Biological Trace Element Research
https://doi.org/10.1007/s12011-021-02574-9

Relationship Between Selenium in Human Tissues and Breast Cancer: a Meta-analysis Based on Case-Control Studies

Xiaopan Zhu[1] · Da Pan[1] · Niannian Wang[1] · Shaokang Wang[1] · Guiju Sun[1]

Received: 2 November 2020 / Accepted: 3 January 2021

Abstract

Breast cancer is a common malignant tumor in women, and the anti-cancer effect of selenium (Se) is recognized. This meta-analysis was designed to determine the relationship between selenium levels in human tissue and breast cancer risk. Literatures published before August 2020 were systematically screened through PubMed, Web of Science, Scopus, and Elsevier. The related publication quality was evaluated by the Newcastle-Ottawa scale. We used random effect models for calculation and conducted sensitivity analysis and evaluation of publication bias. We identified 18 case-control studies, including 3374 women diagnosed with breast cancer and 3582 healthy controls. The results showed that the difference between the case group and the control group was − 0.53 μg/l [95%CI − 0.72 to − 0.34] ($P < 0.001$). Subgroup analysis showed a serum difference of − 1.14 μg/l [95%CI − 1.70 to − 0.58] ($P < 0.001$). The value of plasma was − 0.21 μg/l [95% CI − 0.37 to − 0.04] ($P = 0.014$). The value of toenail was − 0.21 μg/l [95% CI − 0.38 to − 0.03] ($P = 0.021$). In contrast, selenium levels in hair were not significantly associated with breast cancer risk. In the case-control studies, it was observed that selenium level in human tissues was negatively correlated with the risk of breast cancer, which may improve the understanding of the effects of selenium on human health.

Keywords Selenium · Tissue · Breast cancer · Meta-analysis

Introduction

Breast cancer is a malignant tumor occurring in the glandular epithelium of the breast. In 2018, the global age-standardized rate of breast cancer incidence (2,088,849 new cases) before age 75 was 11.6%, second only to lung cancer [1]. Selenium is an essential trace element for human body. Studies have shown that there was a linear relationship between hair selenium content and selenium intake [2]. Blood selenium reflected short-term selenium intake and nail selenium reflected long-term selenium intake [3]. Increasing evidence showed that selenium can play an anti-cancer role through antioxidant damage, inhibiting the proliferation and inducing the apoptosis of cancer cells, inhibiting the genetic mutation of cells and regulating the immune and inflammatory response [4–6]. Selenium compounds combined with anticancer drugs can reduce the proliferative activity of cancer cells [7, 8]. However, there are few studies on the protective effect of selenium on breast cancer, and the results are mixed. In the study of Suzana S [9], the concentration of selenium in the hair of the case group was higher than that of the control group, although the difference was not statistically significant (SMD = 0.21, 95%CI − 0.44 to 0.87, $P > 0.5$), while the concentration in the hair of the case group in the study of Piccinini L [10] was significantly lower than that of the control group (SMD = − 0.96, 95%CI − 1.51 to − 0.41, $P < 0.5$). Therefore, more evidence is needed to test the correlation between selenium and breast cancer. The purpose of this study was to further explore the relationship between selenium in human tissues and breast cancer risk in case-control studies.

Materials and Methods

Literature Search

We systematically searched the English literature published in PubMed, Web of Science, Scopus, and Elsevier from 1990 to August 2020. Search terms were as follows: selenium, serum, plasma, toenail, hair, breast cancer, and related words. The

✉ Shaokang Wang
shaokangwang@seu.edu.cn

[1] Key Laboratory of Environmental Medicine and Engineering of Ministry of Education, Department of Nutrition and Food Hygiene, School of Public Health, Southeast University, Nanjing 210009, Jiangsu, China

Published online: 08 January 2021

study was restricted to human studies. In addition, a list of references of each study, systematic reviews, and meta-analyses were reviewed to identify potential relevant literatures. The included literature was examined and approved independently by two researchers, and disputes were resolved through discussion.

Inclusion and Exclusion Criteria

Studies that met the following criteria were included: published openly, reported an association between selenium and breast cancer risk by measuring selenium concentrations in the following biological samples (serum, plasma, hair, and toenail), specified diagnosis of breast cancer, and data result contained clear mean and standard deviation and was selected when the data was the most sufficient if they were from the same population. Studies were excluded that were animal or vitro experiments, review articles, repeated literature or mechanism studies; nothing to do with human subjects; inappropriate control group; analytical method was not provided; and lack of access to full texts.

Data Extraction and Quality Assessment

From each study, we obtained information about author name, year of publication, country, population age, sample testing methods, and results (sample size/mean/SD). Newton-Ottawa Scale [11] was used to independently evaluate the quality of literatures, and literatures with a score of ≥ 5 were included in the meta-analysis.

Statistical Analyses

The study was combined based on sample size, mean, and standard deviation. The mean variance is calculated using the formula of two integrated variance. The mean variance was calculated by the formula $s^2 = \frac{(N_1-1)\mathrm{SD}_1{}^2+(N_2-1)\mathrm{SD}_2{}^2+\frac{N_1N_2}{N_1+N_2}\left(M_1{}^2+M_2{}^2-2M_1M_2\right)}{N_1+N_2-1}$, where the sample size of subgroup A was N_1, the mean and standard deviation were M_1 and SD_1, and the quantity of subgroup B was N_2, the mean and standard deviation were SD_2, and the standard deviation of the two combinations were S. In previous studies, when $I^2 < 50\%$ and the heterogeneity $P > 0.05$, the fixed effect model was used. Otherwise, the random effects models would be used. The sources of heterogeneity were examined by regression analysis and subgroup analysis. Begg funnel plot and Egger test were conducted to examine publication bias with significance when the value of P is < 0.05. Statistical analysis was performed using STATA version 11.

Results

Literature Search and Study Characteristics

The flow chart of selected articles with literature retrieval and research features is shown in Fig. 1. A total of 321 articles were found through electronic search, and 288 articles were found after elimination of duplicates, most of which were animal and vitro experiments. Finally, after the full text was checked, 18 case-control studies were eligible for inclusion in the meta-analysis, and 1 article was excluded for other reason. There were 6956 participants in 18 case-control studies, including 3374 cases and 3582 controls. We conducted a comprehensive study of the articles containing the raw data, all of which were analyzed on a microgram per liter (μg/l). Table 1 summarizes the basic characteristics of the 18 studies included in this analysis. Eight of the studies were from developed countries, and ten were from developing countries, involving a total of five methods of testing samples. In three studies, the concentration of selenium in human tissues was positively correlated with the risk of breast cancer, while the rest were negatively correlated. According to the random effects model, the total selenium difference between the case group and the control group was − 0.53 μg/l [95%CI − 0.72 to − 0.34] (Fig. 2), based on the year of publication and the name of the author.

Heterogeneity

Due to the high heterogeneity, we used meta regression to examine the source of heterogeneity. When regression analysis was carried out on publication year, countries, biological samples, and detection methods, P value was greater than

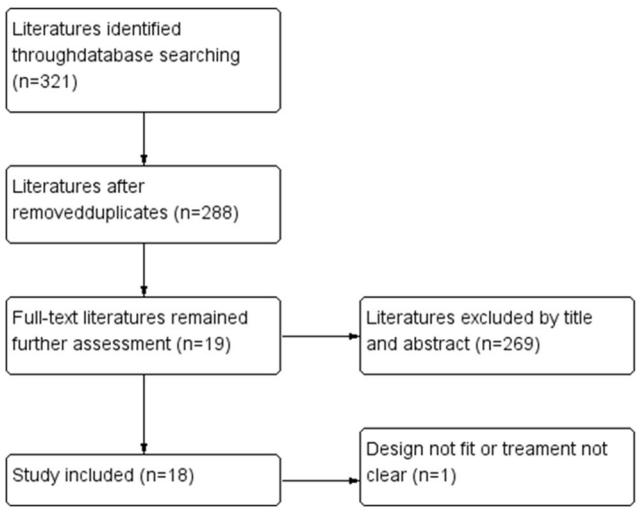

Fig. 1 Flow diagram for selected articles

Table 1 Basic information of included studies

First author (year)	Country	Age	Number		Biological sample	Selenium concentration		Method of measurement	Study score
			Case	Control		Case	Control		
Hunter, D. J. (1990) [12]	USA	30~55	434	434	Toenail	0.823 ± 0.197 μg/g	0.821 ± 0.174 μg/g	Neutron activation analysis	7
Van'T Veer, P. (1990) [13]	Netherlands	25~64	124	236	Toenail	0.63 ± 0.12 mg/kg	0.65 ± 0.18 mg/kg	Neutron activation analysis	7
Van'T Veer, P. (1990) [13]	Netherlands	25~64	92	151	Plasma	89 ± 14 μg/l	93 ± 15 μg/l	Neutron activation analysis	7
Piccinini, L. (1996) [10]	Italy	41~79	38	22	Hair	215.2 ± 112.5 ng/g	338.3 ± 151.95 ng/g	Fluorimetric method	8
Piccinini, L. (1996) [10]	Italy	41~79	38	22	Plasma	71.81 ± 18.12 ng/g	75.06 ± 16.58 ng/g	Fluorimetric method	8
Strain, J. J. (1997) [14]	UK	50~74	96	101	Plasma	584 ± 117 μg/g	603 ± 126 μg/g	Neutron activation analysis	8
Ghadirian, P. (2000) [15]	Canada	35~79	326	120	Toenail	0.92 ± 0.23 mg/kg	0.93 ± 0.18 mg/kg	Neutron activation analysis	7
Mannisto, S. (2000) [16]	Finland	25~75	289	433	Toenail	0.78 ± 0.16 mg/kg	0.82 ± 0.15 mg/kg	Fluorimetric method	7
WenKuo, H. (2002) [17]	China	35~51	68	26	Serum	75.44 ± 30.66 μg/l	99.50 ± 25.83 μg/l	Atomic absorption spectrophotometry	7
Bakir, M.A. (2004) [18]	Syria	25~84	70	50	Serum	0.82 ± 0.26 ppm	1.22 ± 0.31 ppm	Neutron activation analysis	6
Rejali, L. (2007) [19]	Malaysia	49.60 ± 11.00	62	62	Serum	16.24 ± 8.21 μg/dl	23.85 ± 9.80 μg/dl	Atomic absorption spectrophotometry	8
Suzana, S. (2008) [20]	Malaysia	30~66	57	139	Hair	0.06 ± 0.15 μg/g	0.08 ± 0.18 μg/g	ICP-MS	8
Suzana, S. (2008) [20]	Malaysia	30~66	57	139	Toenail	0.06 ± 0.09 μg/g	0.11 ± 0.08 μg/g	ICP-MS	8
Suzana, S. (2009) [9]	Malaysia	30~65	12	36	Hair	0.136 ± 0.152 μg/g	0.114 ± 0.084 μg/g	ICP-MS	8
Suzana, S. (2009) [9]	Malaysia	30~65	12	36	toenail	0.056 ± 0.088 μg/g	0.114 ± 0.085 μg/g	ICP-MS	8
Moradi, M. (2009) [21]	Iran	26~70	45	45	Plasma	132.15 ± 35.37 μg/l	138.40 ± 40.36 μg/l	Graphite furnace atomic absorption spectroscopy	6
Cihan, Y. B. (2011) [22]	Turkey	25~65	52	52	Hair	0.649 ± 0.930 μg/g	5.061 ± 7.597 μg/g	ICP-MS	6
Feng, J. F. (2012) [23]	China	48.3 ± 8.09	56	20	Serum	71.4 ± 7.5 μg/l	81.3 ± 6.7 μg/l	Graphite furnace atomic absorption spectroscopy	8
Ding, X. (2014) [24]	China	26~62	88	84	Serum	91.4 ± 20.0 μg/l	95.8 ± 22.7 μg/l	Atomic emission spectrometer	8
Adeoti, ML. (2016) [25]	Nigeria	31~65	30	30	Serum	45.0 ± 4.6 μg/l	76.4 ± 8.9 μg/l	Atomic absorption spectrophotometry	8
Sandsveden, M. (2017) [26]	Sweden	49~60	1186	1186	Serum	0.99 ± 2.21 ng/ml	0.963 ± 2.29 ng/ml	ICP-SFMS	6
Hashemi, S. M. (2017) [27]	Iran	19~88	142	158	Serum	101.24 ± 17.27 mg/dl	115.36 ± 13.31 mg/dl	Graphite furnace atomic absorption spectroscopy	7

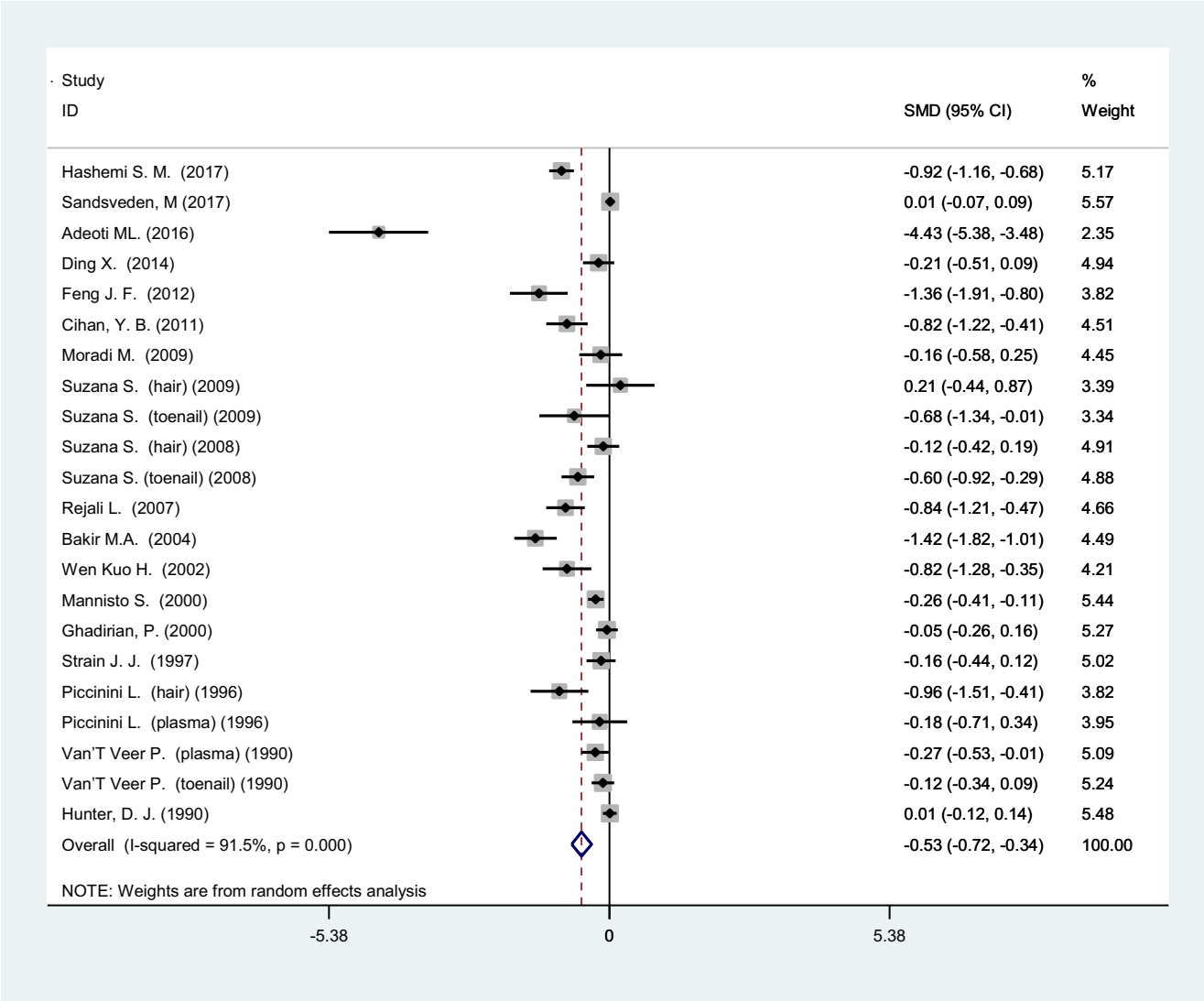

Fig. 2 Forest plot for all studies

0.05, so regression analysis could not determine the source of heterogeneity. When a subgroup analysis of countries was performed, the heterogeneity of results in developed countries was reduced to 67.8%, so the heterogeneity of the overall study may be derived from the literature in developing countries (Table 2).

Sensitivity Analyses and Publication Bias

Sensitivity analysis was performed to assess the effect of excluding any individual studies. Two literatures were excluded in turn, and the results of the remaining literatures were not substantially changed. The Begg funnel plots and Egger checks were used to examine potential publication bias. The funnel plot indicated no evidence of possible publication bias (Fig. 3), and the Egger test P value of 0.090 (more than 0.05) showed the lack of publication bias for all studies.

Discussion

In this meta-analysis, the overall selenium level in the case group was lower than that in the control group, indicating that high levels of selenium in the body can be associated with reduced risk of breast cancer ($P < 0.001$). We analyzed selenium in serum, hair, plasma, and toenails. Selenium levels in serum, toenails, and plasma were negatively associated with the risk of breast cancer ($P < 0.001$, $P = 0.021$, and $P = 0.014$). The association between selenium levels in hair and breast cancer risk was not statistically significant ($P = 0.092$). The above results were consistent with the results of Babaknejad N. et al. [28] on serum whereas different from the results of toenails. This may be because the different types of studies were included. Babaknejad N. et al. analyzed the cohort studies together with the case-control studies, which may be likely to cause confusion. Only case-control studies were included

Table 2 Results of subgroup analyses and sensitivity analyses

Subgroup	Concentration of Se (μg/l)			
	SMD	95%CI	*P* value	I^2
Country				
Developing country	− 0.85	[− 1.20, − 0.50]	0.001	89.9%
Developed country	− 0.14	[− 0.26, − 0.02]	0.020	67.8%
Method of measurement				
Neutron activation analysis	− 0.29	[− 0.57, − 0.01]	0.039	88.9%
Fluorimetric method	− 0.42	[− 0.82, − 0.02]	0.040	66.3%
Atomic absorption spectrophotometry	− 1.46	[− 2.53, − 0.40]	0.007	95.7%
ICP	− 0.32	[− 0.65, 0.01]	0.056	84.6%
Graphite furnace atomic absorption spectroscopy	− 0.80	[− 1.39, − 0.20]	0.008	85.6%
Biological sample				
Serum	− 1.14	[− 1.70, − 0.58]	< 0.001	96.6%
Plasma	− 0.21	[− 0.37, − 0.04]	0.014	0
Hair	− 0.43	[− 0.94, 0.07]	0.092	79.5%
Toenail	− 0.21	[− 0.38, − 0.03]	0.021	73.7%

and analyzed in our study. Our subgroup analysis for countries showed that selenium level in human tissues was negatively correlated with breast cancer in both developed and developing countries (P = 0.020 and P = 0.001). Additionally, the detection method will affect the accuracy of the results. The subgroup analysis results of the detection method in this paper are shown in Table 2. Different ethnic groups have different diet cultures, and different regions lead to different trace element concentration in the environment. High-selenium environment will have an important impact on human health. A high-selenium environment can lead to an increase in selenium levels in the crop, as well as human body. Selenium exposure increases the content of some essential trace elements in wheat, such as copper, and decreases toxic trace elements, such as arsenic [29]. Developing countries in our meta-analysis consist of Asian and African countries while the developed countries include European countries and USA. The latitude span of developing countries is higher than that of developed countries. Therefore, the regional and dietary culture differences in developing countries are also greater. This may account for the heterogeneity of articles in developing countries.

In a review published by Cai X [30], the relationship between selenium and cancer was studied. Although they did not have enough data to analyze dose-response relationships, the forest plot revealed the protective effect of selenium on breast cancer. Vinceti et al. [31] indicated that increased selenium exposure was associated with a higher risk of breast cancer

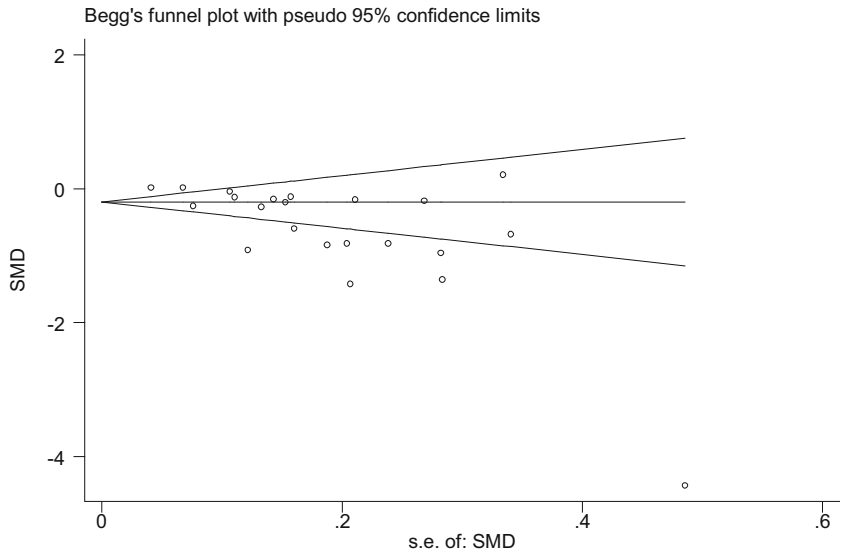

Fig. 3 Begg funnel plot for publication bias analyzed for all studies

than low selenium exposure, but there were few studies and the results were considered inaccurate. Sandsveden M et al. [26] determined that prediagnostic serum selenium is not associated with breast cancer risk. However, many studies have shown that selenium-rich nutrition patterns can reduce the risk of breast cancer. Taking selenium before breast cancer diagnosis can reduce mortality [32]. Organic selenium supplements may slow the growth and metastasis of breast tumor in mice [33]. Sandsveden M.'s [34] another cohort study showed that women with low serum selenium levels had a lower survival rate from breast cancer than women with high serum selenium levels. There are few studies on the relationship between environmental selenium and breast cancer. Also, some studies did not find an association between selenium and breast cancer [24, 35].

There are many studies on the anti-cancer mechanism of selenium. It is generally believed that selenium-containing protein GSH-Px in the body reduces toxic peroxides to non-toxic hydroxyl compounds, thus protecting the structure and function of cell membranes from interference and damage by oxides [36]. Selenium can antagonize the increase of cGMP in tumor cells and inhibit the synthesis of DNA, RNA, and proteins and increase normal cell activity [37, 38]. Selenium can be combined with anti-cancer drugs to induce apoptosis of cancer cells and inhibit M-phase cell proliferation for the treatment of breast cancer [39]. The regulation of immune function by selenium is also the main factor of its anticancer effect. Researchers were able to predict survival in breast cancer patients with serum selenium levels [40]. The antitumor toxicity of selenium nanoparticles is also a research hotspot in recent years [41]. However, excessive selenium content in human body will cause nausea and diarrhea [42] and even possibly increase the risk of other cancers [43] and the risk of death [44]. Therefore, although selenium supplementation in women with low levels after diagnosis may have a positive effect on patients, the amount of selenium supplementation should be conducted under professional guidance.

There are some limitations in our meta-analysis. First, only articles published in English were included, and unpublished negative results may be lost. Second, only case-control studies were analyzed. Small sample size may lead to heterogeneity and lack of studies on stratification of menopause. Third, lack of nutritional and lifestyle information among participants and smoking may lead to confusions and the association between high selenium intake and breast cancer risk is unknown.

In conclusion, this meta-analysis based on case-control studies supports an inverse relationship between selenium concentration and breast cancer risk. Overall, this conclusion may improve our understanding of the effects of selenium on human health and provide reference for the research of preventing breast cancer.

Funding This work was supported by the Danone Dietary Nutrition Research and Education Foundation (DIC2020-08).

Data Availability The datasets generated during and/or analyzed during the current study are available in the Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (http://apps.webofknowledge.com/UA_GeneralSearch_input.do?product=UA&search_mode=GeneralSearch&SID=8BNqgkTsjQELCPcvSXU&preferencesSaved=), Scopus (https://www.scopus.com/search/form.uri?display=basic), and Elsevier (https://www.sciencedirect.com/).

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