CRITICAL REVIEW AND STRATIFIED META-ANALYSIS OF LUNG CANCER RISK IN PETROLEUM REFINERY WORKERS

Thesis for a Master of Public Health, Yale School of Public Health

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ABSTRACT

Several publications have proposed a workplace risk of lung cancer in petroleum refineries, with asbestos as the potential agent. To examine the associations between petroleum refinery work and lung cancer related to occupational asbestos exposure, in addition to smoking and other concurrent occupational exposures, a systematic review and stratified meta-analysis was employed. Cochrane-Mantel-Haenszel statistics were used to combine SMR/SIR data separately for all male and female refinery workers, as well as SMR/SIR and RR/OR measurements for the subset of male maintenance workers, who were exposed to higher levels. Of 219 studies identified in the literature search, 78 studies were selected for critical review, of which 28 were used for meta-analysis. Only three studies reported estimates adjusted for smoking, the strongest risk factor of lung cancer, and of those none found a statistically significant increase for lung cancer risk. Males in cohorts consisting of all refinery workers, which included both blue and white collar workers, had a summary estimate of 0.80 (95% CI: 0.75-0.85) when compared to population controls, all female refinery workers had a summary estimate of 1.27 (95% CI: 0.86-1.87) when compared to population controls. Male maintenance workers exhibited a summary estimate of 0.88 (95% CI: 0.74-1.05) with population controls, and a summary estimate of 1.62 (95% CI: 1.30-2.03) when internally compared to other refinery workers. Subsequent sensitivity and meta-regression analyses showed generational effects, outlying studies, and significant differences between corporate and government/academic studies and between race-adjusted and non-race-adjusted studies. The present study found a lack of methodological consistency, but that overall the present literature did not provide evidence for an association between refinery work and increased lung cancer risk. Accurate quantification of lung cancer risk for refinery workers will depend on addressing these issues, particularly the contribution of smoking to lung cancer risk in this population.

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INTRODUCTION

For the past four decades, researchers sought to investigate the health status of petroleum refinery workers (Baird 1967)(Schnatter 2012). These occupations worked with a variety of manufacturing processes to transform crude oil into different petroleum-based products, such as fuels, solvents, greases, and waxes. These processes involved physical and chemical components that could lead to adverse health outcomes from environmental or occupational exposures for these individuals. Potential exposures included asbestos, petroleum coke, benzene, polycyclic aromatic hydrocarbons, and other chemical as well as physical hazards (Thomas 1980). It has been proposed that asbestos and other concurrent workplace exposures have acted as agents of lung cancer risk, independent of smoking.

ASBESTOS IN PETROLEUM REFINERIES

Asbestos was historically utilized in petroleum refinement operations for two general purposes. The first was for use in piping that involved high (and occasionally very low) temperature fluid transfers, including insulations around pipes as well as gaskets used to seal two pipes together (Gennaro 1994). The second use was for protective screens around high-temperature welding operations (Gennaro 1994). The manufacturing, transportation, assembly, and maintenance of these products lead to the release of asbestos fibers into the air and subsequent asbestos exposure. Direct ambient asbestos monitoring at petroleum refinery plants was scarce. Williams et. al. (2007) synthesized the existing monitoring data for one refinery in Beaumont, Texas, supplemented with available industrial hygiene information from other sources, to estimate the asbestos exposure of specific crafts between 1940 to 2006. The study estimated that the decade of highest asbestos exposure at the refinery was 1940-1950, with decreasing exposures each subsequent decade. This decrease was likely due to four factors: 1) changes in asbestos regulations, 2) increased awareness leading to further respirator use and training, 3) improved engineering controls, and 4) increased replacement of asbestos products with substitutes.

Different occupations at petroleum refineries likely had differing asbestos exposures, and Williams et. al. (2007) ranked 12 job titles by their potential asbestos exposure over time. Insulators ranked as the highest, followed by laborers, masons, maintenance workers, pipefitters, boilermakers, millwrights, carpenters, welders, sheet-metal workers, electricians, and painters. In the literature, maintenance workers at oil and chemical refineries were studied extensively for asbestos exposure and were often identified as having a particularly large potential for chemical exposures in a variety of occupational settings (Lilis 1980)(Finkelstein 1996)(Rosamilia 1999)(Schnatter 2012). Length of maintenance work, asbestos exposure, and petroleum coke exposure at petroleum refineries were

shown to be correlated (Schnatter 2012). In Williams (2007), asbestos exposure estimates for blue collar occupations varied based on what fraction of their work day involved asbestos-containing materials, how likely the work would lead to a release of ambient asbestos, and how common respirator use was for each distinct occupation. Oil refining facilities also employed a variety of white-collar workers, such as engineers, accountants, secretaries, and other scientific, technical, clerical, and administrative positions (Sorahan 2002). Workers in these occupations were not expected to interact with asbestos containing materials during their workdays to the same degree as blue-collar workers. While they did spend time in facilities that used asbestos, white-collar workers' collective asbestos exposure was expected to be significantly lower than that of blue-collar workers. Subsequently, white collar worker's expected risk for asbestos-related diseases would be lower.

ASBESTOS, LUNG CANCER, AND SMOKING

In 1930, Merewether and Price connected asbestos exposure with what is now known as asbestosis in their widely distributed survey of the asbestos industry (Merewether 1930). The inhalation of asbestos fibers was linked to detrimental respiratory health effects. An association between lung cancer and asbestos exposure was reported in 1955 when Richard Doll stated that "the asbestos workers studied suffered an excess mortality from lung cancer" (Doll 1955). This was one year before his seminal paper with Bradford Hill, connecting smoking to lung cancer in the British Doctors Study (Doll 1956). In 1964, Irving Selikoff provided more conclusive evidence of this relationship in a study of insulation workers in the New York City metropolitan area (Selikoff 1964). Evidence suggests inhaled asbestos exposure can lead to lung cancer through multiple mechanisms (Omenn 1994)(Hodgson 2000). While not a direct mutagen, asbestos can serve as both initiator and promoter of lung carcinogenesis in a multi-stage model (Barrett 1989).

Smoking is a key confounder in the relationship between occupational asbestos exposure and increased lung cancer risk. While the early studies of asbestos workers did not take into account smoking status, it is now known that smoking accounts for 80-90% of all lung cancer cases, while occupational exposures account for at most 10% (Tsao 2013). Historically, blue-collar workers tended to smoke at higher rates than white collar workers and the general population, confounding the relationship between many occupational exposures and lung cancer upwards and away from the null (Ham 2011). Lung cancer's relationship with smoking is so enduring and significant that when coarse categories of smoking status, such as "Ever" and "Never" as opposed to a continuous variable such as pack-years, are employed for adjustment, a significant amount of residual confounding due to smoking may remain. This would indicate a higher lung cancer risk falsely attributed to other factors (Richardson 2010).

How the two risk factors of asbestos exposure and smoking interact has been a matter of great uncertainty, as smoking rates between asbestos workers and the general population and

between various trades of asbestos work can differ greatly. In addition, both exposures operate as complex carcinogens, with effects at multiple stages of carcinogenesis. Epidemiological studies of the interaction have, at various times, reported both negative (Berry 1985) and positive (Saracci 1977) interactions, as well as additive (Liddell et al 1984), multiplicative (Hammond et al 1979), and supramultiplicative (Baker 1985) effect modifications. A review paper on the subject reported that the interaction is clearest in occupational studies of high asbestos exposure, such as insulation work, and that the interaction tends to approximate positive, multiplicative effect modification in these studies (Vainio 1994).

An additional confounder in the relationship between asbestos exposure in refinery workers and lung cancer risk is occupational petroleum coke exposure (Lewis 2003)(Schnatter 2012). Petroleum coke is a carbon-based solid that is a byproduct of petroleum refinement processes. Like asbestos, it can be released into the occupational environment as a dust and then inhaled. Both asbestos and petroleum coke have been present in oil refineries, and both could lead to increased lung cancer risk in refinery worker populations (Field 2012).

LUNG CANCER IN PETROLEUM REFINERY WORKERS

Several epidemiological publications have evaluated lung cancer risk in petroleum refinery occupational cohorts. While some studies have specifically evaluated lung related cancers (Gennaro 2000)(Rosamilia 1999)(Shatter 2012), many evaluated several cancers or diseases at once, including ICD-9 162, "[m]alignant neoplasm of trachea, bronchus, and lung," as one diagnosis in many of the cancers surveyed. Previously, two meta-analyses, both conducted by Otto Wong and Gerhard Raabe, evaluated the epidemiology of cancer in the petroleum industry, and were published in 1989 and 2000, respectively. For lung cancer (ICD-9 192) in overall refinery workers, the 1989 study reported a meta-standardized mortality rate of 0.77, while the 2000 study reported 0.81. Both were significant deficits at the 0.05 level.

The present study 1) provided a critical and comprehensive review of the subject, including methodological and exposure literature 2) updated meta-analytic results to give an industry-wide perspective of lung cancer and refinery work epidemiology, including 14 additional years of publications 3) employed a wider selection criteria to evaluate literature beyond standardized cohorts 4) stratified results to examine lung cancer risks among three sub-populations of petroleum refinery workers and two study designs. 5) employed sensitivity analyses and meta-regression techniques to evaluate contributing factors to the heterogeneity of results in the literature.

METHODS

CRITICAL REVIEW

A search was conducted for all relevant literature on the subject of lung cancer incidence and mortality among petroleum refinery workers, including supplementary publications like exposure assessments and smoking prevalence studies. The search involved two components. The first was a standardized systematic review, following PRISMA guidelines, and employed search terms on online databases. Using the terms "(Refinery OR Refineries) AND (Petroleum OR Oil) AND Lung AND Cancer", the staff librarian pulled relevant abstracts from PubMed and the Web of Science. Two investigators independently evaluated these abstracts based on their relevance according to the following criteria:

Include-

Anything that measures lung cancer incidence or mortality in oil refinery workers

OR

Anything that discusses methodological issues related to measuring lung cancer incidence or mortality in oil refinery workers, such as smoking data

OR

Anything that provides exposure information on asbestos within oil refineries

Maybe Include-

It looks like the paper might have some of the above information, but it is unclear from the abstract or title (if abstract not available)

Reject-

The article does not discuss oil refinery workers and lung cancer risk

AND

The article does not discuss exposure at oil refineries

OR

The article is not available in English[1]

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[1] International studies were allowed if in English

A third investigator served as a tiebreaker for inclusion, where any disagreement between the two independent abstract evaluations or any designations of "maybe" was evaluated for final inclusion or rejection.

In addition to the systematic review, any other sources of literature on the subject were sought to fully include all potential publications. This involved two additional searches. The first involved a database from Exponent, Inc. that archived documents related to asbestos. The office librarian applied the same search terms used previously to generate a list of potential publications. One investigator implemented the same inclusion/exclusion criteria above on this list to include an additional set of relevant literature. The final source for the critical review was the most recent meta-analysis that evaluated lung cancer in petroleum refinery workers, Wong and Raabe 2000. Any citation included in their critical review that was not already identified by our search was evaluated using the aforementioned inclusion/exclusion criteria.

Data Identification and Extraction

The quantitative meta-analysis portion of the study involved a subset of literature from the critical review. While the review contained methodological and exposure information for petroleum refinery workers, the meta-analysis relied only on literature where lung cancer risk is quantified in the form of a risk ratio and either a confidence interval or other information through which to calculate a standard error[2]. In addition, no studies could contain overlapping cohorts; each quantitative measure must depend entirely on disjoint sets of individuals. In this case, many refinery cohorts have been studied and updated more than once, leading to multiple publications on similar or same populations. When this occurred, the most recent analysis of a group was included.

All pooled risk estimates in the principal analysis for lung cancer were either completely or partially unadjusted for smoking due to the lack of adjustment in the individual studies. Instead, the potential effect of smoking adjustment on the risk estimates is investigated in the subsequent sensitivity analyses as well as in the discussion.

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[2] In some cohort studies, observed and expected counts of mortality or incidence were included in lieu of confidence intervals. A standard error can be readily calculated from these values for use in a meta-analysis

Stratum	Refinery Worker Subset	Comparison	Effect Measures
I	All Male Refinery Workers	Population	SMR, SIR
II	All Female Refinery Workers	Population	SMR, SIR
III	Male Maintenance Workers	Population	SMR, SIR
IV	Male Maintenance Workers	Internal	RIR, OR

TABLE 1: STRATA USED IN PRINCIPAL META-ANALYSIS

In contrast with the previous meta-analyses, the principal analysis was stratified by three sub-populations and two study designs that may have been subject to different exposures or confounding variables. This stratification also allowed comparison between these groups and study-designs. The four strata of worker lung cancer risks at petroleum refineries are displayed in Table 1. To test gender differences, men and women in total refinery cohorts were each placed in separate strata, I and II respectively. These studies all calculated lung cancer risk compared to control groups outside of petroleum refineries, reporting standardized mortality and incidence ratios. Due to high mortality in lung cancer cases (Tsao 2013), SMRs and SIRs are considered comparable. These total worker refinery cohorts include several blue collar crafts as well as white collar workers. The third and fourth strata look at the subpopulation of male maintenance workers at refineries. This was the refinery craft with higher asbestos exposure that had the most lung cancer risks reported in the literature. These risks were either calculated similarly to Stratum I and II with population controls, Stratum III, or with internal controls groups from within the larger petroleum refinery cohorts, Stratum IV. The latter studies were either cohort studies reporting Relative Incidence Rates (RIR) or case-control studies reporting Odds Ratios (OR).

Data for each stratum were taken from publications in the total review. The number of strata with risk estimates provided varied by study, with some publications providing only one and others providing multiple (see Appendix I). Additionally, some cohort updates included different strata of risk estimates than the prior or original study. Stratum-specific risk estimates from these earlier versions were included if they were not contained in the cohort update.

The data extraction phase involved identifying the appropriate studies for each stratum and collecting risk estimates and measures of variance. In addition, characteristics about each study estimate were recorded before any analyses. Factors for which there were no missing data were publication year, initial year of follow-up, final year of follow-up, median year of follow-up, follow-up

time, whether the study was corporate, university, or government research[3], the location of the refinery or refineries, the population giving rise to the comparison group, whether the study was smoking-adjusted, and whether the study was race-adjusted.

META-ANALYSIS

These meta-analyses employed Cochrane-Mantel-Haenszel summary estimates, which are the most widely used in epidemiological critical reviews (Elwood 2007). The theory behind using the Cochrane method in observational epidemiology is discussed in Appendix II. This method involved inverse variance weighting each individual estimate in a pooled, summary relative risk. When there was evidence of significant heterogeneity ($I^2 > 50\%$), DerSimonian-Laird random-effects estimates were used. Forest plots are presented to display the results. Funnel plots for qualitative investigations of publication bias appear in Appendix III. These methods differ from the previous meta-analyses on the subject, conducted by Wong and Raabe (1989, 2000). Wong and Raabe only included studies that calculated standardized mortality ratios, and their summary estimates simply added the observed deaths from all studies and then divided by the sum of the expected deaths. That method resulted in an interpretable value that is calculated in the same manner as its constituent individual estimates, but it was inherently limited to fixed-effects and could not include risk estimates besides SMR and SIR. This prevented the inclusion of studies that employed internal comparisons. The present study employed a different method in order to include estimates other than standardized mortality or incidence ratios and the necessity to assume random-effects, given the high level of heterogeneity found between several refinery studies.

SENSITIVITY ANALYSES

Following the primary analysis of four strata, four sensitivity analyses were conducted to evaluate how summary estimates and associated heterogeneity statistics changed with further stratum partitioning on *a priori* hypothesized key factors. The first, on Stratum I, tested whether U.S. studies and international studies differ. If they differed significantly, it may suggest that refinery conditions in the U.S. were unique, and that combining U.S. and non-U.S. studies may be inappropriate in Stratum I, the largest of all four strata. The second, also on Stratum I, evaluated a generational effect. Between 1971 and 1975, OSHA unveiled its first guidelines and regulations on occupational asbestos exposure (Berry 1985). Also, over the last half of the 20th century, smoking rates decreased dramatically (Tsao 2013). To test this effect, studies in Stratum I with a median follow-up year up to 1975 were compared to studies with median follow-up year after 1975. The third sensitivity analysis looked at the effect of removing one study, Aronson 1994, from Stratum II,

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[3] In the forest plots, this is labeled as "Type"

all female refinery workers. Unlike the rest of the studies that focused on only refinery workers, Aronson looks at all female workers in Canada and compared disease rates in each occupation to the overall rates in Canadian working women. The final sensitivity analysis evaluated the hypothesis that smoking adjusted studies differ from non-smoking adjusted studies. As smoking was likely a key confounder in this relationship, it was hypothesized that smoking adjustment would provide different risk estimates than crude rates. As all smoking adjusted studies were found in Stratum IV, this stratum was partitioned to see how the summary estimates changed.

Meta-regression

To test whether any of the other recorded factors influence the variability in lung cancer risk estimates *post hoc*, a regression analysis was conducted to identify additional covariates. The regression employed weighted least squares, where the inverse of the variance of each study corresponded to its weight in the parameter estimates. This approach has been used in recent meta-analyses of environmental and occupational epidemiological studies (Koh 2014)(Peluso 2014)(Yu 2014). To maximize statistical power, the dataset combined all four strata and removes any clearly outlying estimates. The identification of these outlying estimates is discussed in the results section. This analysis was meant to be exploratory, as the dataset was a combination of strata measuring potentially differing risks and all identified significant covariates were not previously explicitly hypothesized.

RESULTS

CRITICAL REVIEW

Initial Literature Search - 219 articles	Selection for Critical Review - 78 articles	Meta Analyses - 28 articles total
•PubMed - 50 articles •Web of Science - 68 articles •Archived Asbestos Documents - 58 articles •Wong and Raabe 2000 - 43 articles	•PubMed - 39 articles •Web of Science - 16 articles •Archived Asbestos Documents - 13 articles •Wong and Raabe 2000 - 10 articles	•All male refinery workers - 21 risk estimates •All female refinery workers - 7 risk estimates •Maintenance workers / population controls - 7 risk estimates •Maintenance workers / internal controls - 6 risk estimates

FIGURE 1: FLOW DIAGRAM ILLUSTRATING THE SELECTION PROCESS

In total, the database search, using terms "(Refinery OR Refineries) AND (Petroleum OR Oil) AND Lung AND Cancer" resulted in 50 abstracts from PubMed and 68 abstracts from Web of Science not found by PubMed. These were all peer-reviewed articles found in public databases. 58 publication titles were identified from the archived asbestos database, not included in PubMed or Web of Science, as well as 43 citations in Wong and Raabe 2000 not already identified in any of the three previous databases. These included white papers, government documents, and industry monographs.

78 articles in total fit the selection criteria for the critical review. Appendix I shows each study, with first author, year, journal, meta-analysis stratum, country, study design, and a brief description. The earliest article was "Effects of atmospheric contamination on cancer mortality in petroleum refinery employees", published in 1967 by V. C. Baird, a physician for Humble Oil and Refining Company. It evaluated risk of cancers in aggregate for refinery workers from the understanding of air pollutant risk at the time, which included VOC's, hydrogen sulfide, and general particulates, but not specifically asbestos. In fact, most identified studies of refinery cohorts, while breaking down cancer risk into individual tumor sites, did not explicitly identify asbestos as a risk

factor. The understanding of asbestos as a potential risk factor for refinery workers increased over time. In the most recent published article in the critical review, "Lung cancer incidence in Canadian petroleum workers" in 2012, Schnatter discussed specifically asbestos and petroleum coke as potential contributors to lung cancer incidence in refinery workers.

Countries Represented	U.S. (50 of 78), Canada, Australia, Finland, Sweden, U.K., Italy
Companies Identified	Shell, Humble, Chevron, ExxonMobil, American Petroleum Institute, Imperial, Texaco, Neste

TABLE 2: COUNTRIES AND COMPANIES IDENTIFIED IN THE CRITICAL REVIEW.

The most crucial finding of the critical review was the lack of treatment of smoking as a confounder in the relationship between occupational exposures from refinery work and lung cancer. Only three of the 78 studies included a risk estimate for lung cancer in this population that was adjusted for smoking status: Gun (2006), Schnatter (2012), and Rosamilia (1999). All three are ultimately included in the meta-analysis. However, all other studies identified in the review did not adequately address this topic. Some studies (Lewis 2003) attempted to collect smoking data from medical records but could not provide identifications for enough of the cohort. Others (Tsai 2001) did not consider the difference between refinery worker smoking rates and general population rates as significantly different enough to require adjustment. One potential reason for the lack of smoking-adjustment was that many of the studies identified (Satin 2002)(Sim 2007)(Collingwood 1996) conducted large cancer mortality studies on entire refinery worker cohorts over long periods of time. Lung cancer was one of many diseases examined, so accurate smoking data were not a priority. In addition, especially in early cohorts, smoking status was not readily available in health surveillance. In mortality studies, it was difficult to acquire accurate expected lung cancer rates from the general population stratified by smoking status in addition to age and calendar-time.

Tsai (2001) attempted to retrospectively evaluate smoking rates in this population, independent of lung cancer rates and asbestos exposure. This study looked at self-reported smoking rates in several thousand Shell refinery workers from 1976 to 1997. The employee group spanned several Shell refineries and considered specific sub-groups, comparing rates to the general U.S. population. Their overall finding was that smoking differences were an unlikely confounder in lung cancer studies with population reference groups; refinery workers overall smoked 2% less than the U.S. population. However, larger differences existed within the subgroup analyses. While smoking rates decreased over time, production workers such as laborers, operators, and craftsmen smoked at 8% higher rates on average than staff such as supervisors and office workers. Female refinery workers smoked only 2.1% less than their male counterparts during the 22-year period, while overall female rates in the U.S. during that time were on average 5.7% lower than men.

Including Tsai (2001), seven of the 78 articles in the critical review were non-epidemiological literature that evaluated either a) methodological issues related to measuring lung cancer incidence or mortality in oil refinery workers or b) exposure information on asbestos within oil. One was the aforementioned retrospective exposure assessment of asbestos at a Texas oil refinery (Williams et al 2007). Three additional papers evaluated asbestos exposure in refinery workers by using X-rays to determine if some refinery workers were subject to excess lung abnormalities associated with asbestos. A non-peer reviewed investigation in 1986 by Exxon in their Linden, New Jersey plant looked at 550 workers' chest x-ray charts and found abnormalities "moderate numbers" and that "relationships were found" with estimates of asbestos exposure (Liveright et al 1986). Two papers, Kim et al (2008) and Kipen et al (1991), looked at additional potential confounding factors in a relationship between refinery work-related asbestos exposure and lung cancer, Race and Benzene exposure.

META-ANALYSES

41 lung cancer risk estimates from 28 publications were selected for meta-analysis from the critical review across all four strata. The summary risk ratio for Stratum I of all male refinery workers with population controls was 0.80, with a 95% confidence interval of 0.75 to 0.85, a significant deficit. This value was based on 21 studies. Figure 2 displays a random-forest plot of the results. Of these 21 studies, four were incidence studies, resulting in SIR values, while the other 17 were mortality studies resulting in an SMR value for lung cancer risk. There were no estimates of significantly elevated risk. The average follow-up time was 36.4 years. All employed population controls: 12 used national population lung cancer rates, 6 used state or provincial level rates, and the remaining three used a smaller subdivision. The fixed effect value of 0.81, with 95% confidence interval of 0.79 to 0.84, resulted in an I^2 heterogeneity statistic of 71%, suggesting significant heterogeneity. Therefore, the random effects model was employed for the final summary estimate.

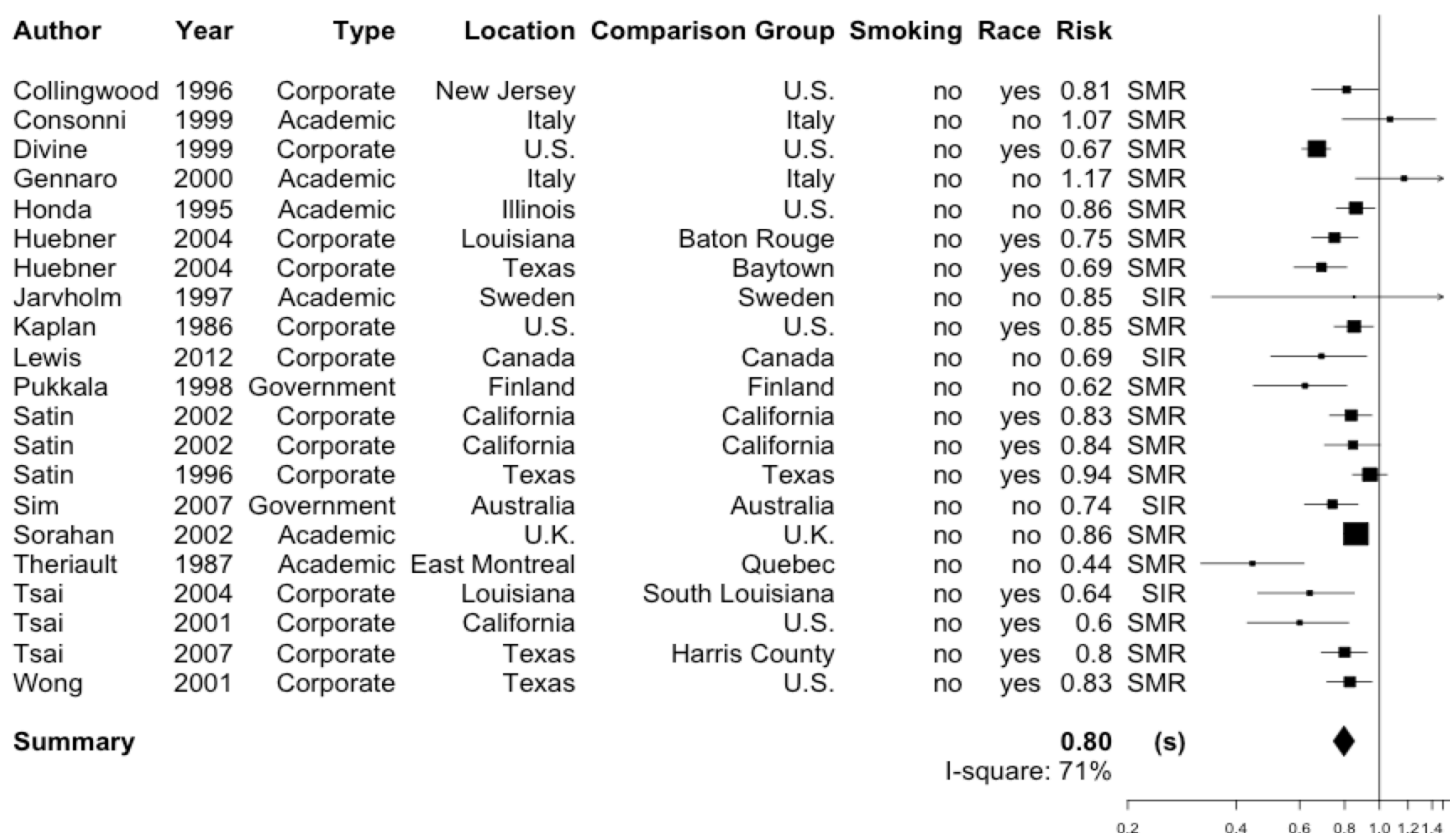| Author	Year	Type	Location	Comparison Group	Smoking	Race	Risk	
Collingwood	1996	Corporate	New Jersey	U.S.	no	yes	0.81	SMR
Consonni	1999	Academic	Italy	Italy	no	no	1.07	SMR
Divine	1999	Corporate	U.S.	U.S.	no	yes	0.67	SMR
Gennaro	2000	Academic	Italy	Italy	no	no	1.17	SMR
Honda	1995	Academic	Illinois	U.S.	no	no	0.86	SMR
Huebner	2004	Corporate	Louisiana	Baton Rouge	no	yes	0.75	SMR
Huebner	2004	Corporate	Texas	Baytown	no	yes	0.69	SMR
Jarvholm	1997	Academic	Sweden	Sweden	no	no	0.85	SIR
Kaplan	1986	Corporate	U.S.	U.S.	no	yes	0.85	SMR
Lewis	2012	Corporate	Canada	Canada	no	no	0.69	SIR
Pukkala	1998	Government	Finland	Finland	no	no	0.62	SMR
Satin	2002	Corporate	California	California	no	yes	0.83	SMR
Satin	2002	Corporate	California	California	no	yes	0.84	SMR
Satin	1996	Corporate	Texas	Texas	no	yes	0.94	SMR
Sim	2007	Government	Australia	Australia	no	no	0.74	SIR
Sorahan	2002	Academic	U.K.	U.K.	no	no	0.86	SMR
Theriault	1987	Academic	East Montreal	Quebec	no	no	0.44	SMR
Tsai	2004	Corporate	Louisiana	South Louisiana	no	yes	0.64	SIR
Tsai	2001	Corporate	California	U.S.	no	yes	0.6	SMR
Tsai	2007	Corporate	Texas	Harris County	no	yes	0.8	SMR
Wong	2001	Corporate	Texas	U.S.	no	yes	0.83	SMR
Summary							**0.80**	(s)

I-square: 71%

FIGURE 2: FOREST PLOT FOR STRATUM I, OVERALL MALE REFINERY WORKERS. (S) MEANS SIGNIFICANT.

Only 7 studies out of all 78 in the critical review evaluated lung cancer risk among female refinery workers and were therefore included in Stratum II. All of these studies used non-refinery reference groups, two studies calculated SIRs and five calculated SMRs. The average follow-up time was 34.4 years. Risk estimates ranged from 0.59 (Lewis 2012) to 4.81 (Aronson 1994). The latter study was a significant increase. This led to a high I^2 statistic of heterogeneity of 57%, and therefore random effects were assumed. The random-forest plot of these studies is shown in Figure 3. The summary risk ratio, assuming random effects, is 1.27, with a 95% confidence interval of 0.86 to 1.87. While the increase was non-significant, the confidence interval does not overlap with that of the overall male refinery worker cohort.

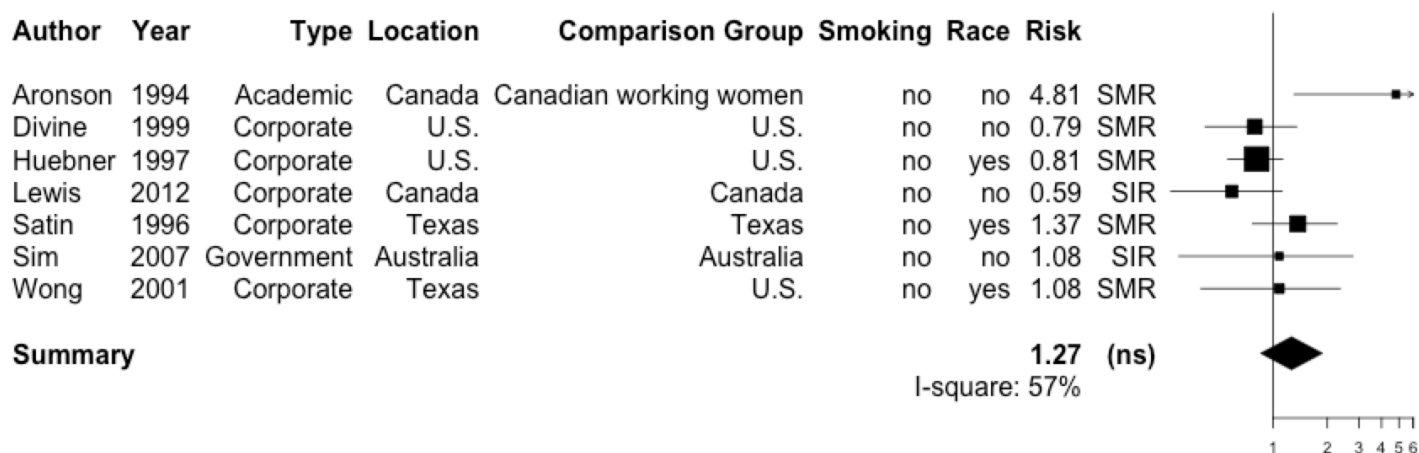| Author	Year	Type	Location	Comparison Group	Smoking	Race	Risk	
Aronson	1994	Academic	Canada	Canadian working women	no	no	4.81	SMR
Divine	1999	Corporate	U.S.	U.S.	no	no	0.79	SMR
Huebner	1997	Corporate	U.S.	U.S.	no	yes	0.81	SMR
Lewis	2012	Corporate	Canada	Canada	no	no	0.59	SIR
Satin	1996	Corporate	Texas	Texas	no	yes	1.37	SMR
Sim	2007	Government	Australia	Australia	no	no	1.08	SIR
Wong	2001	Corporate	Texas	U.S.	no	yes	1.08	SMR
Summary							1.27	(ns)
						I-square: 57%		

FIGURE 3: FOREST PLOT FOR STRATUM II, OVERALL FEMALE REFINERY WORKERS. (NS) MEANS NONSIGNIFICANT.

The first analysis for maintenance workers included estimates based on external population controls in standardized mortality and incidence studies at oil refineries, Stratum III. Based on 7 studies and an average of 41.1 years of follow-up, the summary risk estimate, assuming random-effects, was 0.88 with a 95% confidence interval of 0.73 to 1.05, and an I^2 value of 67%. This estimate was similar, if slightly higher and less precise, to that of the overall male refinery workers compared to external populations. It could be considered an insignificant deficit. There were no estimates that reported a significant increase. Figure 4 displays the random-forest plot.

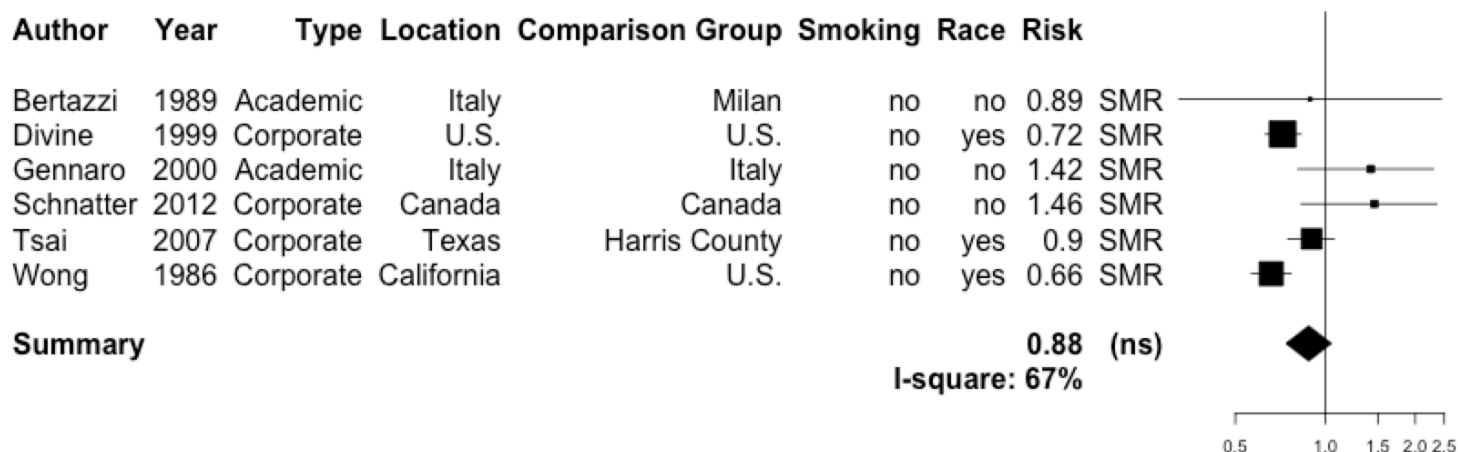| Author	Year	Type	Location	Comparison Group	Smoking	Race	Risk	
Bertazzi	1989	Academic	Italy	Milan	no	no	0.89	SMR
Divine	1999	Corporate	U.S.	U.S.	no	yes	0.72	SMR
Gennaro	2000	Academic	Italy	Italy	no	no	1.42	SMR
Schnatter	2012	Corporate	Canada	Canada	no	no	1.46	SMR
Tsai	2007	Corporate	Texas	Harris County	no	yes	0.9	SMR
Wong	1986	Corporate	California	U.S.	no	yes	0.66	SMR
Summary							0.88	(ns)
						I-square: 67%		

FIGURE 4: FOREST PLOT FOR STRATUM III, MAINTENANCE WORKERS WITH POPULATION CONTROLS

Estimates for maintenance workers with internal controls groups, Stratum IV, came from six studies: two case-control studies (Finkelstein 1996) (Rosamilia 1999) measuring lung cancer risk as an odds-ratio and four cohort studies (Gun 2006a) (Montanaro 2004) (Gennaro 2000) (Schnatter 2012) that measured risk in a relative incidence rate ratio. Both odds ratios and relative incidence rate ratios were combined into one summary estimate. The average follow-up time was 31 years. Three studies specified white-collar or office refinery workers as the internal referent, while the other studies simply used non-maintenance workers, or the rest of the workers in the cohort. Three studies directly adjusted for smoking. Two studies, unadjusted for smoking, (Gennaro 2000)(Montanaro 2004) showed significantly increased risks for lung cancer. The individual risk estimates across these six studies displayed little heterogeneity, with a technically negative I^2 statistic that defaults to 0%. Due to this, a fixed-effects and random-effects estimate both elicit the same summary estimate and confidence interval. The summary risk ratio for male maintenance workers with internal controls was 1.62, with a 95% confidence interval of 1.30 to 2.03, displayed in Figure 5. This was a significant increase, which differs markedly from the population-controlled estimate for maintenance workers.
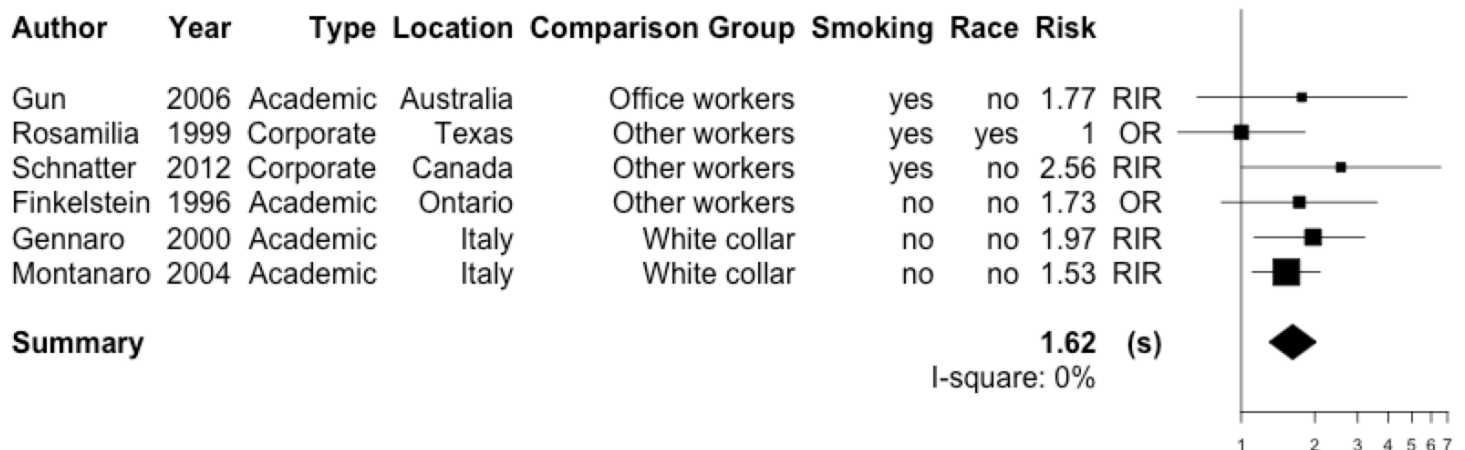
Author	Year	Type	Location	Comparison Group	Smoking	Race	Risk	
Gun	2006	Academic	Australia	Office workers	yes	no	1.77	RIR
Rosamilia	1999	Corporate	Texas	Other workers	yes	yes	1	OR
Schnatter	2012	Corporate	Canada	Other workers	yes	no	2.56	RIR
Finkelstein	1996	Academic	Ontario	Other workers	no	no	1.73	OR
Gennaro	2000	Academic	Italy	White collar	no	no	1.97	RIR
Montanaro	2004	Academic	Italy	White collar	no	no	1.53	RIR
Summary							1.62	(s)

I-square: 0%

FIGURE 5: FOREST PLOT FOR STRATUM IV, MAINTENANCE WORKERS WITH INTERNAL CONTROLS

SENSITIVITY ANALYSES

Sensitivity	Meta Stratum	Category I Summary Risk Estimate (95% CI) – I^2	Category II Summary Risk Estimate (95% CI) – I^2
		U.S. Studies (N=13)	Non-U.S. Studies (N=8)
Geography/ Nationality	I	0.80 (0.77-0.83) – 67%	0.84 (0.79-0.89) – 78%
		Pre-1975 (N=13)	Post-1975 (N=8)
Follow-up Period	I	0.83 (0.80-0.86) – 76%	0.72 (0.68-0.78) – 0%
		w/o Aronson (N=6)	Aronson (N=1)
Unconventional Study Design	II	0.92 (0.73-1.16) – 0%	4.81 (1.31-12.32) – N/A
		Smoking-Adjusted Studies (N=3)	Not Smoking-Adjusted (N=3)
Smoking Adjustment	IV	1.52 (0.97-2.38) – 36%	1.66 (1.27-2.14) – 0%

TABLE 3: FOUR SENSITIVITY ANALYSES USING COCHRANE METHODS

Table 3 summarizes the results from the four sensitivity analyses based on further stratification. The first looked at studies published inside and outside the U.S. just in Stratum I. The stratified analysis on all male refinery worker estimates showed that U.S. studies and Non-U.S. studies had very similar risk estimates. In addition, partitioning the studies this way did not decrease the I^2 heterogeneity statistic.

The second sensitivity analysis focused on follow-up time period. It examines the effect of median follow-up year for cohorts producing lung cancer estimates for all male refinery workers. As displayed in Table 2, the pre-1975 cohorts did display significantly higher risk estimates than the post 1975 estimates, with non-overlapping confidence intervals. Heterogeneity remained approximately the same at 76% in the pre-1975 studies but decreased to 0% in post-1975 studies. Closer examination shows one study, Theriault (1987), was a clear outlier, with the earliest median follow-up year of 1951.5 as well as a risk estimate of 0.44, the lowest of all studies included between all four strata. This was in far contrast from all other pre-1975 studies, which tended to show higher lung cancer estimates. Figure 6 shows this more dramatically and plots the relative risks in stratum I against median follow-up year. While twenty studies showed a clear negative trend, Theriault (1987) stood far outside this.
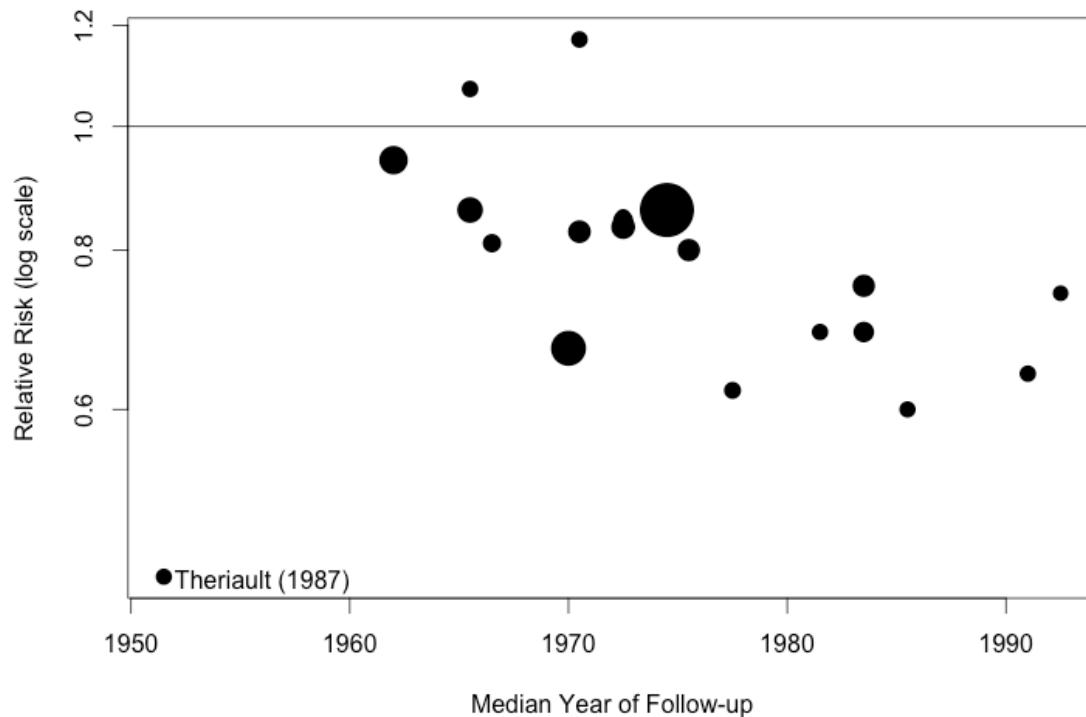
FIGURE 6: LUNG CANCER RISK VS. MEDIAN FOLLOW-UP YEAR IN STRATUM I. SIZE OF DOTS REPRESENTS WEIGHT (INVERSE VARIANCE) OF STUDY.

The third sensitivity analysis focused on Stratum II, all female refinery workers with population controls. As previously reported, the confidence interval for this summary estimate did not overlap with the summary estimate for all male refinery workers, implying a different lung cancer risk for women. However, the forest plot for this stratum, Figure 3, shows one study, Aronson 1994, found a much higher risk estimate than the other six. This study also employed a different study design than all the others. It took health surveillance data on 10% of Canadian working women (both overall and up to age 64) from 568 occupations and industries and 20 cancers: a total of 22,720 comparisons. The study reported 42 specific significant cancer relative risks standardized to other working women, reportedly without a Bonferroni correction[4]. The cancer rates for the subset of women employed at oil refineries was compared to the rest of the working women cohort. This

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[4] The 95% confidence interval from Aronson was 1.31 to 12.32. The study did not report to apply the Bonferroni correction in its estimates. From documentation of the study, an estimated 22,720 comparisons were made. A Bonferroni corrected confidence interval, conservatively accounting for multiple comparisons, would therefore be 0.32 to 72.05.

was in contrast to the other six studies, which only focused on the petroleum refining industry and used general population standardization. Table 3 shows the results of the meta-analysis with Aronson 1994 removed. The summary estimate was 0.92 (0.73-1.16) with 0% heterogeneity. This was in contrast to the initial estimate of 1.27 (0.86 to 1.87) with 57% heterogeneity and appears much more similar to the male estimate of 0.80 (0.75-0.85). Given the drop in I^2, the Aronson study appeared to be a large source of the original heterogeneity, and was also the highest risk estimate amongst all 41 estimates across the four strata. This implied that it was an outlying risk estimate.

The final sensitivity analysis looked at the effect of smoking-adjustment on Stratum IV, lung cancer relative risks for male maintenance workers with internal controls. Only three out of six adjusted for smoking; none found a significant increase. While the full summary estimate was 1.62 (1.30-2.03), the smoking-adjusted studies had a summary estimate of 1.52 (0.97-2.38), a non-significant increase at the 0.05 level. The unadjusted studies had a summary estimate of 1.66 (1.27-2.14). The smoking adjusted studies had an I^2 heterogeneity statistic of 36%, while the full and unadjusted summary estimates both showed 0% heterogeneity. This could have been due to differential treatment of the smoking variable in each of the three smoking-adjusted studies. Gun (2006) employed six categories: Never, 1-19 cigarettes/day, 20-29/day, 30+/day, ex-smoker, Pipe or Cigar only. Schnatter (2012) employed three categories: Never, Current, Unknown. Rosamilia (1999) originally collected data for Never, Current, and Unknown, but ultimately treated Unknown as Current due to similar lung cancer rates. Gun (2006) and Schnatter (2012) employed Poisson regression models to compute adjusted Relative Incidence Rates, while Rosamilia employed conditional logistic regression for adjusted Odds Ratios.

META-REGRESSION

The exploratory meta-regression analysis combined all study estimates across all four strata and also removed the two outlying studies mentioned above, Theriault (1987) and Aronson (1994), resulting in a dataset of 39 estimates. With the outcome variable of the natural log of the relative risk estimates, covariates were tested to determine their contribution to the spread of the values. Restricted to single variable regression, the most significant variable by AIC, R^2, and F-test was the meta-stratum I, II, III, or IV. This confirmed the initial stratification for the main meta-analysis.

The subsequent analyses examined the effect of other singular variables in a multiple regression model with Stratum as the first variable. At the 0.05 level, the significant covariates with Stratum were whether the study was corporate-sponsored or university/government-sponsored research and whether the study was race-adjusted or unadjusted. Table 4 displays the results. Corporate studies and race-adjusted studies led to lung cancer relative risk estimates that were on average 10% lower, independent of Stratum. To avoid over-fitting the small dataset, models with two or more covariates with Stratum or any interactions were not tested. That being said, Table 5 shows

that there was a strong interaction between sponsorship, race-adjustment, and nationality. 20 estimates were simultaneously corporate-sponsored, race-adjusted, and studying populations located in the U.S. 15 estimates were simultaneously University or Government-sponsored, unadjusted for race, and studying populations outside the U.S. Those two categories comprise over 85% of the included study estimates.[5]

Variable	RR ($\exp(\beta)$)	p-value	Adjusted R^2
Corporate (yes/no)	0.90	0.035	33%
Race-Adjusted (yes/no)	0.90	0.037	33%

TABLE 4: SIGNIFICANT COVARIATES IN REGRESSION MODEL INCLUDING STRATUM

	U.S. Studies		Non-U.S. Studies	
	Race-Adjusted	Unadjusted	Race-Adjusted	Unadjusted
Corporate	N = 20	N = 1	N = 0	N = 4
University/Government	N = 0	N = 1	N = 0	N = 15

TABLE 5: CORPORATE AND UNIVERSITY/GOVERNMENT STUDIES AND WHETHER OR NOT THEY ADJUST FOR RACE

Figure 7 graphically explores the issue of race-adjustment further. It plots lung cancer relative risk against median follow-up year for all non-outlying estimates, distinguishing race-adjusted and unadjusted estimates. While Figure 6 shows a clear decreasing trend just in Stratum I, this figure qualitatively shows a divergent trend. Race-adjusted studies fluctuated between a small set of values and showed moderately decreasing lung cancer risk estimates with later cohorts. Unadjusted estimates had a much wider range of values, with some estimates appearing close to race-adjusted estimates while others appearing to actually increase in risk with later cohorts.

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[5] The U.S. variable correlated with Sponsorship and Race-Adjustment, but was nonsignificant in the model and did not show a difference in the first sensitivity analysis in Stratum I. This could be because the other strata had less U.S. studies.
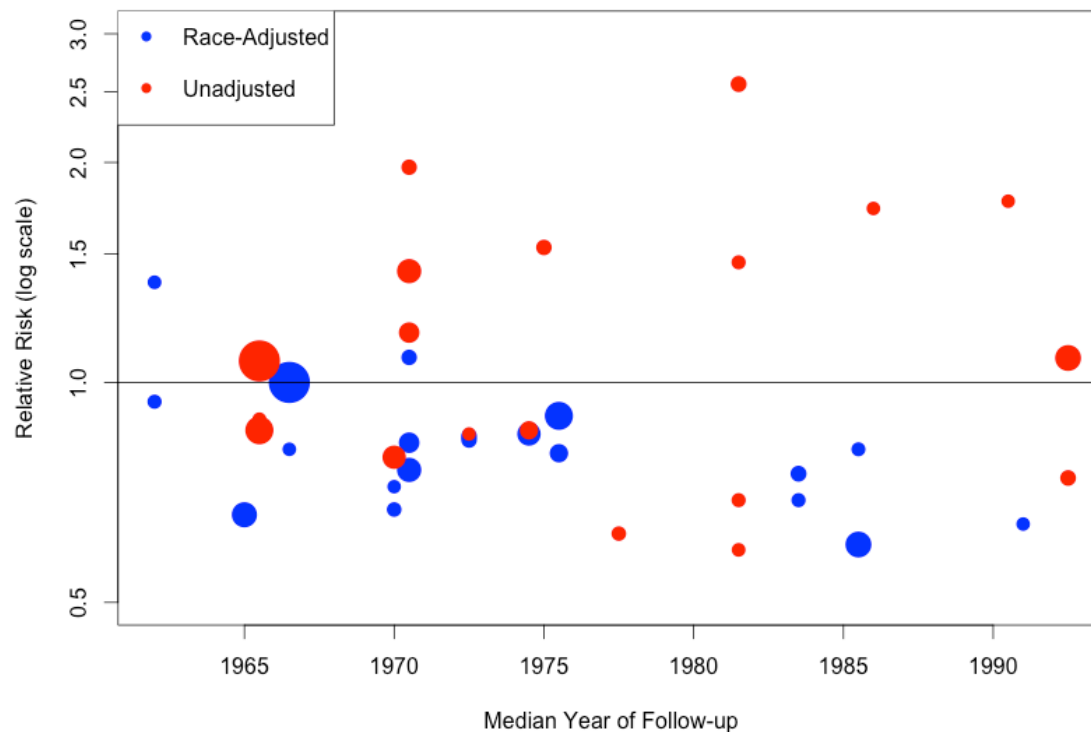
FIGURE 7: LUNG CANCER RISK VS. MEDIAN YEAR OF FOLLOW UP IN ALL STRATA (WITHOUT OUTLIERS), WITH RACE-ADJUSTMENT IDENTIFIED. SIZE OF DOTS REPRESENTS WEIGHT (INVERSE VARIANCE) OF STUDY.

DISCUSSION

The present study represents the first critical review of lung cancer risk in the population of petroleum refinery workers and the first attempt to combine these data in 15 years (Wong and Raabe 2000). While standardized mortality and incidence studies on the topic, reporting SMR and SIR, have consistently shown no elevated risk of lung cancer for males, females, or the subset of maintenance workers in petroleum refinery cohorts (Bertazzi 1989)(Wong and Raabe 1989)(Wong and Raabe 2000)(Sim 2007), many have questioned the legitimacy of these results (Finkelstein 1996)(Gennaro 2000)(Montanaro 2004). Elevated risks are demonstrated when subpopulations such as maintenance, hourly, or skilled trade workers are compared to internal control groups with RIR and OR estimates (Finkelstein 1996)(Gennaro 2000)(Montanaro 2004).

SMOKING AND RACE

The most significant finding of the present study was that the current body of literature on this topic may not be adequate to accurately measure the lung cancer risk in this population. This was principally due to its lack of treatment of smoking status, the cause of 80-90% of lung cancer cases (Tsao 2013). Of the 78 articles selected for the critical review and 41 risk estimates gleaned from them, only three adjusted the risk estimates for smoking status. Several other studies mentioned the importance of smoking as a potential confounder but did not account for it in their risk estimates. Tsai (2001) collected prevalence data on smoking in Shell refinery employees and compared them to national rates, determining that the observed lung cancer SMRs for refinery workers were unlikely to be due to a lack of adjustment for smoking. The present study disagrees with that conclusion due to the heterogeneity of risk estimates in the literature and the gravity of smoking as a risk factor for lung cancer. In addition, the interaction between smoking and occupational asbestos exposure, and the uncertainties about its specific nature, necessitated incorporating smoking as a variable when determining lung cancer risk due to asbestos.

The present study also showed race-adjustment as a potential variable significantly impacting lung cancer risk estimates, and many studies did not adjust for race. Evidence suggests there are significant racial differences in lung cancer rates, and that smoking is an effect modifier (Haiman 2006). Haiman et. al. published an article in *New England Journal of Medicine* reporting that African Americans and Native Americans tended to have higher lung cancer risks among individuals who smoke 0 to 30 cigarettes per day, but that the difference became insignificant for higher smoking rates.

The observed interaction between race-adjustment and nationality offered a potential explanation for why some studies did not race-adjust. Over 90% of studies in the U.S. adjusted for race, as the U.S. is a highly diverse nation. The other represented nations, Canada, Australia, Finland, Sweden, the U.K., and Italy, have largely white populations, so race-adjustment may not have been deemed critical by researchers. These studies did not report the racial distributions in their exposed and comparison populations. However, the meta-regression showed that race-adjustment had a significant effect on results, independent of stratum. Figure 7 shows that almost all the estimates showing increased lung cancer risk were unadjusted for race. In fact, all three of 41 studies that reported a significantly increased risk for lung cancer were unadjusted for race (Aronson 1994)(Gennaro 2000)(Montanaro 2004).

For the third variable in this interaction, corporate sponsorship was shown to estimate lower lung cancer risks than university or government sponsored studies. This could suggest publication bias due to financial incentive. However, funnel plots, presented in Appendix III, showed no visual evidence of bias. In addition, corporate studies were conducted in the U.S. where

adjustment for race was more critical, and race-adjusted studies showed consistently lower risks. Therefore, the results of the present study do not provide evidence for a corporate publication bias over methodological and national differences.

SELECTION OF CONTROLS

The selection of control populations also obscured an accurate determination of increased lung cancer risk in petroleum refinery workers. Most risk estimates selected for meta-analysis in the present study employed external standardization (35 out of 41), comparing lung cancer rates in refinery workers to non-refinery populations. This was the most common way to determine cancer risk in refinery cohorts; the two previous meta-analyses on the topic only included SMRs. However, standardizing against an entire population made correcting for smoking very difficult, as few resources were available to determine lung cancer rates stratified by smoking status in addition to age, sex, calendar time, and race. In fact, race was also often not included in the standardization.

Another concern for standardized population controls in occupational epidemiology is the healthy worker effect. Given the deficit seen in the SMR values, one might conclude that refinery workers had lower lung cancer rates due to selection bias. However, Choi (1992) reported that lung cancer was the least likely disease to be subject to the healthy worker effect out of the common disease classes, due to the long latency of the disease as well as the relatively short period between diagnosis and death. Therefore, it is unlikely that eventual development of lung cancer would prevent an individual from entering a refinery worker cohort, nor would lung cancer diagnosis cause one to leave such a cohort long before death.

Despite this, due to concerns about the healthy worker effect in this population, other researchers turned to internal controls for assessing an increased lung cancer risk in the refinery occupations most likely to be exposed to lung cancer causing agents. Some compared maintenance workers to assumedly unexposed white-collar workers (Montanaro 2004) while others used all other workers at the oil refinery (Schnatter 2012), including white-collar workers. These control populations also came with problems. White-collar workers differ from blue-collar workers in many ways, especially in regards to enduring residual confounders such as smoking status, race, and healthcare access (Fewell 2007). Tsai (2001) specifically found that hourly workers had higher smoking prevalence than salaried workers in petroleum refineries, suggesting that blue-collar workers such as maintenance workers could have higher rates of lung cancer than white-collar workers simply due to smoking.

ASSESSING EVIDENCE FOR ASSOCIATION

The methodological limitations of the studies included for critical review make drawing clear conclusions from a meta-analysis difficult. The quality of a meta-analysis is dependent on the

quality of the published data on which it relies. That being said, the results from this quantitative analysis do not provide evidence for an association between petroleum refinery work and increased lung cancer risk. Only three of 41 lung cancer estimates identified for quantitative analysis showed significant increases (Aronson 1994)(Gennaro 2000)(Montanaro 2004). All were unadjusted for both smoking and race. When stratified, summary estimate based on the largest number of studies resulted in a significant decrease in lung cancer risk, while the other three resulted in a non-significant increase, a non-significant decrease, and a significant increase, respectively. The two increases were based on fewer estimates (7 and 6 out of 41) and were both called into question with subsequent sensitivity analyses. When removing one study with atypical study design and low precision, (Aronson 1994), the summary estimate for female refinery workers went from a non-significant increase with high heterogeneity to a non-significant decrease. Isolating Stratum IV, maintenance workers with internal controls, to only the three studies that adjust for smoking decreased the effect size and made it non-significant.

Pooling these three smoking-adjusted studies did still show an increase, albeit small and nonsignificant. Certainly, if there was a lung cancer risk in this population due to occupational exposure, it would be observed in those occupations that work most closely with the exposures in question. This specific nominal increase could also be due to residual confounding in these studies. Residual confounding is confounding for a variable that remains uncorrected or undetected after an attempt to correct for that variable (Fewell 2007). While these studies employed a relatively coarse number of categories to correct for smoking, as a multidimensional determinant of health status and enduring risk factor for lung cancer, smoking could be measured at a much finer level to capture lifetime exposure. A more quantitative measure such as pack-years is often preferred to current smoking status (Bernaards 2002). In addition, only one of the three studies adjusted for race, another multidimensional confounder. The meta-regression analysis showed that estimates unadjusted for race were 10% higher, on average, than adjusted ones. In fact, the one smoking adjusted study that also corrected for race, Rosamilia (2001), had the lowest lung cancer risk estimate among smoking-adjusted studies: 1.0 (0.55-1.82).

FUTURE STUDY CONSIDERATIONS

It should be reemphasized that the principal finding is that of ignorance: that the data identified for meta-analysis may not properly capture the lung cancer risk from occupational exposure in this population due to serious methodological questions. There could be an increased risk; the current body of literature does not capture that. To identify strategies for investigating this risk in a future study, certain elements of the studies in this review could be incorporated with practices from other occupational studies. Rosamilia (2001) was a matched case-control design, with each lung cancer death case matched with four controls from the same refinery on race and

birthdate. Occupational history within the refinery served as a proxy for asbestos exposure, and smoking data were collected from medical history reports in three categories: Ever, Unknown, and Never. Unknown and Ever were later combined to one "Smoker" category.

Given the lack of smoking and race adjustment in many of the other studies, the case-control design in Rosamilia (2001) may have captured the risk well. However, in a future case-control, certain other factors could be taken into account to more fully adjust for confounding. First, the cases and controls should be limited to hourly workers within the refinery. White-collar workers are too different from blue-collar workers with relation to multidimensional confounding factors to offer an appropriate comparison. Assuming a retrospective design, experienced industrial hygienists should evaluate the occupational histories of both cases and controls to estimate actual asbestos exposure or exposure categories. In addition, they should make estimates for other exposures, such as petroleum coke. Schnatter 2012 identified petroleum coke as an additional petroleum refinery exposure that is associated with increased lung cancer risk after adjustment for smoking. To properly adjust for smoking in this study, pack-years of exposure is preferable to the coarse categories in Rosamilia (2001). Assuming a retrospective design, this level of refinement may not be possible from medical records alone. David B. Richardson described an alternative method for correcting for residual confounding from smoking in occupational studies of lung cancer in *Epidemiology* (Richardson 2010) Richardson proposed that when smoking adjustment is based on coarse categories, risk estimates should also adjust for a disease like COPD. COPD is a fairly common disease that is directly associated with smoking but not typically associated with asbestos or petroleum coke exposure (Miller 1994). Any additional cases of lung cancer due to smoking that are not accounted for in smoking categories could be corrected with COPD status, also gleaned retrospectively from medical records, as a proxy for smoking. Figure 8 displays this relationship. Additionally, an interaction between asbestos exposure and smoking and asbestos exposure and COPD as a proxy for smoking should be examined. Overall, the conditional logistic regression model in this ideal matched case-control design could look as follows:

$$\text{logit(lung cancer mortality)}$$

$$= \beta_0 + \beta_1 Asbestos + \beta_2 PetroleumCoke + \beta_3 Smoking$$

$$+ \beta_4 COPD + \beta_5 Asbestos * Smoking + \beta_6 Asbestos * COPD$$

A study employing this model could more fully capture the lung cancer risk due to asbestos in petroleum refinery workers than the current body of literature.
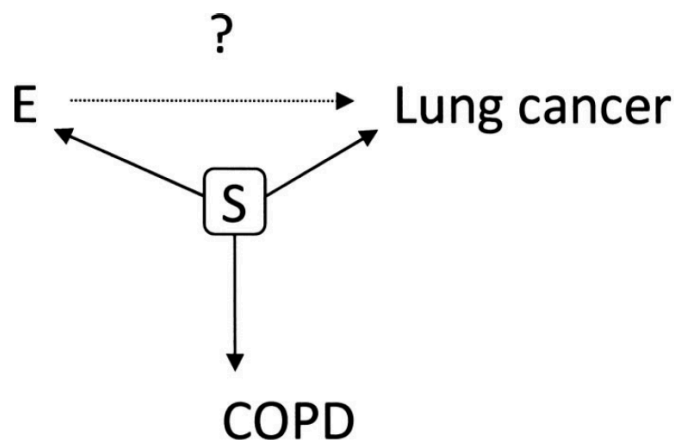
FIGURE 8: DIAGRAM OF A POTENTIAL RELATIONSHIP BETWEEN SMOKING (S), COPD, OCCUPATIONAL EXPOSURE (E), AND LUNG CANCER, TAKEN FROM RICHARDSON (2010)

CONCLUSION

The present study reviews the literature on the proposed association between petroleum refinery work and lung cancer risk due to workplace exposure, including asbestos. It finds that the current body of literature on a whole does not adequately consider important confounders, namely smoking, and therefore the lung cancer risk for this population has not been definitively identified. The quantitative analyses, based on limited data, do not provide evidence for an increased lung cancer risk in this occupational population. However, only a hypothetical future study could provide definitive evidence when fully accounting for important confounding variables. The present study identifies smoking, race, concurrent occupational exposures, and their interactions as key considerations for future studies.

APPENDIX I: CRITICAL REVIEW ARTICLES

First Author	Year	Publisher	I	II	III	IV	Country	Study Design	Description
Alderson	1982	Ann N Y Acad Sci					U.K.	Cohort	The study involved eight refineries in the U. K. of varying size and complexity that have been online since at at the latest the 1950's. The study reported cancer risk estimates for all eight combined.
Aronson	1994	J Occup Med		x			Canada	Cohort	A nationwide retrospective cohort study on female occupational mortality across several industries
Baird	1967	J Occup Med					U.S.	Review	A survey of potential chemical exposures to petroleum refinery workers of medical importance based on the state of knowledge in 1967.
Bertazzi	1989	Int Arch Occup Environ Health				x	Italy	Cohort	Occupational mortality study of unnamed Italian oil refinery
Bisby	1999						Australia	Cohort	Governmental report on health risks to petroleum industry workers, 10th edition.
Collingwood	1996	Int Arch Occup Environ Health	x				U.S.	Cohort	An update to an occupational mortality study of a Mobil refinery in New Jersey
Consonni	1999	Am. J. Ind. Med.	x				Italy	Cohort	Government agency population-based mortality study of unnamed oil refinery in Italy
Cooper	1997	J Environ Pathol Toxicol Oncol					U.S.	Cohort	Overall mortality study of petroleum and chemical workers across ten plants in Texas
Dagg	1992	Br J Ind Med					U.S.	Cohort	Chevron study of two petroleum refinery plants, reporting cause-specific mortality separately among worker cohorts
Divine	1999	Occup Environ Med		x			U.S.	Cohort	Update to previous Texaco mortality study across all company plants, examines changes after 16 years of additional follow-up
Divine	1985	J Occup Med					U.S.	Cohort	Texaco mortality study among refinery, petrochemical, and research workers

Author	Year	Journal					Country	Type	Description
Divine	1998	Occup. Environ. Med.	x				U.S.	Cohort	Subgroup analysis of Texaco company-wide refinery study after additional follow-up
Finkelstein	1999	Am J Ind Med					Canada	Letter to the Editor	Response to Texaco mortality study, pointing out a dose-response relationship between occupational exposure and lung cancer
Finkelstein	1996	Am J Ind Med			x		Canada	Case-control	Case-control of oil refinery workers in Ontario compared to blue-collar workers reporting increased risk of mesothelioma attributed to asbestos exposure
Gamble	2000	J Occup Environ Med					U.S.	Cohort	Examines cause-specific mortality in specifically retired refinery workers at Exxon's three largest U.S. refineries
Gennaro	2000	Am J Ind Med	x			x	Italy	Cohort	Updated analysis of mortality from mesothelioma and lung cancer at two Italian oil refineries
Gennaro	2000	American Journal of Industrial Medicine					Italy	Letter to the Editor	Response to Tsai
Gennaro	2000	American Journal of Industrial Medicine					Italy	Letter to the Editor	Response to Ludwig
Gun	2006	Arch Environ Occup Health			x		Australia	Cohort	Incidence study of industry wide disease risks attributable to asbestos in Australia
Gun	2006	Occup Environ Med					Australia	Cohort	Updated analysis of cancer incidence as well as mortality in the Australian Institute of Petroleum, focusing on 1981-1999
Gun	2004	Occupational and Environmental Medicine					Australia	Cohort	Updated analysis of cancer incidence as well as mortality in the Australian Institute of Petroleum, focusing on 1981-1996
Hanis	1979	J Occup Med					Canada	Cohort	An early mortality study from cancer for refineries of the Imperial Oil Company in Canada. Relative risks were reported without confidence intervals or other metrics of

Author	Year	Journal					Country	Study type	Description
									variance
Honda	1995	J. Occup. Environ. Med.	x				U.S.	Cohort	40-year follow up of refinery occupational cohort in souther Illinois
Huebner	2004	J Occup Environ Med	x	x			U.S.	Cohort	Overall and cause-sepcific mortality study for two ExxonMobil refineries in Louisiana and Texas respectively
Jarvholm	1997	Occup Environ Med	x				Sweden	Cohort	Cancer Incidence study for entire petroleum industry in Sweden, including specific SIR values for refinery workers, in addtion to distribution and manufacturing workers
Kaplan	1986	J Occup Med	x				U.S.	Cohort	Large cohort mortality study of reinfery workers that were members of the American Petroleum Institute, across several companies and states.
Kilburn	1991	Ann N Y Acad Sci					U.S.	Case series	Examines the potential for asbestos disease, particularly asbestosis, in several industries using interviews and x-rays,
Kim	2008	Journal of Toxicology and Environmental Health					U.S.	Cross-sectional	Assessed VOC exposure and chromosomal damage at one time in a refinery worker population
Kipen	1991	American Journal of Industrial Medicine					U.S.	Meta-analysis	Assessed racial differences in cancer rates for several different industries in the United States
Lewis	2003	Occupational and Environmental Medicine	x	x			Canada	Cohort	Cancer Incidence and Mortality for all Canadian refinery workers at ExxonMobil. Contained gender-specific rates
Lewis	2000	J Occup Environ Med					U.S.	Cohort	Subgroup analysis of three-refinery study through ExxonMobil, focused on active and terminated employees
Ludwig	2000	American Journal of Industrial Medicine					Italy	Letter to the Editor	Response to Tsai on the controversy over the Gennaro publication

Author	Year	Journal					Country	Type	Description
Marsh	1991	American Journal of Industrial Medicine					U.S.	Cohort	Mortality study of Chevron's Deer Park oil refinery
Merler	1999	Environmental Health Perspectives					Italy	Review	Discussed the proportion of male cancer rates attributable to occupational exposures in at a country and several-industry -wide level in Italy
Montanaro	2004	Arch Environ Health					U.S.	Cohort	Poisson-regression analysis of asbestos exposure and repiratory cancer mortality in Italian Refinery Workers
Parodi	2003	Occup Environ Med					Italy	Letter to the Editor	Proposes that Stain et al (2002) observed null results for increased lung cancer risk due to the Healthy Worker Effect
Pukkala	1998	J Occup Environ Med	x				Finland	Cohort	Incidence study of industry wide disease risks in the petroleum industry in Finland
Raabe	1998	Am J Ind Med					U.S.	Cohort	Updated study of ExxonMobil's Beaumont, Texas refinery cohort mortality cancer risks
Rosamilia	1999	J Occup Environ Med			x		U.S.	Case-control	Compared rates of lung cancer in maintenance workers with other workers at the Beaumont, Texas refinery. Stratified for smoking status
Rosenman	1991	Ann N Y Acad Sci					U.S.	Case series	X-ray evaluation of potentially asbestos exposed employees at a large il refinery through a NIOSH screening program
Rushton	1993	Environ Health Perspect					U.K.	Cohort	A 39-year follow-up of the U.K. oil refinery and distribution center studies: results for kidney cancer and leukemia
Rushton	1993	Br J Ind Med					U.K.	Cohort	Further follow up of mortality in a United Kingdom oil refinery cohort
Rushton	1981	Br J Ind Med					U.K.	Cohort	Initial investigation of cancer mortality and incidence in the U.K. eight refinery cohort
Rushton	1980	Carcinogenesis					U.K.	Review	Occupational health in the U.K., using petroleum refinery work as one example
Satin	2002	Occup Environ	x				U.S.	Cohort	Updated epidemiological study of workers at two California

		Med							petroleum refineries, 1950-95
Satin	1996	J Occup Environ Med	x	x			U.S.	Cohort	Chevron study with 50-year mortality follow-up of a cohort of oil refinery workers in Port Arthur Texas
Schatter	2012	Occupational and Environmental Medicine			x	x	Canada	Cohort	Lung cancer incidence in Canadian petroleum workers, with both population and internal control groups utilizing Poisson Regression models
Schnatter	1992	Am. J. Ind. Med.					Canada	Cohort	A retrospective mortality study within operating segments of a petroleum company
Schnatter	1993	Environ. Health Perspect.					Canada	Cohort	A retrospective mortality study among Canadian petroleum marketing and distribution workers
Sim	2007	The University of Melbourne	x	x			Australia	Cohort	Governmental report on health risks to petroleum industry workers, 13th edition.
Sorahan	2002	Occup Med	x				U.K.	Cohort	Mortality of United Kingdom oil refinery and petroleum distribution workers, 1951-1998
Theriault	1987	J Occup Med	x				Canada	Cohort	Updated evaluation of cancer mortality in an East Montreal Petroleum Refinery
Thomas	1980	J Occup Med					U.S.	Cohort	Union roll-based occupational cohort study of all-cause and cause-specific mortality in refinery workers in Texas
Tsai	2004	Ann Epidemiol	x				U.S.	Cohort	Cancer incidence among refinery and petrochemical employees in Louisiana, 1983-1999
Tsai	2003	Occup Environ Med					U.S.	Cohort	A mortality and morbidity study of refinery and petrochemical employees in Louisiana
Tsai	2001	Int Arch Occup Environ Health					U.S.	Prevalence study	Trends in cigarette smoking among refinery and petrochemical plant employees with a discussion of the potential impact on lung cancer.
Tsai	2001	Ann Epidemiol	x				U.S.	Cohort	Health findings from a mortality and morbidity surveillance of refinery employees
Tsai	1993	J Occup Med					U.S.	Cohort	Chevron cohort mortality study of two California refinery

							Country		
									and petrochemical plants
Tsai	2000	American Journal of Industrial Medicine					Italy	Letter to the Editor	Tsai questioning the results of Gennaro (2000) which found an increased risk of lung cancer amongst oil refinery workers
Tsai	1997	Journal of Occupational and Environmental Medicine					U.S.	Cohort	Shell prospective cohort study of refinery worker mortality at a facility in Louisiana
Tsai	2007	J Occup Environ Med	x			x	U.S.	Cohort	A 56-year mortality follow-up of texas petroleum refmery and chemical employees, 1948-2003
Williams	2007	Journal of Toxicology and Environmental Health					U.S.	Exposure Assessment	Retrospective exposure assessment of airbome asbestos related to skilled craftsmen at a petroleum refinery in Beaumont, Texas (1940-2006)
Wong	2001	J Occup Environ Med	x	x		x	U.S.	Cohort	An updated mortality study of workers at a petroleum refinery in Beaumont, Texas, 1945 to 1996
Wong	2000	Regul Toxicol Pharmacol					Various	Meta-analysis	Update of fixed-effects meta-analysis of cancer mortality in the petroleum industry, across various sectors and countries
Wong	1989	Am J Ind Med					Various	Meta-analysis	Fixed-effects meta-analysis of cancer mortality in the petroleum industry, across various sectors and countries
Wong	1986	Br J Ind Med				x	U.S.	Cohort	Chevron occupational mortality study of two California petroleum refinery plants

APPENDIX II: META-ANALYSIS IN OBSERVATIONAL EPIDEMIOLOGY

The statistical methodology behind the meta-analyses in the present study derived from the Cochrane Collaboration, most widely used in epidemiological critical reviews, as reported in the third edition of the textbook *Critical Appraisal of Epidemiological Studies and Clinical Trials* (Elwood 2007). These methods were originally designed for combining data from clinical trials. However, these methods are increasingly given wider application in observational epidemiology. In randomized control trials, confounding variables, blinding, and exposure conditions can be controlled; individual study estimates can be more readily assumed to be measuring the same precise biological mechanism, so a summary estimate based on several studies can increase statistical power and provide a more precise estimate for a proposed association (Cochrane Handbook). Under ideal conditions, any deviation of individual study estimates from the more precise summary estimate is assumed to be due to statistical random chance. This assumption can be explored by measures of heterogeneity, or between-study variation. The Cochrane Collaboration recommends calculating an I^2 percentage statistic for summary estimates, which can be interpreted as the percentage of between-study variation not due to chance (Cochrane Collaboration). Sources of between-study variation not due to chance can include different metrics of exposure or outcome, different adjustment for potentially confounding variables, different populations that give rise to samples, and other factors related to study design and study quality.

In addition to providing potentially more precise summary estimates for an association, meta-analysis can be used to identify key characteristics of study heterogeneity, such as potentially confounding variables, sensitive subgroups, and differing exposure conditions for different outcomes. However, the methods of meta-analysis can also be employed inappropriately to numerically produce precise summary estimates that could even show low heterogeneity but are actually inherently nonsensical. Take this hypothetical example. Study 1 examines the association between Exposure A and Disease B. It finds a relative risk estimate and 95% confidence interval of 2.0 (1.5-2.5). Study 2 examines the association between Exposure C and Disease D, both of which are completely unrelated to Exposure A and Disease B. Study 2 also finds a relative risk estimate and confidence interval of 2.0 (1.5-2.5). Using standard Cochrane-Mantel-Haenszel pooling techniques, combining these two disparate studies gives a summary estimate of 2.0, with a narrower 95% confidence interval of 1.7-2.4. The I^2 statistic is 0%, implying there is no variation between these two studies outside of random chance. Of course, as the exposures and diseases are completely unrelated, this more precise estimate measures no true association and there are in fact large differences between the studies, despite the low statistical heterogeneity.

This is an extreme example that illustrates the problem with applying meta-analytic methods in observational epidemiology. It can be very difficult to identify a group of study estimates on an association that truly measure the same exposure and disease, with similar distributions and corrections for key confounders in sample populations. A report from the CDC stated the following: "[T]he extreme diversity of study designs and populations in epidemiology makes the interpretation of simple summaries problematic, at best. In addition, methodologic issues related specifically to meta-analysis, such as publication bias, could have particular impact when combining results of observational studies" (Stroup 2000). Nonetheless, the report also went on the reaffirm the importance of meta-analysis as one of the few ways to rapidly synthesize and evaluate new epidemiological literature, even in the observational setting. This is the case for occupational and environmental epidemiological studies, like the present study, where equipoise generally prevents the use of randomized control trials on humans to test environmental risk factors for disease.

In 1995, representatives from the National Cancer Institute, the Agency for Toxic Substances, the EPA, as well as academic and industry groups published "Guidelines for Application of Meta-Analysis in Environmental Epidemiology" (Blair 1995). These guidelines provided methods for carefully combining environmental epidemiological studies in the uncertain observational setting. It also outlined when a meta-analysis for an environmental association may be useful and when it may not be useful. It reported that a meta-analysis may be particularly useful when:

1. sources of heterogeneity are to be examined formally
2. the relationship between environmental exposures and health effects is not clear
3. when there are many studies but no consensus on the exposure/disease relationship
4. refinement of the estimate of an effect is important
5. there are questions about the generalizability of the results
6. it is clear there is a hazard, but no indication of its magnitude
7. the finding from a single study is to be confirmed or refuted
8. there is a need to increase statistical power beyond that of individual studies
9. information beyond that provided by individual studies or a narrative review is needed

Meta-analysis may not be useful where:

1. the relationship between exposure and disease is obvious without a more formal analysis
2. there is insufficient information from available studies related to disease, risk estimate, or exposure classification
3. there are only a few studies of the key health outcomes
4. there is substantial confounding or other biases which cannot be adjusted for in the analysis

The present study fits many criteria for a useful environmental meta-analysis. In the case of refinery work exposure and lung cancer, there was clear heterogeneity in the literature in terms of study design, source population, and confounder control. The present study investigated each of these sources through the initial stratification, the sensitivity analyses, and the meta-regression analysis. The findings on smoking adjustment and race adjustment were clear. Particularly, race-adjustment, and its interaction with sponsorship and nationality, was not discussed as crucial in any individual study or in previous meta-analyses on the subject; this could only be observed when examining the data in aggregate. While the relationship between asbestos exposure and lung cancer is clear, and there was asbestos at petroleum refineries, the exact nature of the lung cancer risk due to workplace was not established. Debates spanned the published literature on the issue of internal versus external control groups. The present study provides a narrative review of this debate and presents meta-analytic results for both designs side-by-side, along with an evaluation of each method based on the totality of the literature.

That being said, the present study could fit guideline number 4 for when meta-analysis is not useful. The lack of treatment of smoking in the literature could not fully be adjusted for in the analysis. In addition, there was evidence that both studies employing external standardization and those that used internal control groups could each be subject to respective biases. The present study acknowledges that these inherent limitations make summary estimates difficult to interpret. Despite this, a conclusion of lack of evidence for an association could still be drawn. The largest meta-analytic stratum based on 21 studies showed a significant deficit for lung cancer risk. If the pooled estimates are considered misleading, the focus turns to the individual studies. Within them, only three of 41 estimates identified a significant increase in lung cancer risk, and all three were unadjusted for both smoking and race. The only study adjusted for both smoking and race found a lung cancer risk of 1.0. The investigation of individual studies, their pooled estimates, and the investigation of the importance of adjustment across the published literature could only be accomplished through a full critical review, meta-analysis, and meta-regression.

APPENDIX III: FUNNEL PLOTS FOR EACH STRATUM

For all plots, the size is the inverse of the standard error for each estimate, the effect is the lung cancer estimate on the log scale, the vertical dashed line corresponds the reported summary estimate, and the horizontal solid lines correspond to the 95% confidence interval for each estimate. Evidence for publication bias occurs when plots sharply deviate from a general funnel shape.
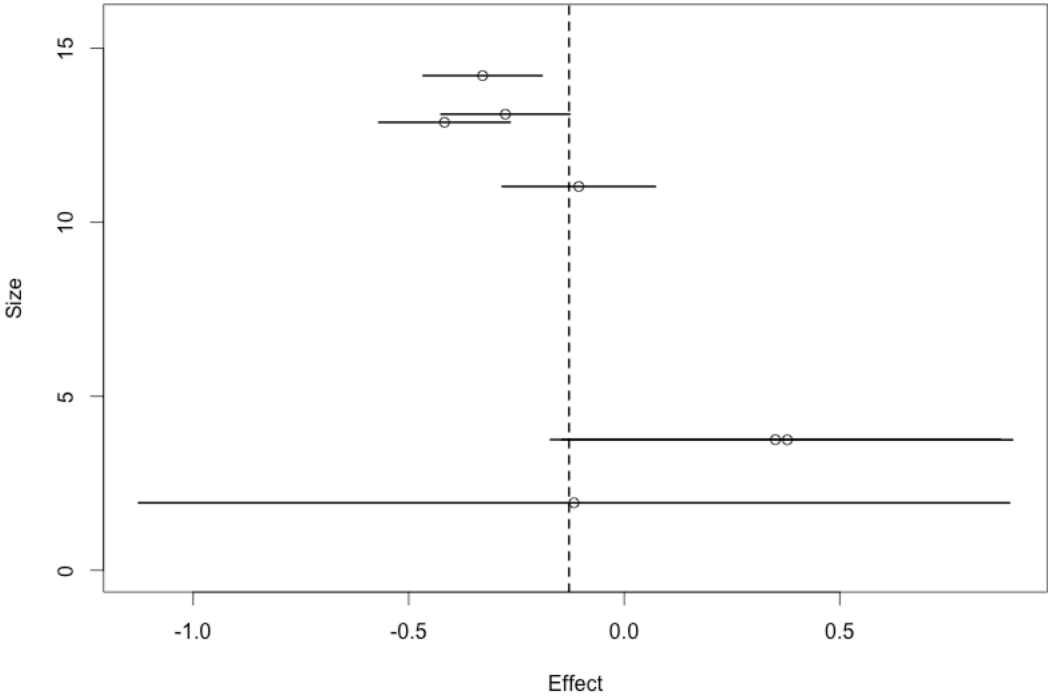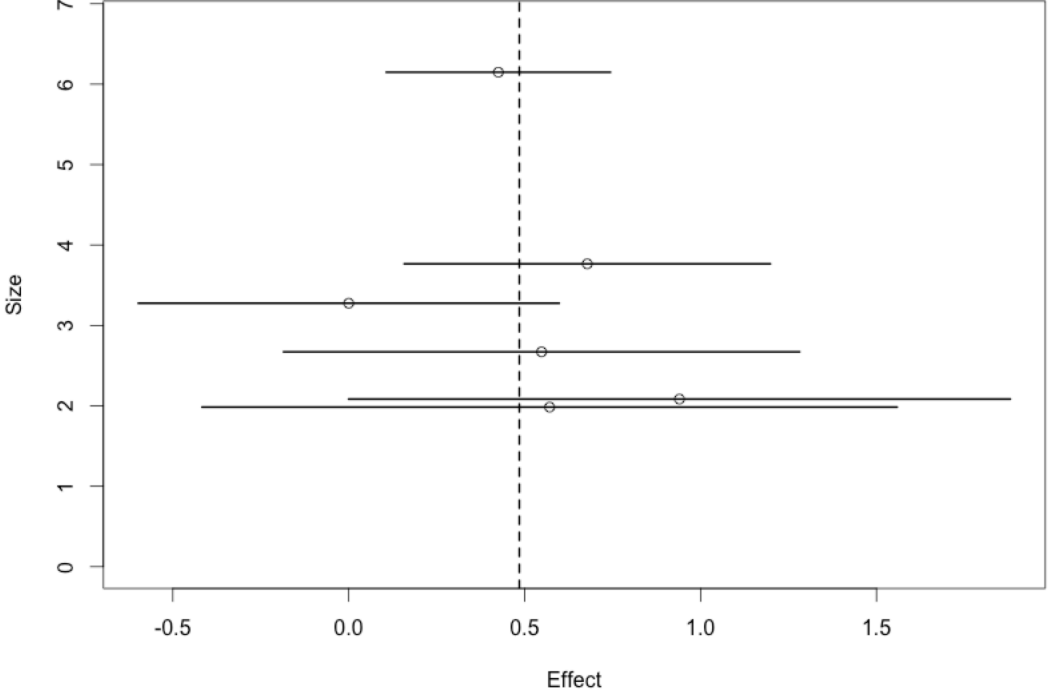
Stratum I:
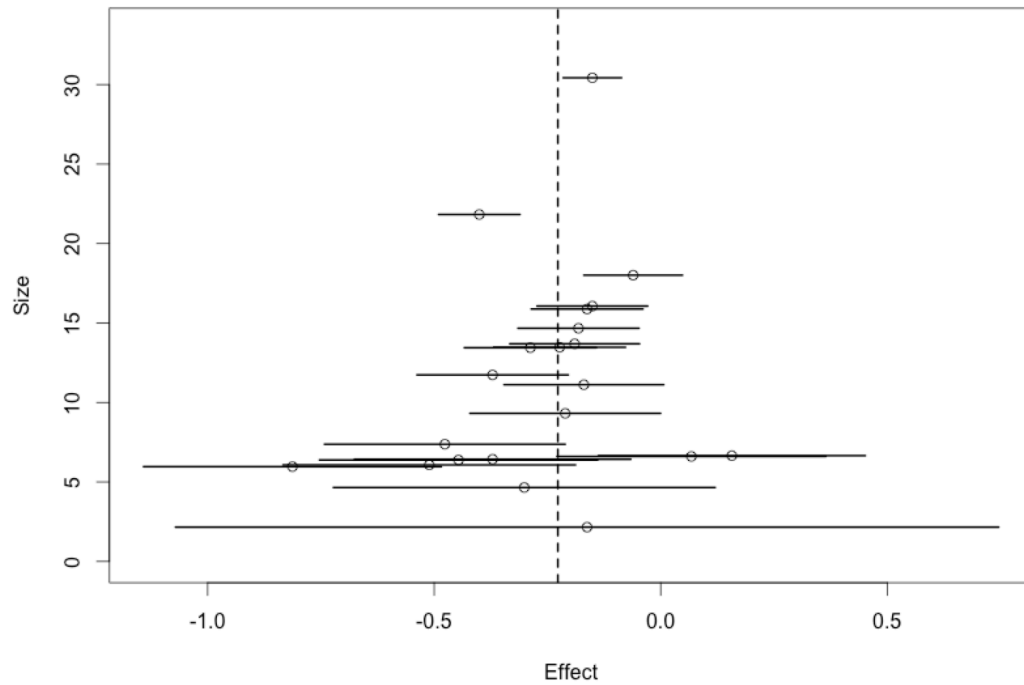
Stratum II:
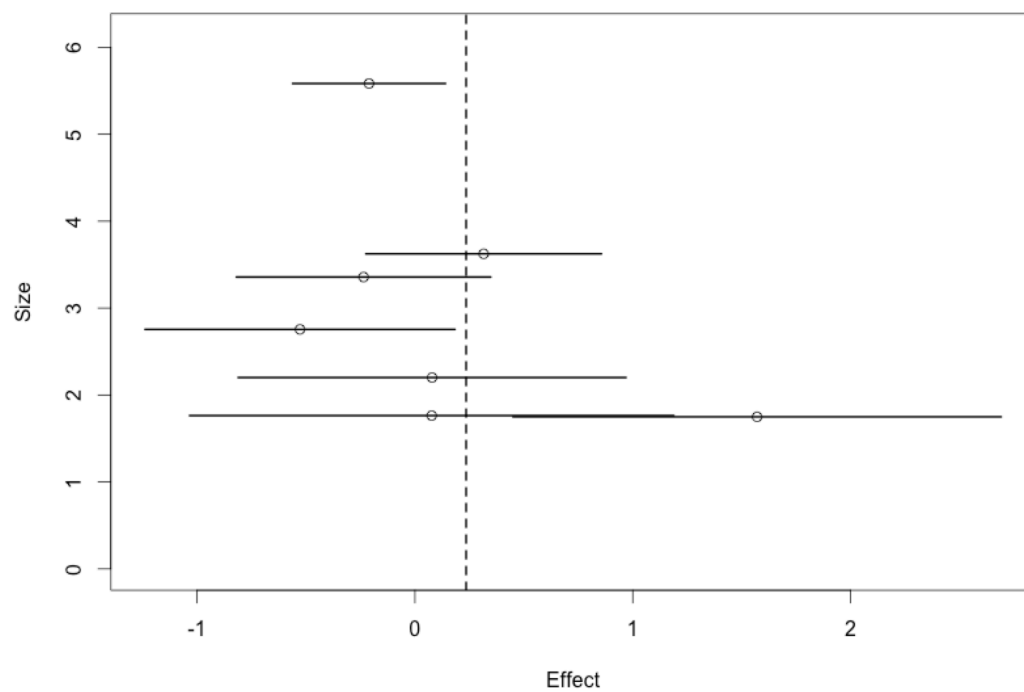
Stratum III:

Stratum IV:

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