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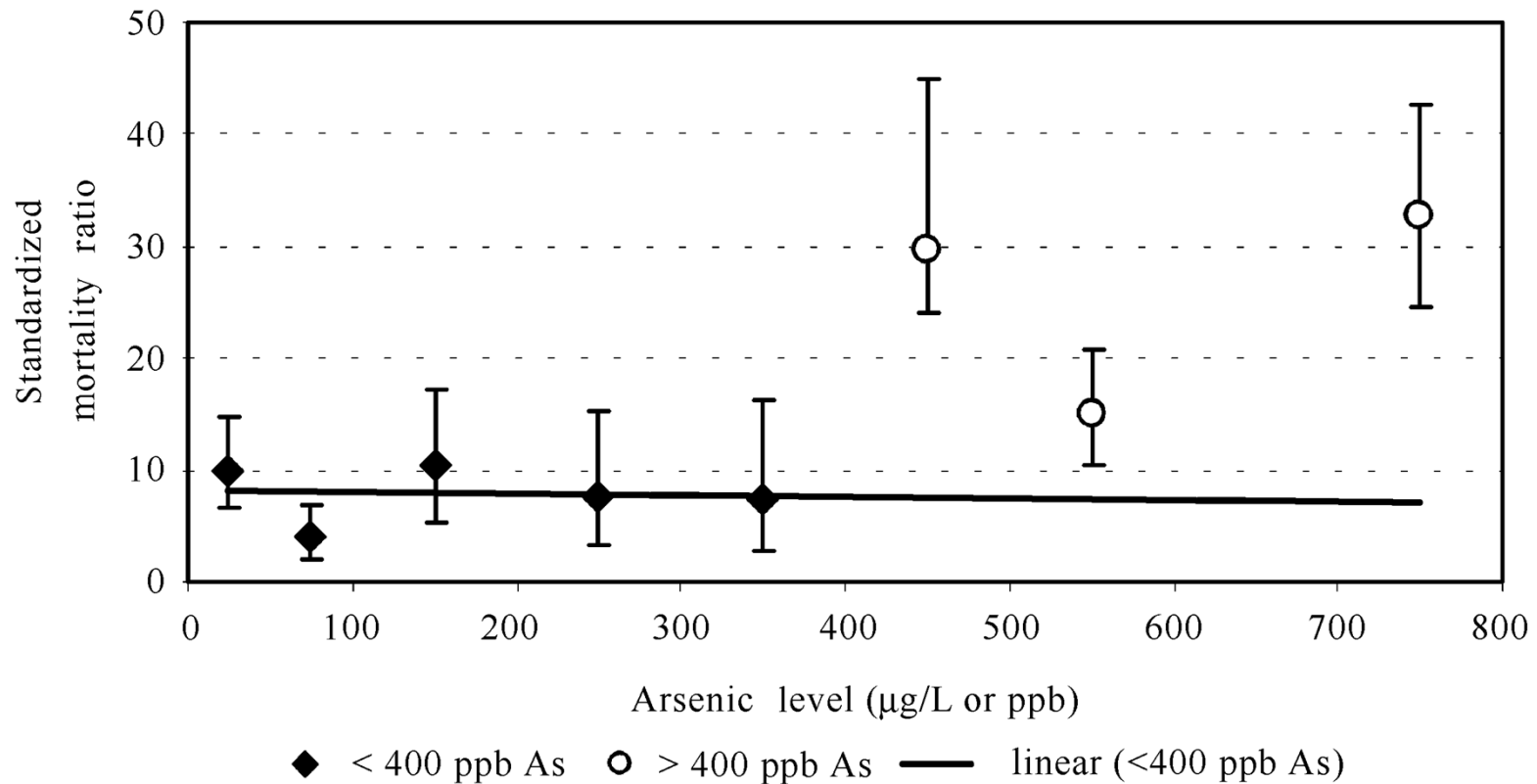
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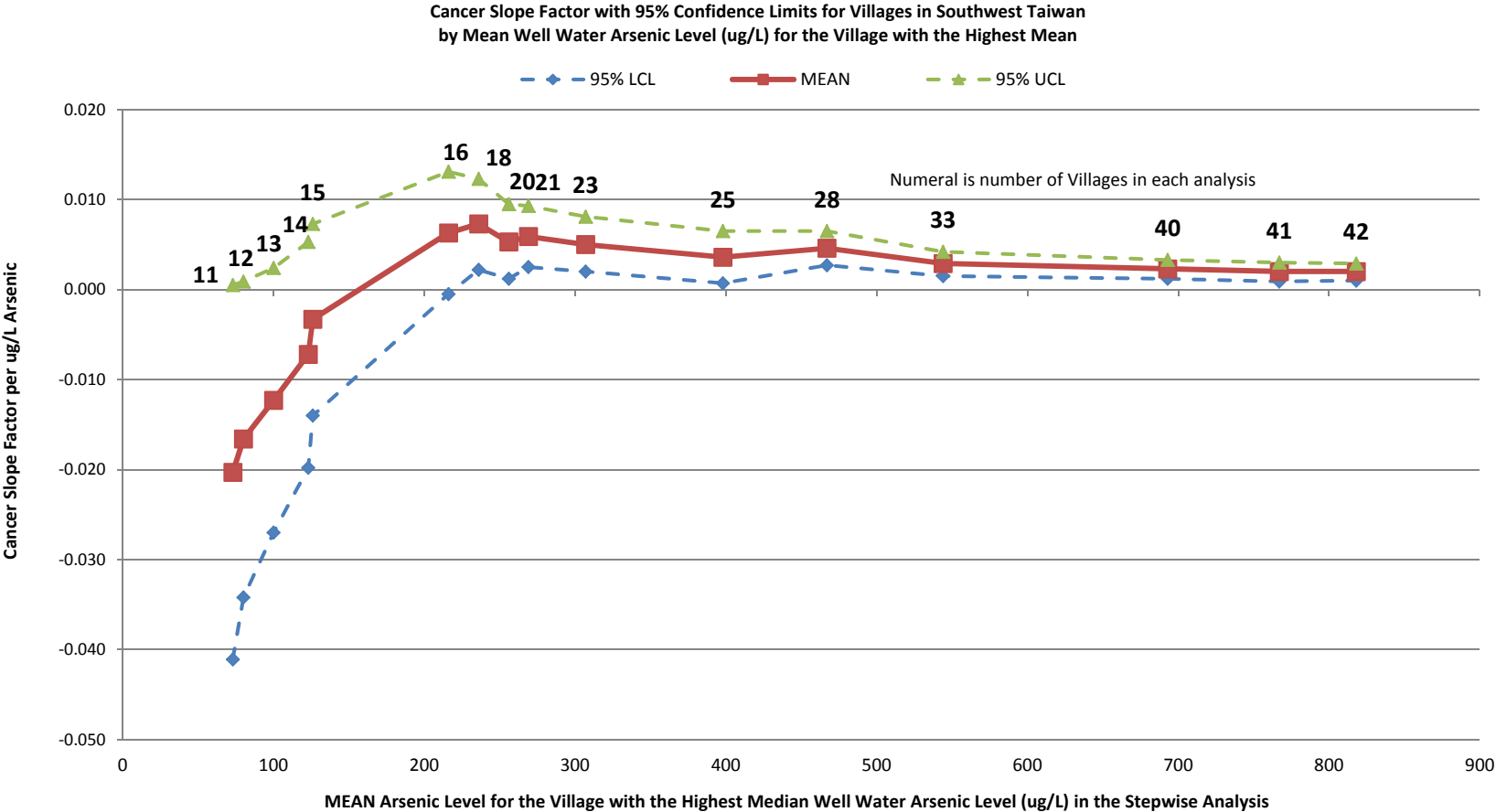
Science Issue 3: Integrating Results of Epidemiologic Studies

Methods to Separate out High Exposure Outcomes - SMR

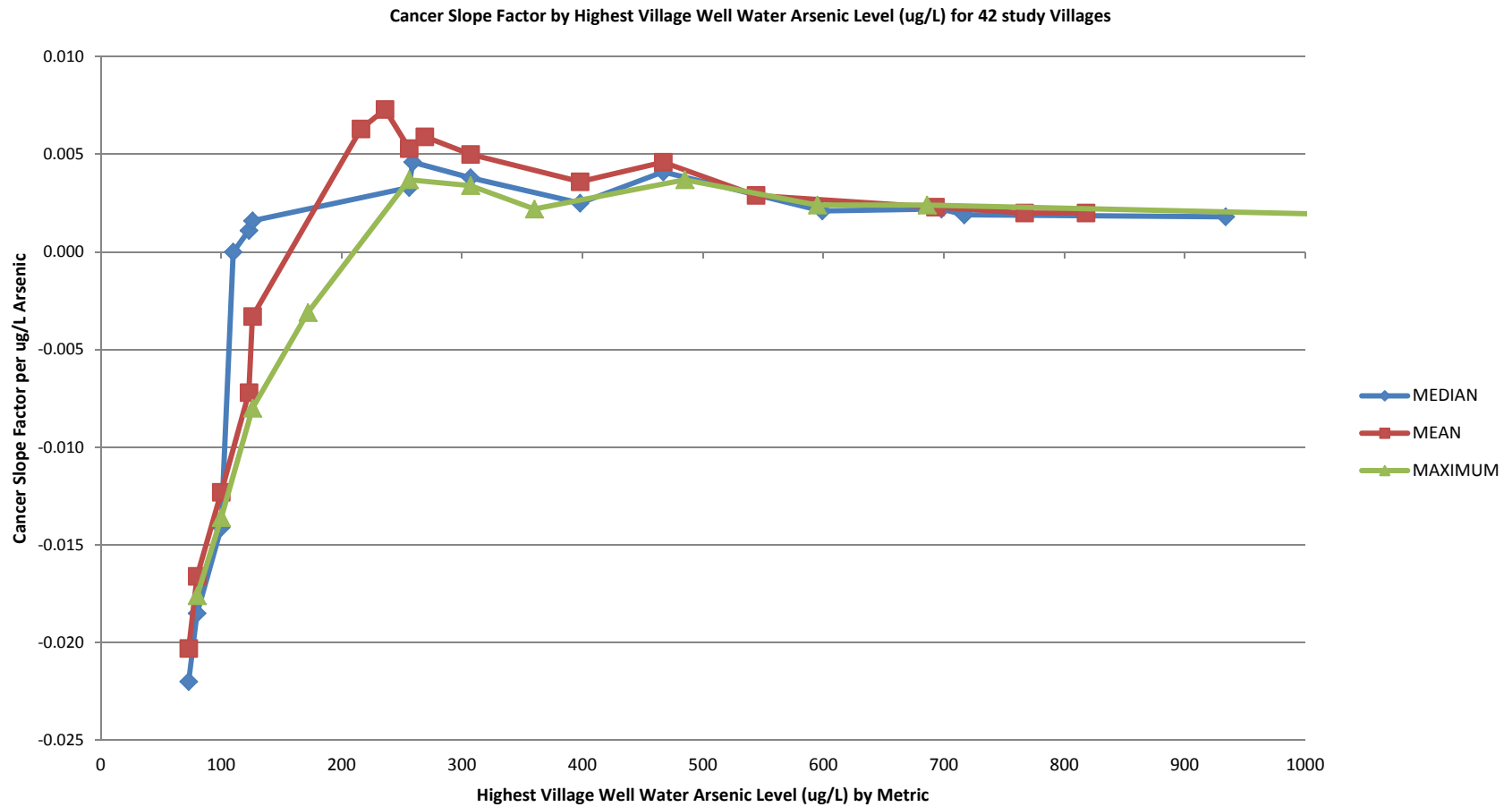


Bladder Cancer Mortality (Data from Morales, 2000)

Methods to Separate out High Exposure Outcomes – Reiterative Poisson



Comparison of Metrics



Systematic review of the Association between Lung Cancer Risk and Low Levels of Arsenic in Drinking Water

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ABSTRACT

Background: Multiple studies have demonstrated the increased risk of bladder and lung cancers with exposure to drinking water containing inorganic arsenic at levels in the hundreds of micrograms/liter. The risks at lower levels are uncertain. A systematic review and meta-analysis of the risk of bladder cancers with exposure to drinking water has found no increased risk at arsenic exposures below 200 ug/L with the exception of studies limited to tobacco smokers.¹ No such analysis has been reported with respect to lung cancers.

Materials and Methods: Our comprehensive literature search yielded a final set of 11 papers with 17 study populations from 4 continents that reported the risks of lung cancer from lower levels of arsenic exposure in drinking water. Risk ratio and exposure metric data were extracted. Results were stratified into exposures at <10 ug/L, 10-100 ug/L, 100-200 ug/L, and >200 ug/L.

Results: The 11 studies had 4 risk estimates in the <10 ug/L range, 18 in the 10-100 ug/L range, 9 in the 100-200 ug/L range, and 5 just above 200 ug/L. The mean and median risk estimates were 0.98 and 1.04 for <10 ug/L, 1.04 and 1.04 for 10-100 ug/L, 1.36 and 1.54 for 100-200 ug/L, and 2.22 and 1.97 for >200 ug/L. An arsenic-associated risk was seen among smokers only above 200 ug/L.

Conclusion: Lung cancer risk with exposure to arsenic in drinking water was not seen to rise at levels below 100 ug/L. Increased risks were observed at 100-200 ug/L and at >200 ug/L. These results are consistent with those of bladder cancer risk with exposure to arsenic in drinking water; However, bladder cancer studies have generally separated out the risk for smokers from that of non-smokers.

BACKGROUND

Multiple studies have demonstrated the increased risk of bladder and lung cancers with exposure to drinking water containing inorganic arsenic at levels in the hundreds of micrograms/liter.^{2,3} The risk of lung cancer at lower ingested arsenic levels are uncertain. A systematic review and meta-analysis of the risk of bladder cancers with exposure to drinking water has found no increased risk at arsenic exposures below 200 ug/L with the exception of studies limited to tobacco smokers.¹ Reviews of studies of ingested arsenic and lung cancer find associations between arsenic exposure and lung cancer at high concentration levels but not at low levels.⁴⁻⁶

METHODS

Electronic literature bases (PubMed, Embase, Scopus, and Web of Science) were searched along with a review of those articles to assemble 20 papers with stratified arsenic concentration data before narrowing down to 11 papers that fit the inclusion/exclusion criteria. The 11 papers consisting of 17 study populations from 4 continents. Exposure estimates were either the point estimate reported in the source paper or if the source paper gave a range of exposure a midrange was calculated. Exposures were then separated into 4 strata: <10 ug/L, 10-100 ug/L, 100-200 ug/L, and >200 ug/L. Exposures greater than 250 ug/L were not used. Relative risks were extracted from the source papers or calculated for each paper using the lowest arsenic concentration as the reference. Crude data is reported where possible.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> Exposure to arsenic from drinking water ≥ 2 strata of arsenic concentration levels Reference group <50 ug/L, and first strata <200 ug/L Study must provide a relative risk or the raw data to calculate one 	<ul style="list-style-type: none"> Duplicate data Data Mistakes Small percentage of cases have exposure data

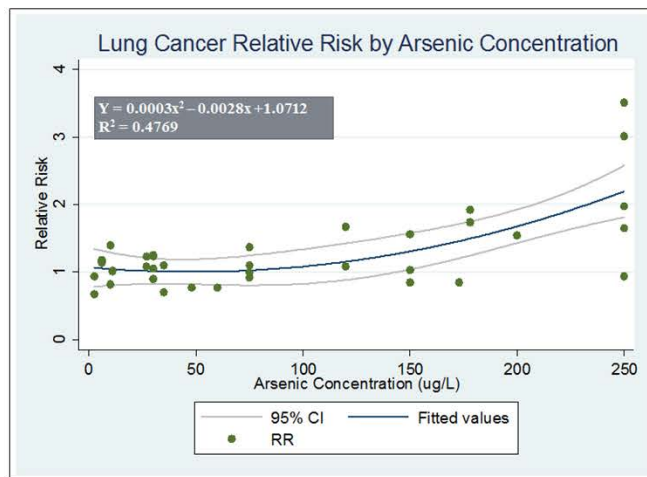
RESULTS

Paper	Author	Year	Location	Design	Risk	Sub-Populations	Period	Outcome	Relative Risk			
									<10 ug/L	<100 ug/L	100-200 ug/L	>200 ug/L
1a	Buchet ⁷	1998	Belgium	Ecological	SRR	Males	1981-1991	Mortality	0.94	0.82, 1.05		
1b	Buchet ⁷	1998	Belgium	Ecological	SRR	Females	1981-1991	Mortality	0.67	1.40, 1.24		
2	Chen ⁸	2010	NE Taiwan	Cohort	RR	-	1991-1994	Incidence		1.10, 0.99	1.54	
3	Dauphine ⁹	2013	CA & NV, US	Case Control	OR	-	2002-2005	Incidence		0.77	0.85	
4a	Ferreccio ¹⁰	2006	Chile	Cohort	SMR	1985-1992	1985-1992	Mortality			1.03	3.51
4b	Ferreccio ¹⁰	2006	Chile	Cohort	SMR	1993-2002	1993-2002	Mortality			0.85	3.01
5	Ferreccio ¹¹	2013	Chile	Case Control	OR	-	2007-2010	Incidence		0.77		
6a	Han ¹²	2009	ID, US	Ecological	IR	Males	1991-2005	Incidence	1.14	1.23		
6b	Han ¹²	2009	ID, US	Ecological	IR	Females	1991-2005	Incidence	1.18	1.08		
7a	Hopenhayn-Rich ¹³	1998	Argentina	Ecological	SMR	Males	1986-1991	Mortality			1.67, 1.92	
7b	Hopenhayn-Rich ¹³	1998	Argentina	Ecological	SMR	Females	1986-1991	Mortality			1.08, 1.74	
8a	Meliker ¹⁴	2007	MI, US	Cohort	SMR	Males	1979-1997	Mortality		1.02		
8b	Meliker ¹⁴	2007	MI, US	Cohort	SMR	Females	1979-1997	Mortality		1.02		
9	Morales ³	2000	SW Taiwan	Cohort	SMR	-	1973-1986	Mortality		0.92	1.56	1.97
10a	Mostafa ¹⁵	2008	Bangladesh	Case Control	OR	Smokers	2003-2006	Incidence		1.25, 1.37		1.65
10b	Mostafa ¹⁵	2008	Bangladesh	Case Control	OR	Non-smokers	2003-2006	Incidence		0.90, 1.10		0.94
11	Smith ¹⁶	2009	Chile	Case Control	OR	-	1994-1996	Incidence		0.7		

*Adjusted relative risks are shown in italics.

The 11 studies had four results at <10 ug/L (range 0.67-1.18; mean 0.98), 18 results at 10-100 ug/L (range 0.7-1.40; mean 1.04), 9 results at 100-200 ug/L (range 0.85-1.92; mean 1.36), and 5 results at 200-250 ug/L (range 0.94-3.51; mean 2.22).

Polynomial regression of the 36 data points ($y = 0.00003x^2 - 0.0028x + 1.0712$) showed significant association for the quadratic term ($p = 0.037$) but not for the linear term ($p = 0.42$). Data points outside of the 95% CI are symmetrically distributed. The lower 95% CI exceeds 1.0 only above approximately 150 ug/L.



CONCLUSION


Polynomial regression of lung cancer relative risk on drinking water arsenic level showed a significant fit to a quadratic model. Lung cancer risk with exposure to arsenic in drinking water was not seen to rise at levels below 100 ug/L with significant risk above about 150 ug/L. Increased risks appeared at 100-200 ug/L and at >200 ug/L. The major limitations of this analysis are not being able to validate exposure values and rarely being able to stratify by smoking. Like for bladder cancers, increased risks are not seen below 100 ug/L arsenic.

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<u>Criteria</u>	<u>Chen 2010a</u>	<u>Dauphine 2013</u>	<u>Ferrecio 2013b</u>	<u>Mostafa 2008</u>
Randomization	n/a	n/a	n/a	n/a
Allocation Concealment	n/a	n/a	n/a	n/a
Comparison Group	++	++	++	++
Confounding (Design)	++	++	++	++
Unintended Exposure	++	++	++	+
Experimental Conditions	n/a	n/a	n/a	n/a
Protocol Deviations	+	+	+	+
Blinding (During Study)	n/a	n/a	n/a	n/a
Missing Outcome data	++	++	+	+
Blinding (Outcome Assessment)	+	++	+	+
Confounding (Analysis)	-	-	-	-
Exposure Characterization	++	+	-	- 
Outcome Assessment	++	++	++	++
Outcome Reporting	+	+	+	+
Internal Validity	++	++	++	+
Risk Tier with Question 11 included	Low Risk	Low Risk	Prob High Risk	Prob High Risk
with Question 11 excluded	Low Risk	Low Risk	Low Risk	Low Risk

Odds Ratios and Arsenic Strata

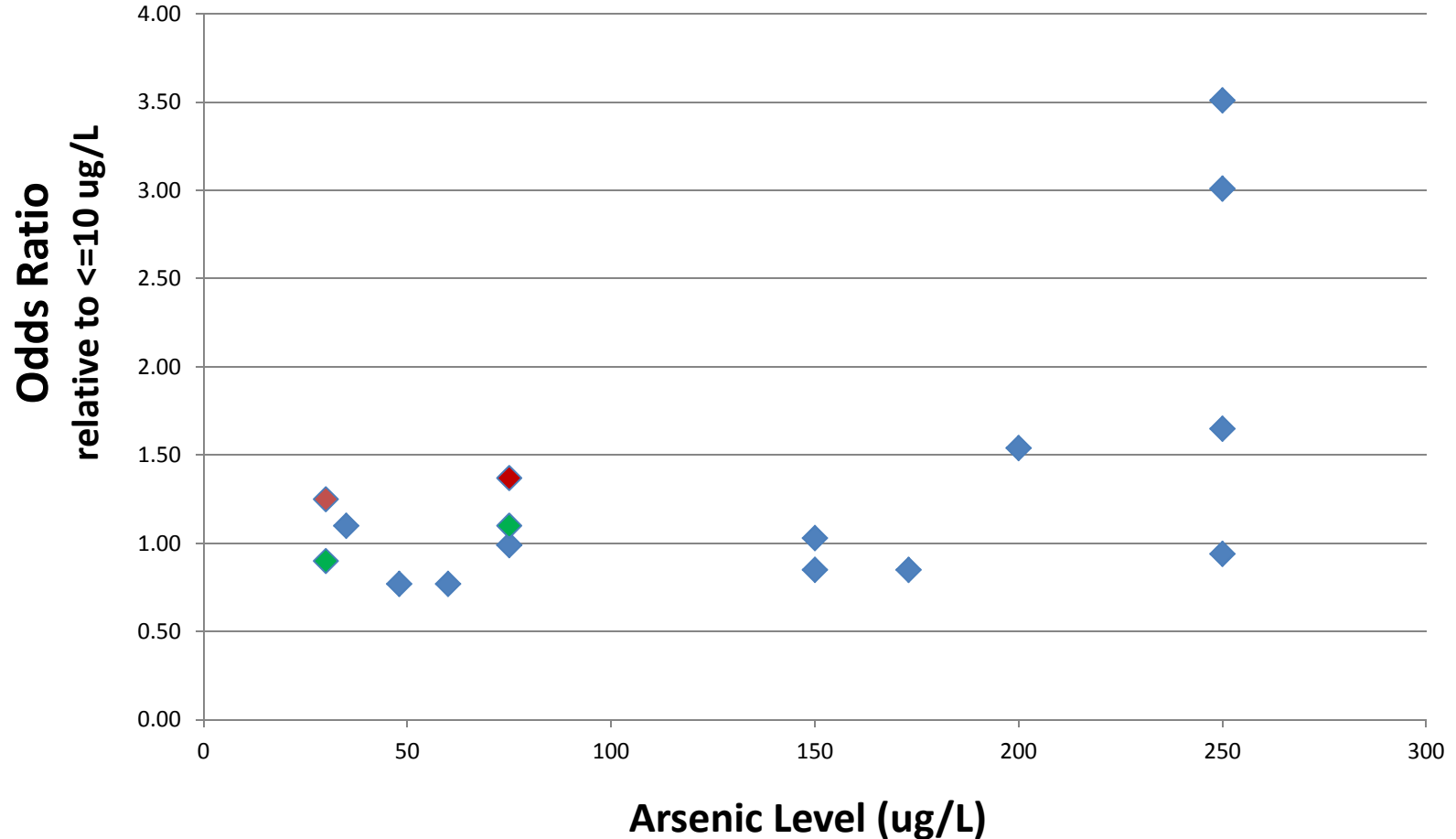
Author	Year	Population	< 10 ug/L	< 100 ug/L	~ 100-200 ug/L	> 200 ug/L
Chen	2010	11 yr F/U -> 2006	1.00	1.10, 0.99	1.54	
Dauphine	2013	2002-2005	1.00	0.77	0.85	
Ferreccio	2006	1985-1992	1.00		1.03	3.51
Ferreccio	2006	1993-2002	1.00		0.85	3.01
Ferreccio	2013	2007-2010	1.00	0.77		
Mostafa	2008	Non-smokers*	1.00	0.90, 1.10		0.94
Mostafa	2008	Smokers*	1.00	1.25, 1.37		1.65

* 2003-2006

Exposure and Outcome Data

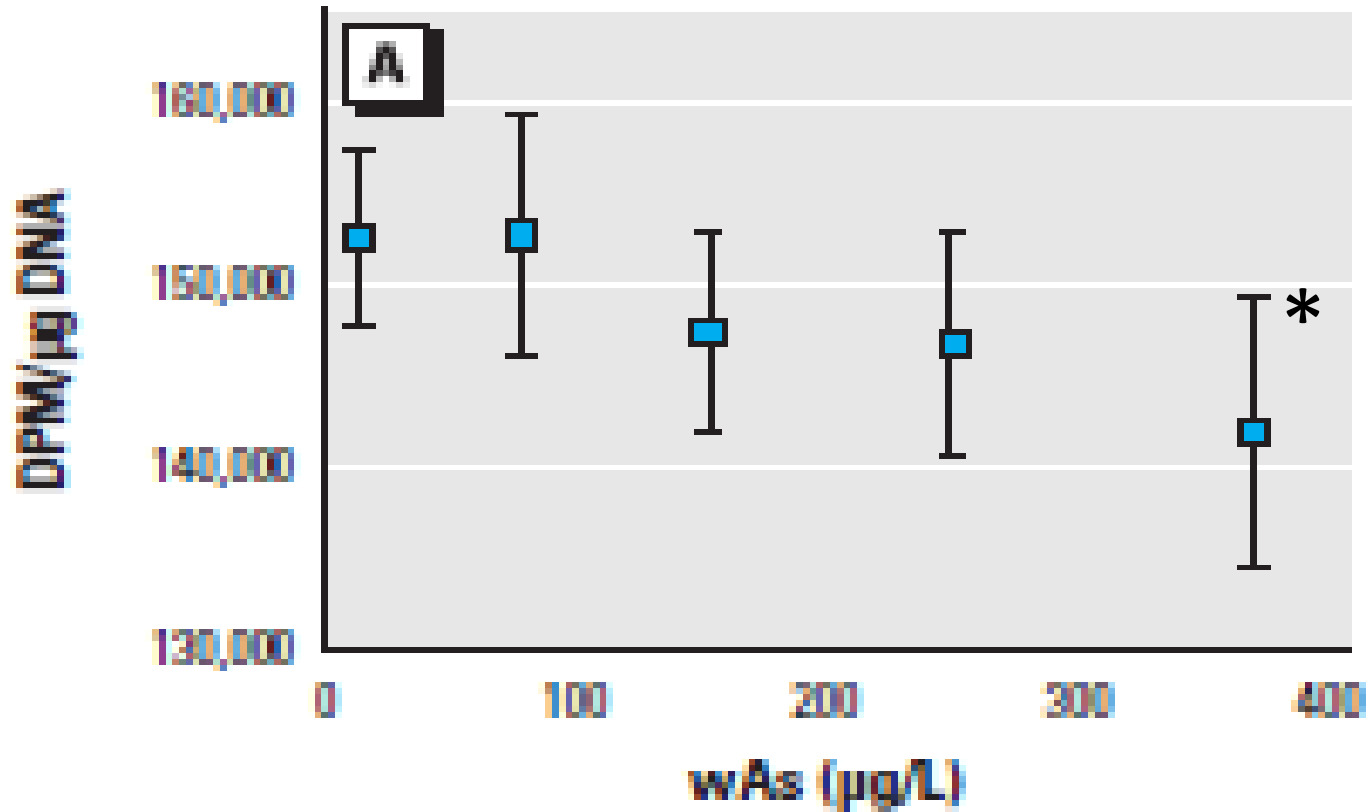
Author	Year	As	RR
Mostafa	2008	30	1.25
Mostafa	2008	30	0.90
Chen CL	2010	35	1.1
Dauphine	2013	48	0.77
Ferreccio	2013	60	0.77
Chen CL	2010	75	0.99
Mostafa	2008	75	1.37
Mostafa	2008	75	1.10
Ferreccio	2006	150	1.03
Ferreccio	2006	150	0.85
Dauphine	2013	173	0.85
Chen CL	2010	200	1.54
Ferreccio	2006	250	3.51
Ferreccio	2006	250	3.01
Mostafa	2008	250	1.65
Mostafa	2008	250	0.94

Lung Cancer Odds Ratios by Arsenic Exposure Level



Red = Smoker; Green = Non-smoker; Blue = Unspecified

Niedzweicki et al. (EHP 2013)



* Statistically significantly different from lowest level

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