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High and Low Selenium Exposure and Cancer Risk: A Meta-meta-analysis †

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Abstract: Selenium was discovered in the first quarter of the 19th century and classified as a chalcogen belonging to the 16th group, along with oxygen, sulfur, tellurium, and polonium. Selenium plays a crucial role in the activation of antioxidant enzymes in the body and helps reduce oxidative stress by preventing cell damage. It is believed to have cancer-protective effects, including mechanisms such as reducing DNA damage, regulating cell growth, supporting the immune system, and engaging in epigenetic interactions. These are attributed to the antioxidant properties of selenium. The purpose of this paper was to elucidate the effect of selenium exposure on the incidence and mortality of various cancer types using the meta-meta-analysis method.

Keywords: selenium; cancer; DNA damage; meta-analysis; exposure

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1. Introduction

Selenium, a chemical element, made its debut in the scientific realm during the early 19th century and was subsequently categorized as a chalcogen, grouping it within the 16th column of the periodic table alongside oxygen, sulfur, tellurium, and polonium. It assumes a pivotal role in orchestrating the activation of various antioxidant enzymes within the human body, effectively contributing to the intricate balance of oxidative and antioxidative processes [1-3]. By harnessing its antioxidative prowess, selenium works diligently to thwart the deleterious impacts of oxidative stress, preventing cellular damage that can otherwise culminate in a cascade of adverse health outcomes [1-4].

As science delves deeper into selenium's intricacies, an expanding body of research has underscored its potential cancer-protective properties. These protective effects are conjectured to stem from a multifaceted interplay of factors. Notably, selenium is speculated to function as a guardian against carcinogenesis through a spectrum of mechanisms. Firstly, its capacity to curtail DNA damage has garnered significant attention, contributing to the preservation of genomic stability and averting potential mutations that could catalyze the cancerous transformation of cells [2-6]. Moreover, selenium's role in regulating cell growth has emerged as another critical facet, wherein it exercises control over the delicate balance between cell proliferation and apoptosis, preventing uncontrolled growth that is emblematic of malignancies. Additionally, selenium's engagement in epigenetic interactions, wherein it influences gene expression without altering DNA sequences, has emerged as a promising avenue. These interactions, often mediated by the

modification of histones and DNA methylation, further contribute to the maintenance of cellular homeostasis and guard against the onset of carcinogenic processes [1-7].

The purpose of this paper was to elucidate the effect of selenium exposure on the incidence and mortality of cancer using the meta-meta-analysis method.

2. Methods

To ensure a rigorous and exhaustive exploration of the subject matter, a comprehensive and systematic literature search was meticulously conducted across related databases, including PubMed/Medline, Web of Science (WoS), and Scopus. This methodical approach aimed to capture an extensive collection of relevant studies, employing a well-defined set of predetermined keywords tailored to the research objectives.

The research methodology encompassed both primary and secondary meta-meta-analyses, involving the amalgamation of odds ratios (OR) and relative risks (RR) for outcomes documented in the chosen meta-analyses. A comprehensive analysis was conducted to synthesize all available data, culminating in a unified pooled estimate. This analytical framework enabled a comprehensive assessment of the multifaceted interplay between selenium and cancer-related outcomes, fostering a nuanced understanding of the subject matter.

The variability in outcomes across various studies was assessed through the $\chi 2$-based Cochran's Q test (with a significance level set at $p < 0.05$) as well as the I^2 statistics. These analytical tools were employed to measure the importance of heterogeneity among the collected data. The meta-meta-analyses were conducted using both random-effects and fixed-effects models, with the appropriate method selected based on the level of heterogeneity present in the data. The potential publication bias was identified based on the outcome indicated by Egger's linear regression asymmetry test [8] and Begg and Mazumdar's rank correlation test [9]. The statistical significance across all meta-meta-analyses was assessed at the conventional two-tailed p-value threshold of < 0.05. The statistical computations for the meta-meta-analyses were conducted using Prometa3® [10], in conjunction with the R statistical software version 4.2.0 [11]. These analyses were carried out in accordance with well-established guidelines for meta-analytic methodologies, ensuring a rigorous and systematic approach to the data evaluation process.

3. Results & Discussion

A comprehensive analysis was conducted on a total of 22 reports containing 16 eligible meta-analyses [12-27] that adhered to the inclusion criteria, aiming to evaluate the association between selenium exposure and cancer incidence as well as mortality. Through a pooled analysis encompassing 18 reports originating from 16 separate meta-analyses that examined the link between selenium exposure and cancer risk, a remarkable finding occurred.

In the pooled analysis of 18 reports from a total of 16 meta-analyses [12-27] evaluating selenium exposure and cancer risk, higher selenium exposure was associated with a 22% lower risk of cancer (OR = 0.78, 95% CI: 0.72-0.85, $p < 0.001$) (Figure 1a). Considerable and remarkable heterogeneity was detected across the studies incorporated in the analysis (Q = 105.5, df = 17, I^2 = 83.8%, $p < 0.001$). As a result, the meta-meta-analysis was executed utilizing a random effects model. According to the Begg and Mazumdar's rank correlation test (z = -0.49, $p = 0.622$), there was no evidence of publication bias in the study reports (Figure 1b).

Similarly, a parallel pooled analysis involving four meta-analyses [12, 15, 21, 22] that investigated selenium exposure and cancer-related mortality confirmed this trend. The outcome highlighted a significant correlation between increased selenium exposure and reduced mortality rates (RR = 0.88, 95% CI: 0.83-0.94, $p < 0.001$) (Figure 2a). No significant heterogeneity was observed among the studies enclosed in the analysis (Q = 2.02, df = 3, I^2 = 0.00%, $p = 0.568$). Therefore, the meta-meta-analysis was carried out using a fixed

effects model. The results of Egger's linear regression asymmetry test (Intercept = -0.59, t = -0.87, p = 0.476) and Begg and Mazumdar's rank correlation test (z = -0.68, p = 0.497) indicated no publication bias in the study reports (Figure 2b).

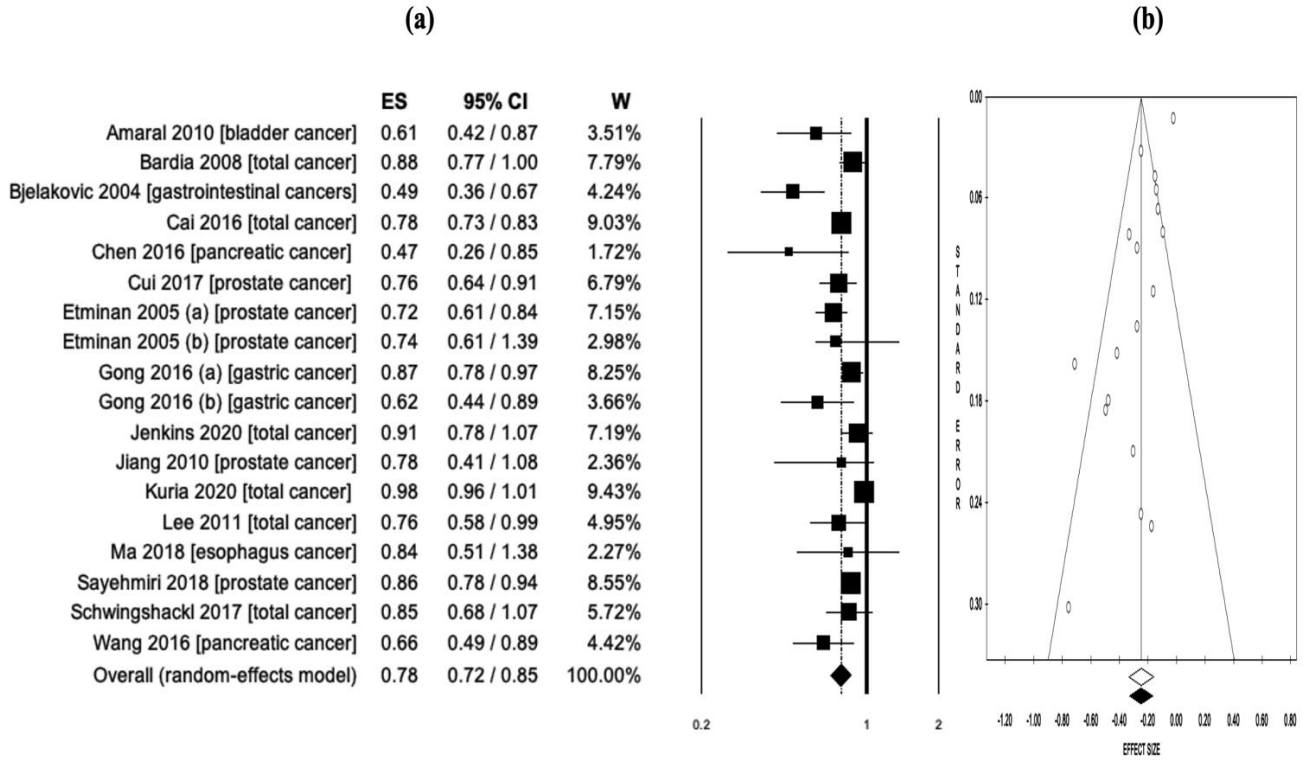

Figure 1. (a) The pooled effect size (ES) associated with selenium exposure (low and high exposure) and cancer risk, and **(b)** the funnel plot depicting the relationship between selenium exposure and cancer risk [12-27].

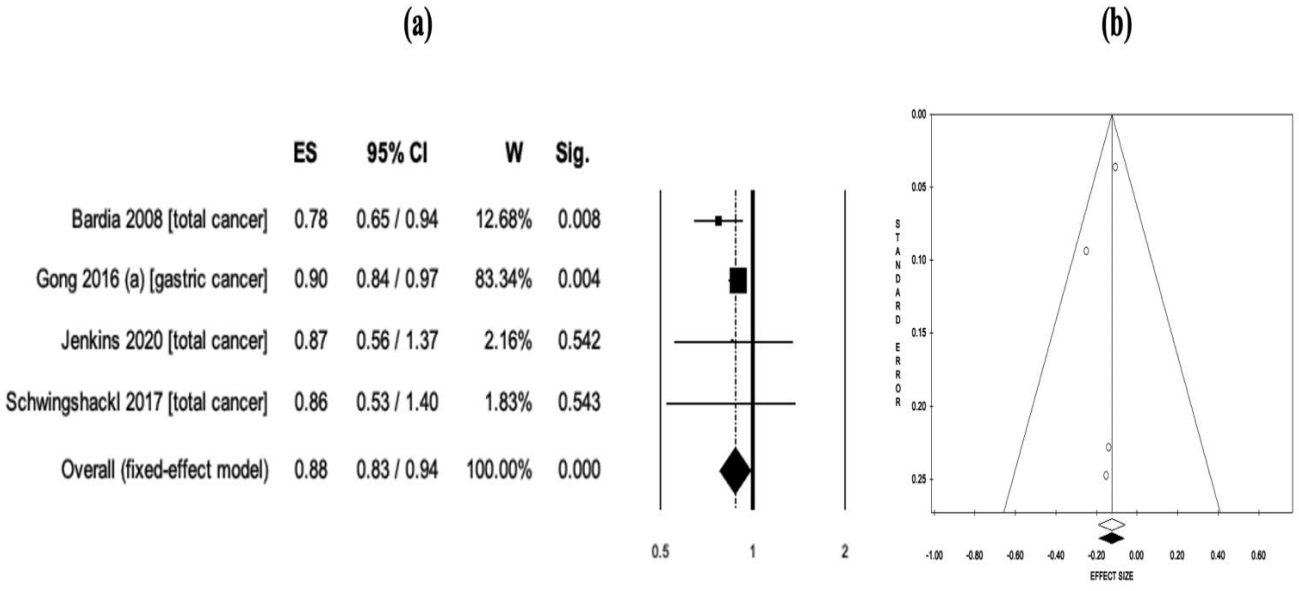

Figure 2. (a) The pooled effect size (ES) associated with selenium exposure (low and high exposure) and cancer mortality, and **(b)** the funnel plot depicting the relationship between selenium exposure and cancer mortality [12, 15, 21, 22].

In a recent meta-analysis conducted by Kuria et al. [28], which incorporated 37 primary studies, it was reported that selenium at recommended daily levels of 55 μg/day demonstrated a reduced risk of cancer (RR = 0.94, 95% CI: 0.90-0.98, $p < 0.05$). Moreover, various meta-analyses evaluating selenium exposure and the risk of pancreatic cancer [29], prostate cancer [30], gastric cancer [31], and bladder cancers [32] have emphasized the protective effects of selenium against cancer. In this paper, high selenium exposure was associated with a 22% lower risk of cancer (OR = 0.78, 95% CI: 0.72-0.85, $p < 0.001$), and concurrently, higher selenium exposure was found to be linked with reduced mortality (RR = 0.88, 95% CI: 0.83-0.94, $p < 0.001$). These findings notably highlight the significance of selenium's protective effects against cancer.

4. Conclusions

Taken together, the findings of this paper highlight the potential efficacy of selenium in reducing cancer risk and cancer-related mortality. Furthermore, this investigation posits that elevated levels of selenium exposure may serve as a reasonable strategy for not only preempting but also managing cancer. The findings also support the potential role of selenium in cancer prevention and highlight its importance as a possible intervention for improving health outcomes in individuals at risk of cancer. Furthermore, considering the cancer types and dose-response relationships, it is crucial and critical to plan more comprehensive and well-designed prospective studies and randomized controlled trials.

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Conflicts of Interest: The entirety of the authors involved in the execution of this study announces that they have no conflicts of interest to declare. No financial, personal, or professional affiliations exist that may exert any potential influence or bias upon the outcomes and conclusions presented within this research. This unequivocal declaration is made with the purpose of upholding transparency and safeguarding the credibility and objectivity of the conducted study.

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