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THE RELATION BETWEEN EXPOSURE TO ENVIRONMENTAL SELENIUM AND CANCER RISK: A FAILURE OF OBSERVATIONAL RESEARCH?

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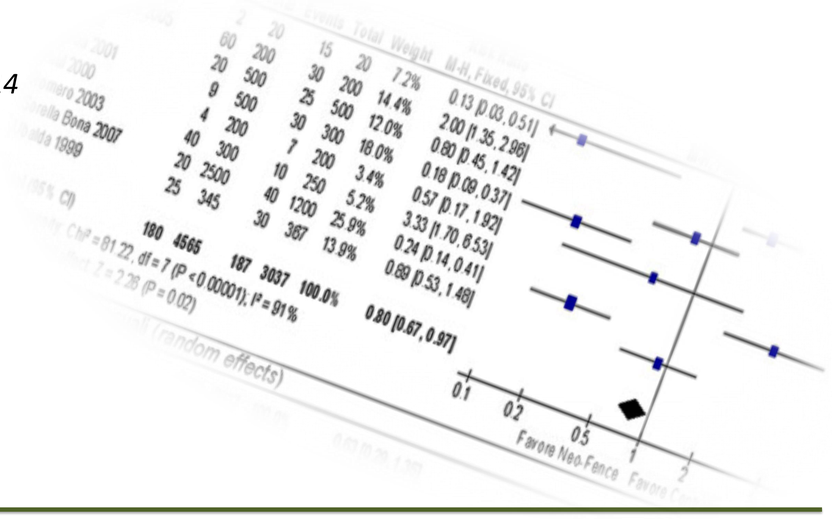

Introduction

Selenium is a metalloid element with both nutritional and toxicological properties. Changes in environmental exposure to selenium might modify cancer risk, according to epidemiologic and laboratory studies. However, such relation is extremely controversial, since the first observational studies and one randomized controlled trial (RCT) originally suggested an inverse relation between selenium intake and cancer, while most recent studies including the large RCTs carried out in the US have shown no effect or adverse effects on cancer risk.

Methodology

We meta-analysed the results of fifty-six observational (cohort and cohort-nested case-control) studies, including over 1,200,000 participants, and of nine randomized controlled trials (RCTs), with 46,304 total participants, using random effects models. We pooled the incidence of any cancer and of prostate cancer, one of the most commonly investigated outcomes, which was originally suggested to be prevented by increasing selenium intake.

Results

For observational studies, we found a reduced cancer incidence (summary OR 0.69, 95%CI 0.53-0.91). In contrast, RCTs showed that selenium supplementation had little effect on the risk of any cancer (RR 0.94, 95%CI 0.81-1.10), and limiting the analysis to trials with a low risk of bias, the RR further approached unity (1.01, 95%CI 0.93-1.10) (Figure 1).

For prostate cancer, observational studies indicated a considerably decreased risk (OR 0.72, 95%CI 0.62-0.86), while RCTs showed little evidence of a beneficial effect of selenium supplementation (RR 0.92, 95%CI 0.75-1.12). When we limited the analysis to RCTs with low risk of bias, no effect whatsoever on prostate cancer risk emerged (RR 1.01, 95%CI 0.90-1.14) after selecting only trials with low risk of bias (Figure 2).

Fig. 1. Pooled analysis for any cancer in all RCTs studies (a) and in only RCTs at low risk of bias (b)

a. All RCTs studies

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Karp 2013	169	1040	83	521	24.7%	1.02 [0.80, 1.30]
NPCT 2002 (1)	105	621	137	629	26.1%	0.78 [0.62, 0.98]
SELECT 2009 (2)	837	8752	824	8696	49.2%	1.01 [0.92, 1.11]
Total (95% CI)		**10413**		**9846**	**100.0%**	**0.94 [0.81, 1.10]**
Total events	1111		1044			

Heterogeneity: Tau² = 0.01; Chi² = 4.49, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 0.71 (P = 0.48)

Risk Ratio IV, Random, 95% CI
0.05 0.2 1 5 20
Favours experimental Favours control

(1) We used the data from Duffield 2002
(2) We used the data from Lippman 2009

b. Only RCTs at low risk of bias

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Karp 2013	169	1040	83	521	12.6%	1.02 [0.80, 1.30]
NPCT 2002 (1)	105	621	137	629	0.0%	0.78 [0.62, 0.98]
SELECT 2009 (2)	837	8752	824	8696	87.4%	1.01 [0.92, 1.11]
Total (95% CI)		**9792**		**9217**	**100.0%**	**1.01 [0.93, 1.10]**
Total events	1006		907			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

Risk Ratio IV, Random, 95% CI
0.05 0.2 1 5 20
Favours experimental Favours control

(1) We used the data from Duffield 2002
(2) We used the data from Lippman 2009

Fig. 2. Pooled analysis for prostate cancer in all RCTs studies (a) and in only RCTs at low risk of bias (b)

a. All RCTs studies

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Algotar 2013	24	234	26	232	11.7%	0.92 [0.54, 1.55]
Karp 2013	16	1040	9	521	5.6%	0.89 [0.40, 2.00]
Marshall 2011	48	135	49	134	23.6%	0.97 [0.71, 1.34]
NPCT 2002 (1)	22	457	42	470	12.7%	0.54 [0.33, 0.89]
SELECT 2009 (2)	432	8752	416	8696	46.4%	1.03 [0.90, 1.18]
Total (95% CI)		**10618**		**10053**	**100.0%**	**0.92 [0.75, 1.12]**
Total events	542		542			

Heterogeneity: Tau² = 0.02; Chi² = 6.22, df = 4 (P = 0.18); I² = 36%
Test for overall effect: Z = 0.85 (P = 0.39)

Risk Ratio IV, Random, 95% CI
0.05 0.2 1 5 20
Favours experimental Favours control

(1) We used the data from Duffield 2002
(2) We used the data from Lippman 2009

b. Only RCTs at low risk of bias

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Algotar 2013	24	234	26	232	5.0%	0.92 [0.54, 1.55]
Karp 2013	16	1040	9	521	2.1%	0.89 [0.40, 2.00]
Marshall 2011	48	135	49	134	13.5%	0.97 [0.71, 1.34]
SELECT 2009 (1)	432	8752	416	8696	79.4%	1.03 [0.90, 1.18]
Total (95% CI)		**10161**		**9583**	**100.0%**	**1.01 [0.90, 1.14]**
Total events	520		500			

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

Risk Ratio IV, Random, 95% CI
0.05 0.2 1 5 20
Favours experimental Favours control

(1) We used the data from Lippman 2009

Conclusions

The results of the most recent, well-designed RCTs investigating the relation between selenium and risk of any cancer or of prostate cancer have been entirely disappointing, suggesting no effect or adverse effects of the metalloid (such as an increased risk of skin cancer), in contrast with a previous RCT and with several observational studies. It is not clear why observational and experimental studies yielded such different results. The causative factors may include exposure misclassification in the observational studies, which were based on overall selenium content in peripheral biomarkers and not on levels of single selenium compounds in target tissues, or more generally confounding and other biases or effect modification by genetic factors. Overall, methodological issues concerning the relation between selenium and cancer risk have important implications for epidemiological research and for public health recommendations.

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