk. Because of this 3-year time-lag covariate, cancers with no associated LDIR exposure at least 3 years before diagnosis, including therefore those occurring within 3 years of MI, were not included. To explore whether longer time lags would affect our results, we performed sensitivity analyses using 5- and 7-year time-lag covariates.

To control for medical care access, we performed adjustments for rural patients (identified by Canadian postal codes with 0 in the second position) and for those who visited a general practitioner in the previous year. This was performed to control for “brought to medical attention” bias, wherein patients previously disconnected from the healthcare infrastructure could be found to have a previously undiagnosed cancer at the time of presentation with MI. Furthermore, exclusion of any patient receiving a cancer diagnosis within 1 year of MI was used to further minimize this potential bias.

Particularly radiosensitive cancers (thyroid, hematologic, bronchogenic, and breast) were also examined in isolation. Additionally, given that many of the imaging procedures studied irradiate a specific anatomic region, anatomically defined cancer groups were created: thorax/chest, abdomen, head-and-neck/central nervous system, bone/soft tissue, and hematologic. To determine site-specific hazard ratios (HRs), diagnosis of an initial cancer was not mutually exclusive of subsequent cancer diagnoses. For example, if a patient was diagnosed with colorectal cancer (abdominal group) and subsequently with non—small cell lung cancer (thorax/chest group), both cancers were used to determine their respective site-specific risks. For the overall determination of cancer risk, a patient was considered a “case” at the time of their first eligible cancer diagnosis.

Time-dependent Cox proportional hazards models were used to examine the association between LDIR exposure and cancer. For these adjusted risk analyses, only patients with qualifying cardiac LDIR exposure were included. We performed adjustment for potentially important variables, including age and gender, and also noncardiac LDIR and co-morbidities. After adjustment, to determine the extent to which residual confounding may have influenced our results, we determined the prostate cancer risk, which in the Life Span Study (LSS) was not related to LDIR exposure; hence, any observed risk would serve as a “negative control” variable. The relation between continuous variables and the outcome was evaluated for linearity, and the proportional hazard assumption was tested for all variables (continuous and noncontinuous). All analyses were performed with SAS statistical software package (SAS Institute, Cary, North Carolina).

Results
The cohort consisted of 56,606 men (68%) and 26,255 women (32%). Women were generally older than men (Table 1). Both female gender and advanced age were associated with a greater prevalence of co-morbid conditions such as hypertension, diabetes, congestive heart failure, chronic renal failure, and stroke.

Women had a slightly less mean cardiac LDIR exposure in the first year after MI compared with men (14.6 ± 14.4 mSv for women vs 16.8 ± 14.4 mSv for men). Patients across the age strata received similar levels of radiation (1.09, 1.17, 1.15, and 0.99 mSv per 100 person-years for ages 45 to 54, 55 to 64, 65 to 74, and ≥75 years, respectively). The crude exposure stratified by age was 17.8, 18.6,
18.1, 16.5, and 10.5 mSv for ages <45, 45 to 54, 55 to 64, 65 to 74, and ≥75 years, respectively. Young men (<55 years) had the highest median cardiac LDIR exposure (15.0 mSv), whereas older women (≥75 years) had the lowest (7.0 mSv). The types of procedures were evenly distributed across gender strata, except percutaneous coronary intervention, which was performed consistently less frequently in women (Figure 2).

During follow-up, a total of 12,020 cancers were diagnosed. Using the time-dependent model with the 3-year retrospective time lag that excluded cancers with no associated radiation exposure at least before 3 years, 6,934 new cancers were included in the analysis. The median time-to-cancer-diagnosis (of those cancers included in the analysis) after index MI was 5.6 years. The annual cancer incidence was similar in men and women (2.12 vs 1.96 per 100 person-years), whereas it progressively increased with advancing age (0.6, 1.25, 2.19, 3.08, and 2.72 per 100 person-years for ages <45, 45 to 54, 55 to 64, 65 to 74, ≥75 years, respectively). Variables independently associated with a cancer diagnosis, independent of LDIR exposure, included age, noncardiac LDIR, and access to care— as reflected by visits to a general practitioner during the past year (Table 2).

For each millisievert of cardiac LDIR, women were more likely to develop a cancer (HR 1.005, 95% confidence interval [CI] 1.002 to 1.008) than men (HR 1.002, 95% CI 1.001 to 1.004) after adjusting for age, noncardiac LDIR, and other covariates (p for interaction = 0.014). Women exposed to LDIR demonstrated a significantly increased incidence of cancers of the thorax (Table 3), mostly driven by a greater risk of incident bronchogenic cancers. Although there was no statistically significant interaction between LDIR exposure and breast cancer incidence, the number of observed new cases of breast cancer was low. Men exposed
to LDIR had higher hematologic cancer rates than the unexposed, as they did for head-and-neck/central nervous system and bone/soft tissue cancers. Thyroid cancer incidence was low, and the CIs for this risk ratio did not permit reliable determination of potential interaction. Despite being a prevalent cancer, prostate cancer, which served as negative control, was not associated with LDIR exposure (HR 1.003, 95% CI 0.999 to 1.006; n = 1,112 cancers).

In contrast to gender, for each millisievert of cardiac LDIR, age was not an independent predictor of developing cancer, within the age range of this cohort (median age [interquartile range] 63.2 [53.1 to 74.0] years), age by cardiac LDIR interaction term p = 0.93).

The overall HR of cancer per millisievert exposure was 1.003 (95% CI 1.002 to 1.005) using the 3-year time lag. In sensitivity analysis, increasing the time lag to 5- and 7-years did not appreciably affect the results: 1.005 (95% CI 1.003 to 1.007) and 1.005 (95% CI 1.003 to 1.006), respectively, although the number of cancers included in the analyses decreased with longer lags to 3,584 and 1,480 cancers, respectively.

Discussion

We found, similarly to previous nonmedical LDIR cohorts, that women were at greater RR of developing a subsequent malignancy compared with men after similar exposure to LDIR. Although young age is an important determinant of the carcinogenic potential of LDIR, over the older age range in this cohort, it was neither expected nor observed to be associated with greater relative cancer risk. In addition to establishing gender-specific risks, these results support the hypothesis that medical sources of LDIR affect malignancy risk. It must be emphasized, however, that these are small RRs and that the absolute risk difference on a population level would be expected to be very small. Additionally, we and others have shown that LDIR incurred after MI is primarily comprised of therapeutic procedures with known clinical benefit. Indeed, the benefits of many medical procedures likely outweigh the potential risks, and clinicians should be very wary of deferring useful interventions for the fear of LDIR risk, doing so only when procedures are truly unnecessary or when alternative non-LDIR-emitting technology is available. Overall, these findings support the “as low as reasonably achievable” (ALARA) principle, which encourages all possible reductions in LDIR dose for a given imaging or therapeutic procedure, as is echoed for cardiovascular procedures in the American Heart Association/American College of Cardiology’s Appropriateness Criteria.

Most organizations overseeing the use of radiation-related technologies—including the US National Research Council BEIR VII, the International Commission on Radiological Protection, the US National Council on Radiation Protection and Measurements, and the United Nations Scientific Committee on the Effects of Atomic Radiation—endorse the “linear no-threshold” model for LDIR risk. Although medical sources of LDIR would hence be expected to confer malignancy risk, proof of this risk and determination of its exact magnitude have been difficult to ascertain owing to the need for large sample sizes. For example, the LSS included data from approximately 94,000 atomic-bomb survivors (matched with approximately 27,000 controls). After rigorous exclusion of patients with preexisting cancer, our study included data from almost 83,000 initially cancer-free subjects exposed to medical LDIR. As in the LSS, multivariate regression analyses demonstrated a significantly increased cancer risk proportional to the amount of LDIR incurred.

Women have previously been shown to be at greater RR of cancer than men for a given LDIR dose. This may relate to relatively smaller body sizes for the same amount of radiation. For example, women have greater bronchogenic carcinoma risk than men when exposed to equivalent doses.
of LDIR: the BEIR VII report estimated that a 100-mSv lung dose would be associated with an excess risk of lung cancer of 246 cases/100,000 in a 20-year-old woman, but with only 149 cases/100,000 in a 20-year-old man.\(^2\) Indeed, in our study, the risk of bronchogenic cancer appeared to drive the overall risk among women, in keeping with previous observations about medical imaging wherein the thorax lies in the field of radiation.\(^2\) Overall, the relative increased lifetime attributable risk estimates in women compared with men have been estimated at about 2.4-fold,\(^2\) closely resembling the approximately 2.5-fold increased RR than that we observed.

Age has clearly been shown to be an important factor modulating malignancy risk associated with LDIR exposure.\(^1\)\(-\)\(^3\) This risk asymptotically decreases in the first and second decades of life and remains relatively constant thereafter.\(^1\),\(^3\) Therefore, it is not surprising that over the age range of patients with MI, no interaction between patient age and malignant potential of LDIR was seen.

The overall risk of cancer in this cohort is somewhat greater than what was observed in the LSS. The LSS overall found an excess RR (equal to RR greater than what was observed in the LSS. The LSS age and malignant potential of LDIR was seen.\(^0.5/\text{sievert}^{16,17}\)

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The overall risk of cancer in this cohort is somewhat greater than what was observed in the LSS. The LSS overall found an excess RR (equal to RR greater than that we observed.\(^1\)\(-\)\(^3\) This could relate to an elevated prevalence—compared with the population at large—of smoking among these patients with coronary artery disease, although this could not be directly ascertained from our databases. There is compelling evidence, from both LSS\(^19\) and experimental animal studies,\(^20\) that smoking multiplicatively increases cancer risk (especially bronchogenic, as observed in our study) when accompanying concomitant LDIR exposure. Finally, the mechanism of radiation exposure was quite different: perhaps, burst exposure versus repetitive exposures influenced cancer risk. Whatever the reason for the difference in overall cancer incidence, drawing direct comparisons with the data from the LSS is difficult because of important differences in these cohorts. Nonetheless, the risks presented herein agree generally with the LSS, and the similarly observed magnitude of difference in gender-specific risks lends additional support to the association found. It bears emphasizing that these are RR and that the overall absolute risk would be expected to be quite low.

Our study has several potential limitations. First, follow-up was limited, as data collection began in 1996. Despite this, we observed an increase in cancer incidence during a shorter time-period than was found in the LSS. Given that our cohort had a greater overall incidence of cancer, perhaps the patients in our cohort were more “at risk” for cancer (based on age, smoking, obesity, and other factors), and as such the latency time to cancer was shorter. The possibility of synergistic interaction between smoking and LDIR may have also accelerated this process.\(^19\),\(^20\) Nevertheless, to control for the importance of latency time, we used a time-dependent regression analysis that incorporated a 3-year time-lag covariate to allow for cancer “gestation” time after exposure and confirmed the results using sensitivity analyses with 5- and 7-year time lags. Second, despite multivariate adjustment for possible confounders, the possibility of residual confounding could remain. To determine if residual confounding was present, we looked at the risk of developing prostate cancer, which the LSS did not find to be associated with LDIR exposure,\(^6\) and found no significant increase in prostate cancer risk with progressive LDIR exposure. Third, although confounding by indication can be a concern in this type of study, it should not be a concern here given that these cardiac procedures (catherization, myocardial perfusion imaging, multiple gated acquisition scan) are rarely undertaken as part of the work-up of a suspected cancer. Furthermore, we adjusted for noncardiac test radiation. Finally, individualized measurement of radiation dose on a population level was not possible, and therefore, we used published current estimates of radiation dose per procedure.\(^5\) Nevertheless, potential measurement errors of this kind would be expected to bias the results toward the null, and hence, the findings of significance should not be discounted.

Disclosures

The authors have no conflicts of interest to disclose.