

Gender Disparity in Cardiovascular Mortality following Radiation Therapy for Hodgkin's Lymphoma: A Systematic Review

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Abstract

Background Radiation-induced coronary artery disease (R-CAD) has become an increasingly recognized phenomenon. Although the clinical relationship between radiation therapy and CAD risk is well known, there has been very little investigation of the gender relationship to radiation-induced CAD events and resulting cardiovascular (CV) mortality. We study the gender variation in the incidence of CV events/mortality related to R-CAD in Hodgkin's Lymphoma (HL) patients.

Methods The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used in this systematic review and network meta-analysis. PubMed, google scholar, and Cochrane databases were searched to identify prospective and retrospective observational studies comparing women and men following radiation treatment for Hodgkin's lymphoma. 10 studies were included (4 prospective, 6 retrospective). The primary outcome was incidence of cardiovascular events and mortality. The secondary outcome was all-cause mortality. Meta-regression for age was also performed.

Results Of 13,975 patients including 41% females and 59% males, CV events/mortality was noted to be significantly higher in women compared to men (OR 3.74, 95% CI 2.44-5.72, $p < 0.001$). All-cause mortality was also higher in women compared to men (OR 1.94, 95% CI 1.10-3.44, $p < 0.023$). On meta-regression analysis, elderly populations have a higher rate of mortality which was even higher for women than men (coefficient = 0.0458, $p = 0.0374$).

Conclusions Women have a higher rate of CAD related CV events/mortality and all-cause mortality compared to men in radiation treated patients. These data highlight the need for increased surveillance to better monitor for CAD in female patients treated with mantle or mediastinal radiation.

Introduction

Radiation-induced coronary artery disease (R-CAD) has become an increasingly well recognized entity. R-CAD is the second most common cause of morbidity and mortality in patients treated with radiotherapy for breast cancer, Hodgkin's lymphoma (HL) and other prevalent mediastinal malignancies.(1, 2) The risk of R-CAD increases with the frequency and duration of radiation therapy and amount of radiation used. (1–5)

In the United States, approximately 8,500 people were diagnosed with HL in 2010.(3–5) Nearly half of the patients do not have complete response to chemotherapy alone, and require further salvage treatment with radiotherapy and/or autologous stem cell transplant.(6, 7) For decades, mantle or mediastinal field radiotherapy has been a therapeutic option with cure rates shown to be as high as 85%, however, this therapy inadvertently leads to potential exposure of cardiac structures to radiation.(3, 5) Patients who have survived such radiation treatments are now presenting with higher rates of CAD related events such as myocardial infarction, heart failure, ischemic cardiomyopathy, and/or arrhythmias, with complications generally occurring 5–10 years or longer after treatment.(3–6, 8–10)

There are minimal studies examining the role of gender, especially as an independent, non-traditional risk factor for increased cardiovascular (CV) mortality among patients treated with radiation. In this systematic review, we assess the role of gender in the incidence of CV events/mortality related to CAD in Hodgkin's Lymphoma (R-HL) patients who were treated with radiation.

Methods

Search Methods and Study Selection

This systematic review and meta-analysis conducted by the principles set in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. We performed an electronic database search through MEDLINE/PUBMED, EBSCO, EMBASE, Thomson Reuters' Web of Science, the Cochrane Library, Google Scholar, and Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov in October 31, 2019 and updated in April 1, 2020 using standardized methods searching for the following keywords: "Radiation-Induced Coronary Artery Disease, Hodgkin's Lymphoma, Radiation, Mediastinal Tumors." We also performed extensive hand searching by screening references of included studies and review articles for additional citations. Titles and abstracts were screened for the exclusion of unrelated articles. The references of all included articles were reviewed for additional relevant articles. No language restrictions were assumed for the included articles.

All retrospective and prospective studies examining the rate of radiation-induced CAD in patients with HL were considered eligible. All studies were considered for inclusion irrespective of patients' baseline conditions, background therapy, study follow-up or language of publication.

Whenever possible the adverse events were reported according to the Common Terminology Criteria for Adverse Events (CTCAE). We considered our lenient inclusion criteria to be reasonable as radiation-induced coronary-artery disease was only studied for Hodgkin's Lymphoma. Furthermore, our inclusion criteria increased the power of the findings. The records retrieved through electronic database search were screened independently by 2 authors.

Data extraction

Suitable studies were evaluated for the inclusion in the review through full-text assessment. Study selection and data extraction were performed independently. If different data were available for the same trial, we considered the most recent report or the updated data from ClinicalTrials.gov. Using a data extraction table, the required information from each article including first author's name, publication year, study design, sample size, mortality from cardiovascular diseases or all-causes, and incidence of cardiovascular events (including myocardial infarction, abnormal stress test, received revascularization via coronary intervention or bypass, stroke, ventricular arrhythmias, heart failure, pericardial or valvular heart disease, and/or presence of carotid intimal media thickness) were recorded. The table was completed by the first author and verified by an additional member of the study team.

Study characteristics and results were extracted independently into a standardized form. Risk of bias was evaluated through the Cochrane Risk of Bias Tool. Disagreements throughout this process were resolved by consensus. When needed data was not directly found in the published articles, we obtained such data from the authors through response letters/e-mail or via reviewing their supplemental reports.

Meta-Analysis

The data statistical analysis was performed through the Hartung-Knapp-Sidik-Jonkman (HKSJ) method in using Comprehensive Meta-analysis software. A secondary analysis was performed using the Mantel-Haenszel method and random effects models through MATLAB. A fixed 0.5 correction was added when one arm presented zero-events to avoid computational problems. Q statistics of Chi-square value test and I² index (inconsistency index) were used to evaluate the heterogeneity of individual studies contributing to the pooled estimate.

The I² statistics measures the percentage of total variation between studies attributed to interstudy heterogeneity rather than random, and we used the Sidik-Jonkman estimator to derive tau² and subsequently I². Statistical heterogeneity was considered substantial if I² > 50%. The 95% prediction intervals were estimated to assess dispersion of the effect size in different settings, deriving whether true effects are to be expected for 95% of similar recently conducted studies. The 95% prediction intervals were put into perspective with the results of pooled analyses. We performed a subgroup analysis according to the type of control group (active or placebo). The impact of follow-up time and drug exposure in the risks of ventricular arrhythmias was also ascertained through Hartung-Knapp method for meta-regression using follow-up time (months) as a covariate. Reporting, publication, bias tests for funnel plot asymmetry were only used if a minimum of 10 studies were included in the meta-analysis. All statistical tests were two-tailed, and the type I error rate was set at 5%. Risk Ratio (RR) was also estimated and the 95% confidence interval (95% CI) was used to estimate the precision of pooled results from studies. Fixed and random effects methods using the Comprehensive Meta-Analysis software program were used to calculate odds ratios as estimates of summary relative risks (RR), along with 95% confidence intervals.

As recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group methodology, two reviewers independently assessed all the critical outcomes in the following domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Quality assessment was performed by two different assessors and a third assessor in case of discrepancies.

Reporting, publication, and bias tests for funnel plot asymmetry were used. All statistical tests were two-tailed, and the type I error rate was set at 5%. To check for publication bias, we used the Begg test and Egger test. Only two-sided tests with a significance level of 0.05 were used. Confidence intervals (CIs) of individual studies were determined or approximated from the available data. A sensitivity analysis was also conducted, in which each study was omitted in turn. Heterogeneity was described using the I² statistic, which was quantified as low (< 25%), moderate (25–75%), or high (> 75%). Publication bias was assessed using funnel plots and the Egger and Begg test. Study quality was assessed using the

Newcastle Ottawa scale (0 to 9 points) using the methodology described by Downs and Black (Appendix A).

Results:

STUDY SELECTION AND PATIENT CHARACTERISTICS. The process of study selection is presented in Fig. 1. Our initial literature search yielded 488 potential studies for review. Following exclusion of review articles, case reports, retrospective studies, abstracts, studies with insufficient data, and articles with overlapping study populations and redundant data, a total of 10 studies were included in the final analysis (Table 1). All studies were conducted in the USA, Europe, and Canada. 4 studies were retrospective studies and 6 were prospective studies. The number of patients in each study varied with over 6000 patients in the largest study and 40 patients in the smallest study. Among 13,975 patients, 41% were females and 59% males with a weight mean age of 40 years.

Rates of Cardiovascular Events and Mortality. The cumulative incidence of cardiovascular events and mortality was approximately 3-times higher in women compared to men (OR 3.74, 95% CI 2.44–5.72, $p < 0.001$) [Figure 2]. All-cause mortality was also almost 2-times higher in women compared to men (OR 1.94, 95% CI 1.10–3.44, $p < 0.023$) [Figure 3]. Similar results were noted both in fixed and random effect models.

On meta-regression analysis (Fig. 4), both groups had higher mortality with advancing age but this was even higher for women with definite increase at approximately 50 years of age (coefficient = 0.0458, $p = 0.0374$).

Funnel plot analysis (appendix C) did not reveal asymmetry around the axis for the treatment effect in the assessed outcomes ($p < 0.05$ by Begg and Mazumdar's test or Egger's test), We have also performed Q and I^2 analyses to assess for heterogeneity (appendix B)

Discussion

To our knowledge, this is the first systematic review and meta-analysis specifically assessing gender disparity in cardiovascular mortality following radiation therapy for Hodgkin's lymphoma. Previously, mantle field or mediastinal radiation has been proven in several studies to significantly raise the risk for cardiovascular diseases independently of traditional cardiac risk factors as well.(4, 8) Our analysis revealed that for women, such radiation therapy significantly raises CV events and mortality by three-fold and raises all-cause mortality by almost 2 fold.

Interestingly, studies have shown that the risk of CAD and related CV mortality increases when combined with the traditional risk factors and radiation exposure.(8, 10) For example, diabetes had been linked to cause further hospitalizations and hypertension and hyperlipidemia were two times as likely to develop ischemic cardiac disease among patients with R-HL.(8, 11) Our study further demonstrated that with aging, the incidence of CV events markedly increased for female patients. While all the studies evaluated

in this meta-analysis were independently corrected for the traditional cardiac risk factors for CAD, such as hypertension, hyperlipidemia, diabetes, and tobacco use, it should be noted that the majority of the studies did not clearly comment on the use of specific medical therapies for these conditions.

Additionally, high-dose mediastinal irradiation (cumulative dose of 35–40 Gy), increases cardiovascular disease and mortality in long-term survivors.(12–14) Mediastinal radiation treatment incidentally exposes a greater volume of the heart within the radiation field, leading to increased risk of endothelial damage and promotion of atherosclerosis.(15, 16) In our analysis, most patients received over 30 Gy of radiation (Table 1). It should be recognized that in recent years, changes in radiation field size and technique have led to a significant reduction in cardiac exposure resulting in less cardiotoxicity than previously identified.(3, 17)

The National Comprehensive Cancer Network (NCCN) currently recommends the following cardiovascular screening guidelines for survivors of Hodgkin lymphoma: annual blood pressure, serum glucose, and lipid screening as well as aggressive management of cardiovascular risk factors.(18–20) The American College of Radiology Appropriateness Criteria Expert Panel on Hodgkin Lymphoma Follow-up recommends stress test and echocardiogram every 5 to 10 years after treatment as appropriate, broad recommendations.(1) We suggest development of specific screening guidelines for high risk patient groups treated with mantle field or mediastinal radiation, including female gender, radiation doses over 30 Gy, concomitant use of cardiotoxic chemotherapy, and/or having one or more traditional CV risk factors.

STUDY LIMITATIONS. We acknowledge certain limitations associated with this study. Since this is a study-level analysis, it is not possible to make definitive conclusions about gender risks for patients with radiation-induced CAD. We identified only 10 retrospective and prospective observational cohort studies, accounting for an overall smaller sample size. None of the selected studies matched men and women with Hodgkin’s disease (HD) to radiation therapy dose, age of HD diagnosis, and how CVD was diagnosed. The studies did not specify the dose, frequency, and duration of radiation therapy for their patient populations. These findings may have led to a different course of CAD and subsequently CV mortality. Our study population mostly consisted of Caucasian nations. Most of the selected studies included young patients with a median age of 40 years. As with any meta-analysis of observational studies, variations in the inclusion criteria and endpoints are all potential sources of heterogeneity among studies. We could not access patient-level data to allow adjustment for other covariates that might influence the incidence of CVD, including medications, laboratory data, and other imaging parameters.

Conclusions:

The risk of cardiovascular events and mortality is substantial for women with HL and radiation-induced CAD. Moreover, the rate of all-cause mortality was also higher in women compared to men. The findings demonstrate the need for vigilant screening for cardiovascular disease among cancer patients and survivors who have received mediastinal radiation.

Abbreviations

R-CAD

radiation-induced coronary artery disease

HL

Hodgkin's lymphoma

CV

cardiovascular

OR

odds ratio

CI

confidence interval

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Declarations

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Authors' contributions

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Figures

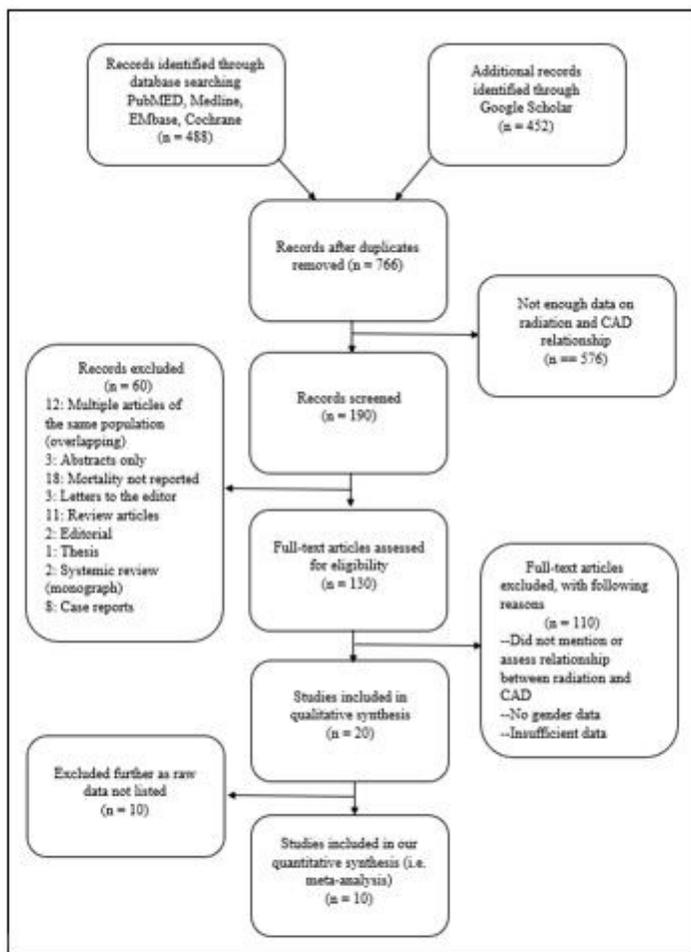


Figure 1

PRISMA FLOW CHART OF STUDIES SCREENED AND INCLUDED IN META-ANALYSIS

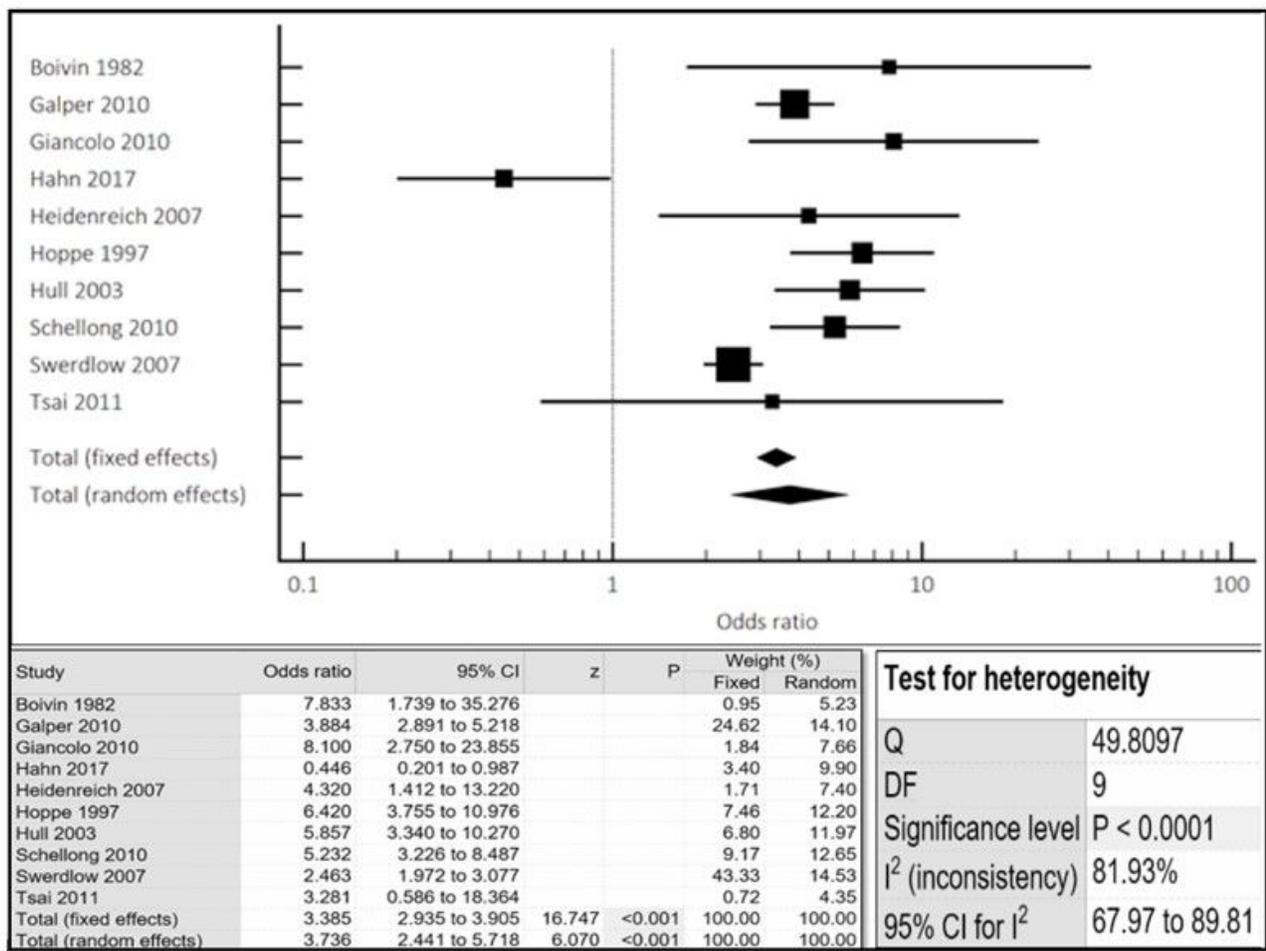


Figure 2

CUMULATIVE INCIDENCE OF CV EVENTS/MORTALITY NOTED IN R-HL FEMALES COMPARED TO MALES VIA COMBINED FIXED AND RANDOM EFFECTS ODDS RATIO, CONFIDENCE INTERVAL AND WEIGHT OF STUDIES FOR CV EVENTS/MORTALITY FOR R-HL FEMALES COMPARED TO MALES VIA COMBINED FIXED AND RANDOM EFFECT. TEST FOR HETEROGENEITY OF STUDIES FOR R-HL FEMALES COMPARED TO MALES VIA COMBINED FIXED AND RANDOM EFFECTS.

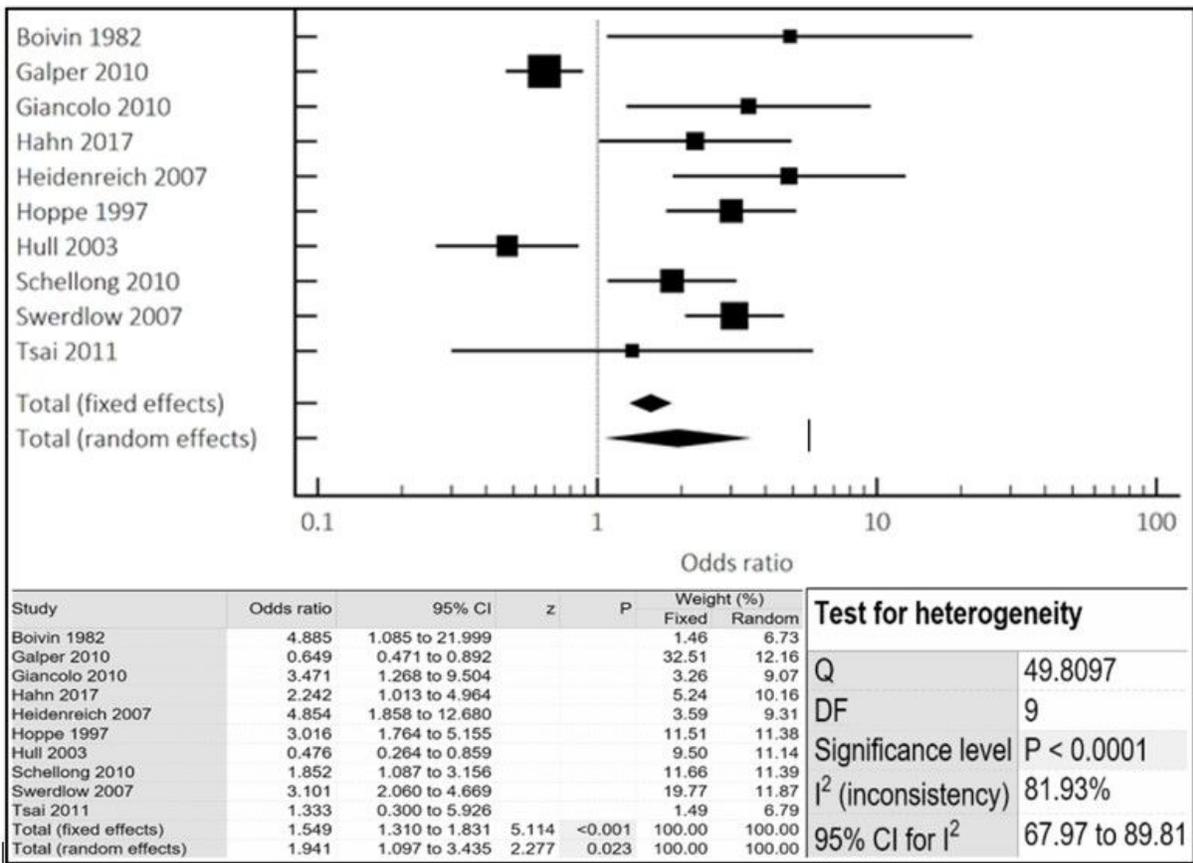


Figure 3

CUMULATIVE INCIDENCE OF ALL-CAUSE MORTALITY NOTED IN R-HL FEMALES COMPARED TO MALES VIA COMBINED FIXED AND RANDOM EFFECTS ODDS RATIO, CONFIDENCE INTERVAL AND WEIGHT OF STUDIES FOR ALL-CAUSE MORTALITY FOR R-HL FEMALES COMPARED TO MALES VIA COMBINED FIXED AND RANDOM EFFECTS. TEST FOR HETEROGENEITY OF STUDIES FOR R-HL FEMALES COMPARED TO MALES VIA COMBINED FIXED AND RANDOM EFFECTS

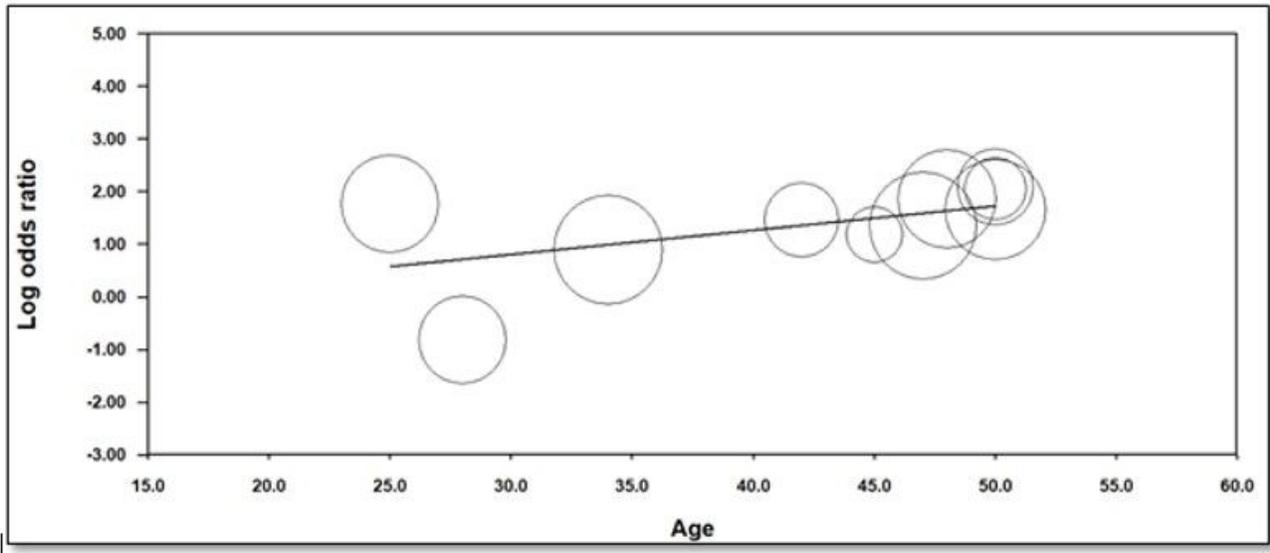


Figure 4

META-REGRESSION TO ASSESS FOR INCIDENCE OF CV EVENTS/MORTALITY OF RADIATION TREATED FEMALE PATIENTS WITH AGING